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Series Preface

The Practical Veterinarian was developed to help veterinary students, veterinarians, and veterinary technicians quickly find answers to common questions. Unlike larger textbooks, which are filled with detailed information and meant to serve as reference books, all the books in The Practical Veterinarian series are designed to cut to the heart of the subject matter. Not meant to replace the reference texts, the guides in the series complement the larger books by serving as an introduction to each topic for those learning the subject for the first time or as a quick review for those who already have mastered the basics.

The titles are selected to provide information about the most common subjects encountered in veterinary school and veterinary practice. The authors are experienced and established clinicians who can present the subject matter in an easy-to-understand format. This helps both the first-time student of the subject and the seasoned practitioner to assess information often difficult to comprehend.

The editor and authors hope that the books in The Practical Veterinarian series will meet the needs of readers and serve as a constant source of practical and important information. We welcome comments and suggestions that will help improve future editions of the books in this series.

Shawn P. Messonnier, D.V.M.

Preface

This book was written to provide the busy practitioner and the veterinary student a source of information concerning the more common intoxications in the United States. Veterinary toxicology is a very broad-based discipline with literally thousands of possible toxicants. The list was reduced using a core knowledge guidance paper written by the diplomates of the American Board of Veterinary Toxicology.

Chapter 1 presents an initial discussion of the absorption, distribution, metabolism, and elimination of veterinary toxins and provides the reader with a framework for a rational therapeutic approach. It also provides the reader with information concerning calculations involved in veterinary toxicology. This begins the process of understanding the estimation of dose that is critical to differentiating between exposure and intoxication.

Chapter 2 provides the reader with some “reminders” of possible toxins based upon the patient’s clinical signs. Chapter 3 discusses the pathophysiology of selected intoxications and gives the reader some deeper insight into the processes by which these poisons produce their clinical effects. It also provides a rational approach to symptomatic or antidotal therapy.

Chapter 4 represents the bulk of this book, which is dedicated to individual monographs of specific toxins that are arranged alphabetically. This chapter should provide the reader with the requisite information to diagnose and treat a veterinary toxicosis. Chapter 5 concerns antidotal therapy and provides a quick access to the relatively limited number of antidotes that are available to the veterinarian. Chapter 6 discusses some of the basics of diagnostic toxicology as well as other sources of information that may be beneficial to the reader.

It is my hope that this text provides the reader with a greater understanding of veterinary toxicology and most importantly the information necessary to diagnose and treat our veterinary patients.

I would like to take this opportunity to thank some individuals who made this whole process possible. I first would like to thank my colleagues who are diplomates of the American Board of Veterinary Toxicology. I am greatly indebted to their original and clinical research (performed and published) that serve as the backbone of this text. I would also like to thank Leslie Kramer from Butterworth–Heinemann

who patiently guided me through the process of putting these pages together. I am thankful that my sons, Adam, Alex, and Andrew, will soon see the fruits of this labor. Most especially, I am forever indebted to my loving wife, Karen, who supports me always in all things.

J. D. R.

1

Overview of Veterinary Toxicology

Introduction

The art and science of toxicology are only slightly younger than humankind. Early in the development of hunting and warfare, there is evidence of the use of poisoned arrows to gain tactical advantage. The principles of toxicology predate poison arrows—they are as old as bacteria and rooted in plants. The vascular plants developed many successful chemical strategies to discourage or prevent predation by herbivorous insects and animals. Today tens of thousands of potential toxins can affect our veterinary patients, and there are fewer than two dozen specific antidotes. Imagine treating the entire spectrum of infectious diseases with only 24 antibiotics.

