1

General Toxicological Principles

Gary D. Osweiler, DVM, MS, PhD

- Toxicology is the science and study of how poisons affect organisms.
- Dosage is the most important factor that determines response to poisons.
- Toxicity is the quantitative amount of toxicant required to produce a defined effect.
- Hazard or risk of toxicosis depends on toxicity of the agent, and probability of exposure to the toxicant under conditions of use.
- Acute, subacute, and chronic toxicity are different chronological quantitations of chemical toxicity and are determined by relative dosage and time of exposure.
- LD_{50} values are useful for comparison of toxicity among chemicals but do not define the nature of toxicosis or the safe dosage for a majority of animals.
- The lowest known clinical toxic dosage is of greatest value for clinical toxicology.
- Many factors can alter an animal's response to toxicants, including those inherent in the toxicant, the animal, the environment, and the combinations of these major factors.
- Clinical toxicology evaluation depends heavily on determination of exposure and evidence for the contribution of interacting factors that can alter toxicity.
- Common quantitative expressions of dosage and concentration are essential for thorough toxicological evaluation and prognosis.

Toxicology is the study of poisons and their effects on living organisms. In veterinary medicine, this has come to mean an understanding of sources of poisons, circumstances of exposure, diagnosis of the type of poisoning, treatment, and application of management or educational strategies to prevent poisoning.[1-3] More so than many of the specialties in veterinary medicine, toxicology is based on the important principle of dose and response. That is, there is a graded and possibly predictable response based on increasing exposure to the toxicant. In the words of Philipus Aurcolus Theophrastus Bombastus von Hohenheim-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] Although alchemy has long since been abandoned, Paracelsus' principle of what makes a poison is still true and relevant in the daily practice of nutrition, therapeutics, and toxicology. Today, with emphasis on synthetic drugs, natural or alternative therapies, and the rapidly growing field of nutraceuticals, there is increasing need to be aware of the dosage and response principle for both beneficial and detrimental effects in the daily practice of veterinary medicine. Many of the toxicants discussed in this book will provide examples of the point at which the 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.[2-4] Clinicians must consider all of these possibilities when working to diagnose a potential toxicosis or apply therapeutic agents to their patients.

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, including the dynamics of absorption, distribution, storage, metabolism, and elimination; mechanisms of action; principles of treatment; and dose-response relationships. Although some of these important principles will be mentioned, a full discussion of such factors is beyond the scope of this chapter.

Toxicology literature is best understood if some basic terminology is remembered. A *poison* or *toxicant* is usually considered 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 biological sources and are generally classified as *biotoxins*. Biotoxins are further classified according to origin as *zootoxins* (animal origin), *bacterial toxins* (which include *endotoxins* and *exotoxins*), *phytotoxins* (plant origin), and *mycotoxins* (fungal origin).[2-4]

Poisons may be categorized as organic, inorganic, metallic, or biological. A further distinction is made by some between synthetic and natural agents. Synthetic agents may have been designed specifically as toxicants that may have a very broad or very narrow range of toxicity and/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.[3,4] The word toxic is used to describe the effects of a toxicant (e.g., the "toxic" effects of organophosphate insecticides may be described as cholinesterase inhibition: vomiting, salivation, dyspnea, and diarrhea). However, toxicity is used to describe the quantitative amount or dosage of a poison that will produce a defined effect. For example, the acute lethal dosage to cats of ethylene glycol would be described as 2 to 5 mL/kg body weight. The toxic effects of ethylene glycol are acidosis and oxalate nephrosis. Finally the state of being poisoned by a toxicant, such as ethylene glycol, is toxicosis.