In human medicine, the diagnosis and management of intoxication are simplified by the following:

- Toxidromes: clinical syndromes strongly associated with certain toxins
- Greater access to diagnostic tools
- Fewer financial restraints

In veterinary medicine, the diagnosis and management of intoxication pose the following challenges:

2 Overview of Veterinary Toxicology

- Numerous species with differing presentations
- Malicious poisoning
- Treatment of herds of animals
- Maintaining the safety of the food supply

It is paramount for veterinarians to understand the more commonly encountered toxins and to treat patients accordingly. The rewards are to return patients to their normal states and to prevent future cases of poisoning. Always remember—*Treat the patient, not the poison.*

Toxicology

- Toxicology is the study of poisons and their effects on normal physiologic mechanisms.
- Information and concepts come from the following disciplines:
 - pharmacology
 - mathematics
 - chemistry
 - ecology
 - zoology
 - botany

Definitions

- LD50: lethal dose 50
 - the dose of a toxin that causes the death of half of a group of animals
 - generally only useful for an idea of the relative danger posed by an agent
 - many LD50 data are obtained from observations of rats
- LC50: lethal concentration 50
 - the concentration of a toxin that causes the death of half of a group of animals
 - generally used for toxins in air or water

- Toxicity
 - the quality of being poisonous
 - the dose (e.g., mg/kg) of a poison that elicits a response
 - often inappropriately used to equate *toxicosis*
- Toxicosis
 - a clinical syndrome associated with exposure to a poison (e.g., acetaminophen toxicosis)
 - the physiologic response to a toxin
 - not the same as *toxicity*

Scope of Veterinary Toxicology

The toxins that affect the more common domestic species are extremely diverse. The types of toxins often encountered include:

- Metals
- Mycotoxins
- Feed-related intoxicants
- Pharmaceutical agents
- Pesticides
 - insecticides
 - herbicides
- Biotoxins
 - plants
 - poisonous animals* (insects)
 - venomous animals* (snakes, insects)
 - bacterial toxins

*A poisonous animal contains a toxin within its body and must be ingested to elicit toxicosis. A common veterinary example includes blister beetles (cantharidin toxicosis), which is discussed in Chapter 4. A venomous animal produces a toxin *and* has a delivery mechanism (e.g., fangs or stinger) to inject the toxin into the prey. Common examples would include bees, wasps, and rattlesnakes.

The Metabolic Fate of Toxins

The Dose Makes the Poison

- This fundamental precept of toxicology has been attributed to Paracelsus.
- A dose-response relationship must exist (Figure 1–1).
- The greater the dose, the more likely that toxicosis will occur.
- Some toxins exhibit a steep dose-response relationship and are considered highly toxic.

Exposure Is Not Equal to Intoxication

- To cause intoxication, a substance must be absorbed and delivered to the site of action at a concentration high enough to elicit a physiologic response. For example, the presence of poisonous plants in a pasture is not enough; there must be evidence of consumption of these plants.

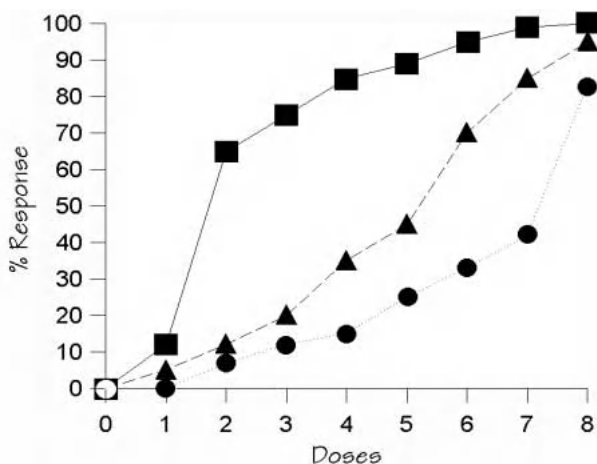


Figure 1–1 Example of dose-response relationship for three hypothetical toxins. The *squares* represent a toxin with a steep dose-response curve. If the response in this chart were mortality, the squares would present the greatest risk and the *circles* the least risk.

- Different animals in a herd may consume different plants or forage.
- There are individual and species variations in susceptibility to toxins.
- The clinical signs observed must correlate with the suspect plant.

Toxicokinetics

- Study of the metabolic processes that occur after exposure to a toxin (absorption, distribution, biotransformation, and elimination)
- Mathematical description of the movement of a toxin into the body (absorption), to the target organ (distribution), and out of the body (elimination)
- Concentration of a toxin at the site of action depends on
 - dose
 - physicochemical properties of the toxin or drug
 - absorption
 - distribution
 - specific tissue affinity
 - rate of metabolism
 - rate of elimination
- The fate after exposure to toxins is influenced by
 - toxin or drug factors
 - host factors or physiologic factors

Animal Factors

- Age
 - Organ perfusion
 - Organ function (hepatic and renal)
 - Membrane permeability
 - pH of tissue or compartment
 - Species
 - Gastrointestinal anatomy and physiology
-

- Examination of the cumulative effects of metabolic processes allows classification by means of two different kinetic processes: zero-order and first-order elimination kinetics (Figures 1–2 and 1–3).

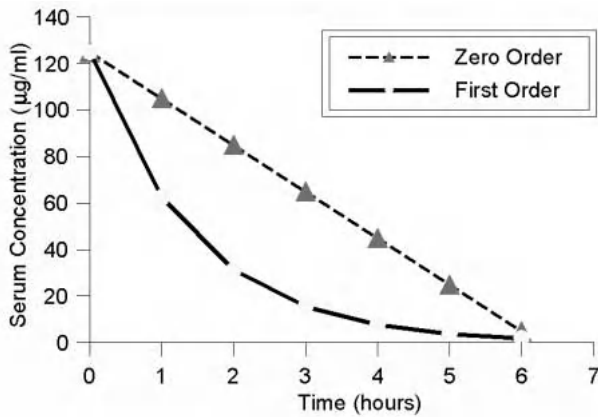


Figure 1–2 Comparison of zero-order and first-order elimination kinetics. Y-axis is linear serum concentration. Zero-order kinetics show a straight line in this graph, representing a direct relationship between time and decreased serum concentration of the hypothetical toxin.

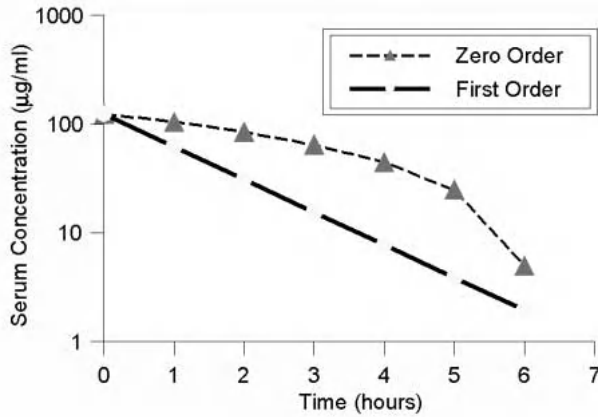


Figure 1–3 Comparison of zero-order and first-order elimination kinetics. Y-axis is a logarithmic increase in serum concentration. First-order kinetics show a straight line in this graph, representing a direct relationship between time and the decrease in serum concentration of the hypothetical toxin.

ZERO-ORDER KINETICS

- Occur with only a few drugs:
 - ethanol
 - methanol
 - ethylene glycol
 - aspirin
- Dose dependent and saturable
- Rate of elimination independent of serum concentration of toxin
- Linear on reticular graph
- Constant rate of elimination; the same quantity of toxin or drug is eliminated per unit time (e.g., 25 µg eliminated per hour)

FIRST-ORDER KINETICS

- Occur with most drugs
- Quantity eliminated proportional to concentration of toxin present within the body at any point in time
 - rate decreases as concentration of the toxin decreases
 - constant percentage eliminated per unit time (e.g., 7.25% of the toxin is eliminated every 4 hours)
- Half-life of the toxin independent of the dose
- Linear on semilog graph