Mammalian and other vertebrate toxicities are usually expressed as the amount of toxicant per unit of body weight required to produce toxicosis. *Dosage* is the correct terminology for toxicity expressed as amount of toxicant per unit of body weight.[2-4] The commonly accepted dosage units for veterinary medicine are milligrams per kilogram (mg/kg) body weight. However, toxicity can also be expressed as moles 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.[2-4] 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. For clinical toxicology, the examples in Table 1-1 generally 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 can be poisoned by relatively lower body weight dosages than can smaller mammals.[4] However, other factors, such as species differences in metabolism or excretion or specific differences in receptor sites can alter this generalization. *Dose* is a term for the total

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

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 some species, generally make the "dose" approach of little practical value.

A commonly used means to compare the toxicity of compounds with one another is the *median lethal dosage*, also known as the acute oral LD_{50} in a standard animal, such as the laboratory rat. The LD_{50} value is usually based on the effects of a single oral exposure with observation for several 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 regularly increasing dosages. In some cases a multiple-dosage LD_{50} is used to show the acute effects (typically up to 7 days) produced by multiple dosages in the same animals. Increasing dosage levels are usually spaced at logarithmic or geometric intervals. 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).

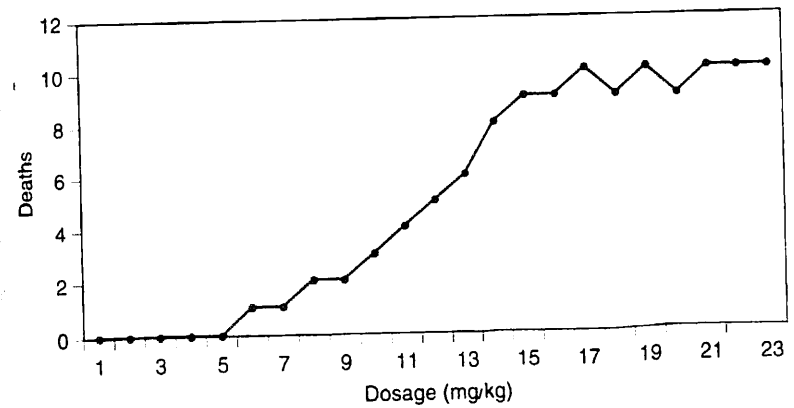

Figure 1-1. Dose-response curve for a typical LD_{50} study.

The end point of an LD_{50} study is death, and the published LD_{50} value says nothing about the severity of clinical signs observed in the surviving animals or the nature of the clinical effects.[2,4] Twenty or more animals may be used to arrive at a good estimate of the LD_{50}, which limits the use of LD_{50} values in most animals of economic significance. In some species, such as birds and fish, the oral toxicity is often expressed on the basis of the concentration of the substance in the feed or water. The acute oral toxicity for birds is often expressed as the LC_{50}, meaning the milligrams of compound per kilogram of feed. For fish, the LC_{50} refers to the concentration of toxicant in the water.

Other terms are used in the literature to define toxicity of compounds. The highest nontoxic dose (HNTD) is the largest dose that does not result in hematological, chemical, clinical, or pathological drug-induced alterations. The toxic dose low (TDL) is the lowest dose to produce drug-induced alterations; twice this dose will not be lethal. The toxic dose high (TDH) is the dose that will produce drug-induced alterations; administering twice this dose will cause death. The lethal dose (LD) 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.

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 several days or weeks, the terms subacute or chronic toxicity may be used. Subacute may refer to any effects seen between 1 week and 1 month, whereas chronic often refers to effects produced by prolonged exposure of 3 months or longer. These definitions obviously leave a large gap between 30 days and 90 days. The term subchronic is sometimes used to define this time period, although others avoid the problem in semantics by stating the time period involved. For example, a study could refer to a 14-day toxicity trial with the toxic dosage being 5 mg/kg.

Duration of exposure can greatly affect the toxicity. The single-dose LD_{50} of warfarin in dogs is approximately 50 mg/kg, whereas 5 mg/kg for 5 to 15 days may be lethal. In rats the single-dose LD_{50} of warfarin is 1.6 mg/kg, whereas the 90-day LD_{50} is only 0.077 mg/kg. On the other hand, rapidly inactivated or excreted compounds may have almost the same 90-day LD_{50} as the single dose LD_{50}. For example, 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. Conversely, animals may develop tolerance for a compound such that repeated exposure serves to increase the size of the dose 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. The ratio of the acute to chronic LD_{50} dosage is called the *chronicity factor*.[3] Compounds that have strong cumulative effects have larger chronicity factors. In the foregoing examples the chronicity factors are as follows: warfarin, 20; caffeine, 1.3; and potassium cyanide, 0.04.

From a public health and diagnostic toxicology perspective, it is essential to know the exposure level that will not cause any adverse health effect. This level is usually referred to as the *no observed adverse effect level* (NOAEL).[3] It can also be thought of as the maximum nontoxic level. This is the amount that can be ingested without any deaths, illness, or pathophysiological alterations occurring in animals fed the toxicant for the stated period of time. Usually a NOAEL in laboratory animals is based on chronic exposures ranging from 90 days to 2 or more years, depending on the species. The no-effect level is the largest dosage that does not result in detrimental effects.

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 would be 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. 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.[4]

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 biological variation can be due to many factors and is the reason that 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

curve is important and is not revealed from the LD_{50} value alone. An LD
with a very steep dose-response slope indicates a toxicant or drug h
a very narrow margin between no effects and maximal lethal effects.
Although such compounds may be dangerous to use as therapeutics, th
could be very effective pesticides because of lower probability of survi
of target animals.

FACTORS THAT INFLUENCE TOXICITY

Many factors inherent in the toxicant, the animal, or the environment ca
alter a toxicity value determined under defined experimental condition
The toxicity of a compound will vary with the route of exposure. Usu
routes of exposure are oral, dermal, inhalation, intravenous, intraper
toneal, and subcutaneous. In addition, the most potent routes of exposur
are usually the intravenous, intrapulmonary, and intraperitoneal routes. I
clinical veterinary toxicology, oral and dermal routes of exposure are th
most common, and these routes generally delay the absorption and diffus
exposure over a longer period of time. A daily dosage of toxicant mixe
in food and consumed over a 24-hour period may cause much less effe
than that same dosage given as a bolus at one specific time. However, reten
tion in the gastrointestinal tract, including enterohepatic cycling, an
dermal or hair retention of poisons can significantly prolong the exposur
or exposures.[2-4] Another factor that can accentuate the toxic effects of a
compound is concurrent organ damage as a result of other causes. This i
most important for diseases that alter liver or kidney function, leaving th
animal with insufficient resources to metabolize and excrete toxicants.

Species and breed differences exert important influences on toxicity
The familiar example of cats and their intolerance to phenolic com
pounds results directly from their lack of glucuronyl transferase, which i
necessary to produce glucuronides for the excretion of phenolic metabo
lites. A common example is acetaminophen, which is quite toxic to cat
partly as a result of ineffective excretion of the toxic metabolite. In addi
tion, 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. As a result, the cat is more likely to be
poisoned by agents that induce methemoglobinemia.[4] 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 more susceptible.

Many environmental and physiological factors can influence the toxic
ity of compounds, and one should remember that such factors, or others

ly unknown, can substantially influence an individual's response to
nts. Entire publications are devoted to drug and chemical interac-
and the reader is encouraged to be aware of toxicological interactions
re illustrated throughout this text. Some examples of factors that
response to toxicants are presented in Table 1-2.

Table 1–2
ctors that May Alter Response to Toxicants

teration or Change	Mechanism or Example
rities or contaminants	Some older phenoxy herbicides were contaminated with a highly toxic dioxin byproduct of manufacturing, leading to chronic toxicosis from the dioxin.
nges in chemical mposition or salts 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).
tability or decomposition chemical	Some organophosphate insecticides under adverse storage conditions can decompose to form more toxic degradation products.
nization	Generally, compounds that are highly ionized are poorly absorbed and thus less toxic.
hicle effects	Nonpolar and lipid-soluble vehicles usually increase toxicity of toxicants by promoting absorption and membrane penetration.
otein binding	Binding to serum albumin is common for many drugs and toxicants, limiting the bioavailability of the agent and reducing toxicity.
emical 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.
Biotransformation	Prior exposure to the same or similar chemical may induce increased metabolic activity of microsomal mixed function oxidases (MFOs). Foreign compounds activated by MFOs can then be conjugated by phase II metabolism and excreted. If toxicants are activated by MFO activity, toxicity may be

Continued

Table 1-2
Factors that May Alter Response to Toxicants—cont'd

Alteration or Change	Mechanism or Example
	increased. Liver disease, very young or very old animals, and specific breeds or strains of animal can alter ability of MFO to begin metabolism followed by phase II detoxification of foreign compounds.
Liver disease	Reduced synthesis of glutathione, metallothioneine, 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.

BIOLOGICAL VARIATION AND TOXICITY DATA IN VETERINARY PRACTICE

Biological 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 biological 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 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 toxicological evaluation in a suspected exposure.

CALCULATIONS FOR TOXICOLOGY

As indicated earlier, the basis for toxicological effects is the dose versus response relationship. In a practical clinical situation, the dosage is often

defined. Rather, an animal is ill with clinical signs that suggest toxicosis and there is potential exposure to a known or suspected amount of toxicon 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, µg/g, or percentage, and the concentration in the food must be related to a known toxicity based on milligram 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 on 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 a feed 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.

EXPRESSING 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, µg/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, parts per million (ppm), parts per billion (ppb), and parts per trillion (ppt). For correct toxicological 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 milligram per kilogram body weight of animal, but may receive a label or statement

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
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
1%	10,000 ppm
(Convert % to ppm by moving decimal point 4 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 lbs
1 liter	0.908 quarts
1 gallon	3.785 liters
1 teaspoon	5 milliliters
1 tablespoon	15 milliliters
1 cup	8 ounces or 227 milliliters
1 quart	32 ounces or 946 milliliters

of analysis that expresses the feed, water, or bait concentration as proportional or weight/weight relationships. The accurate assessment of toxicological risk depends on the ability to convert different toxicological 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

If the toxicity of cholecalciferol rodenticide is 2 mg/kg of body weight and the bait concentration is 0.075%, is a 2-oz package of bait likely to be toxic to a 35-lb dog 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
- Weight of the animal at risk
- Concentration of toxicant in the food or bait

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

- 35-lb dog/(2.2 lb/kg) = 15.9 kg
- 0.075% is 750 mg cholecalciferol/kg or 0.75 mg cholecalciferol/g of bait
- Two ounces of bait × 28.35 g/ounce = 56.7 g bait

Thus total consumption of cholecalciferol is expressed as:

- 56.7 g bait × (0.75 mg cholecalciferol/g bait) = 42.5 mg cholecalciferol consumed
- 42.5 mg cholecalciferol/15.9-kg dog = 2.67 mg/kg

From the calculations, it is apparent that this exposure could cause a high 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

Continuing the bait example to another scenario, assume that vitamin D at 2000 IU/kg/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?

Solution:

In this case, the needed information is expanded from problem 1, because we do not know the amount of contaminated material consumed.

- From current knowledge, food intake for a 35-lb dog would be 2.5% of body weight
- Recall from problem 1 that a 35-lb dog is 15.9 kg:
  15.9 kg × 0.025 = 0.3975 kg (amount ingested in one day)
- 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

In this clinical example, the daily dosage of 55 IU/kg on a body weight basis is about 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 parts per million (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

In a dog having neurological signs and a suspected salt toxicosis, toxicology laboratory results are returned indicating a serum sodium value of 3600 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 will be 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.
- Since 1 ppm = 1 mg/L, and 1 mg/dL = 10 mg/L, then dividing ppm by 10 = mg/dL (3600 ppm divided by 10 = 360 mg/dL).
- mEq/L = mg/dL × valence × 10/atomic weight = 360 × 1 × 10/23 = 156.5 mEq/L

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

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 2000 parts per billion (ppb) on a continuing basis, will the toxic dosage be exceeded on a daily basis?

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 problem 2, a reasonable intake would be 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: 2000 ppb = 2000 µg/kg = 2 mg/kg or 2 ppm; at 2 mg/kg × 0.25 kg the food consumed contains 0.5 mg aflatoxin
- Calculate the dosage of aflatoxin in mg/kg of body weight: 0.5 mg/10 kg BW = 0.05 mg/kg

Alternatively a formula to convert ppm to mg/kg of body weight is:

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

$$\frac{2 \text{ mg/kg} \times 0.25 \text{ kg feed}}{10 \text{ kg}} = 0.05 \text{ mg/kg of body weight}$$

Conclusion: 2000 ppb (2 ppm) dietary aflatoxin is not an LD_{50} dosage of aflatoxin in the dog.

To quickly convert mg/kg of body weight dosage to dietary ppm, use the following formula:

$$\text{Dietary ppm} = \frac{\text{mg/kg body weight}}{\% \text{ of body weight eaten daily}}$$

$$\text{e.g., } \frac{0.5 \text{ mg/kg BW}}{0.025} = 2 \text{ ppm} = 2000 \text{ ppb}$$

Continued

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)

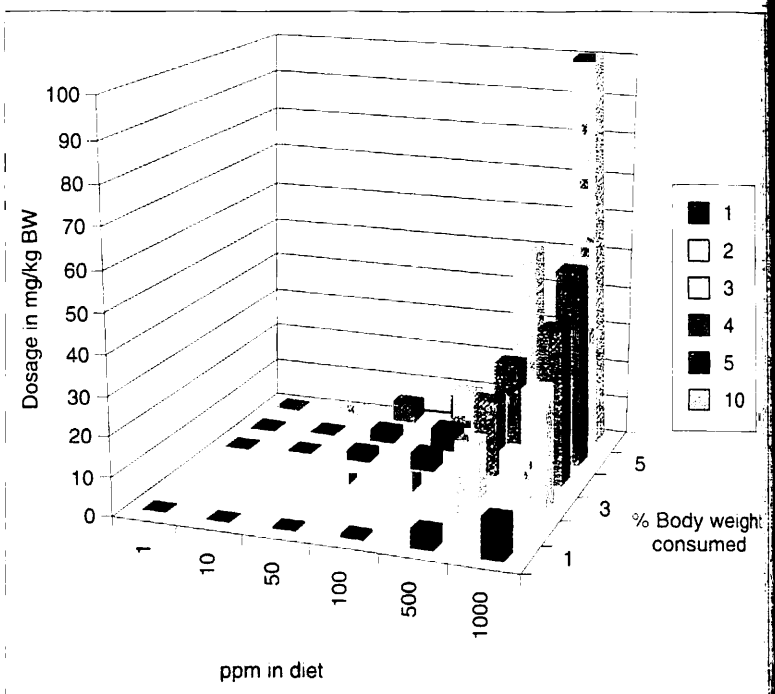

Figure 1-2. Relationships of food intake and body weight dosage.

REFERENCES

Beasley VR, Dorman DC, Fikes JD, Diana SG, Woshner V: *A Systems Affected Approach to Veterinary Toxicology*, Urbana, Ill, 1999, University of Illinois.

Eaton DL, Klassen CD: *Casarette and Doull's Toxicology: The Basic Science of Poisons*, ed 6, 2001, New York, McGraw-Hill.

Osweiler GD, Carson TL, Buck WB, Van Gelder GA: *Clinical and Diagnostic Veterinary Toxicology*, ed 3, Dubuque, Iowa, 1985, Kendall Hunt.

Osweiler GD: *Toxicology*, The National Veterinary Medical Series, Philadelphia, 1996, Williams & Wilkins.

Spoo W: Concepts and Terminology. In Plumlee KH, editor: *Clinical Veterinary Toxicology*, St Louis, 2004, Mosby.