Absorption***General***

- Most important veterinary toxicants are absorbed by oral or dermal routes.
- Rate of absorption is different for different routes of exposure
 - intravenous > pulmonary > intraperitoneal > intramuscular > oral > cutaneous
 - differences due to
 - physicochemical characteristics of the barriers
 - number of layers or complexity of the barriers

- Prevention of absorption is clinically important in the management of intoxication.
 - gastric decontamination processes
 - emesis
 - activated charcoal: cathartic therapy
 - gastric lavage
 - whole-bowel irrigation
 - dermal decontamination processes
 - washing the skin

Mechanisms of Absorption

PASSIVE DIFFUSION

- Penetration of the cell membrane by the toxin
- Cell membrane well designed to exclude most larger, polar substances
- Barrier composed of a lipid-rich bilayer
 - many proteins (external and transmembrane)
 - multiple pores of different size
- Most common mechanism of transport for drugs and toxins
- Not energy dependent
- Not saturable
- Rapid diffusion of lipid-soluble compounds
 - A relative indicator of passive diffusion is the lipid solubility often called the octanol-water partition coefficient.
- Rapid diffusion of nonionized, polar compounds
- Effect of charge or ionization
 - The importance of the charge of a toxin cannot be overstated.
 - Many toxins exist as ionized and nonionized species in physiologic fluids.
 - A charged species is less likely to cross a biologic membrane.
 - The relative ratio of ionized to nonionized depends on the pH of the fluid and pKa of toxin.
 - The Henderson-Hasselbalch equation describes the effect of change (see later).

ACTIVE TRANSPORT

- An energetic process (requires adenosine triphosphate) that moves solutes or toxins against their concentration or electrochemical transmembrane gradients
- Requires a protein carrier
- Saturable
- Selective

Henderson-Hasselbalch Equation

- The Henderson-Hasselbalch equation is a mathematical representation used to describe the relationship of body compartment pH and physicochemical properties of a drug to the ionization of the drug (Figure 1–4).

$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]}$ <p style="text-align: center;">or</p> $\% \text{ ionized} = \frac{100}{1 + \text{antilog}(\text{pKa} - \text{pH})}$	$\text{pH} = \text{pKa} + \log \frac{[\text{HA}]}{[\text{A}^-]}$ <p style="text-align: center;">or</p> $\% \text{ ionized} = \frac{100}{1 + \text{antilog}(\text{pH} - \text{pKa})}$
(A)	(B)

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog}(\text{pKa} - \text{pH})}$$

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog}(3.5 - 1.4)}$$

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog}(2.9)}$$

$$\% \text{ ionized} = \frac{100}{1 + 794}$$

$$\% \text{ ionized} = \frac{100}{795}$$

$$\% \text{ ionized} = 0.13 \text{ or } 99.87\% \text{ nonionized}$$

(C)

Figure 1–4 Formulas for predicting the percentage ionization of aspirin (pKa = 3.5) in the stomach of a dog (pH, 1.4). (A) Weak acid. (B) Weak base. (C) The compound probably would be absorbed from the stomach of a dog.

- The Henderson-Hasselbalch equation explains only part of the total absorption equation.
- The degree of ionization can be overcome by other physiochemical factors.
- The surface area of the small intestine is very large.
Most toxins are absorbed in the small intestine because of the large surface area and long transit time.
- The most noted exception in veterinary medicine is the rumen.
The rumen is a 45 to 50 gallon fermentation vat.
Residence time in the rumen is longer than that in the stomach.
Absorption of some compounds is greater from the rumen (e.g., nitrate and nitrite intoxication in ruminants).

GASTROINTESTINAL ABSORPTION

- The toxin must pass several barriers before it enters the systemic circulation (Figure 1–5).
- The lumen of the gastrointestinal tract is continuous with the external environment.

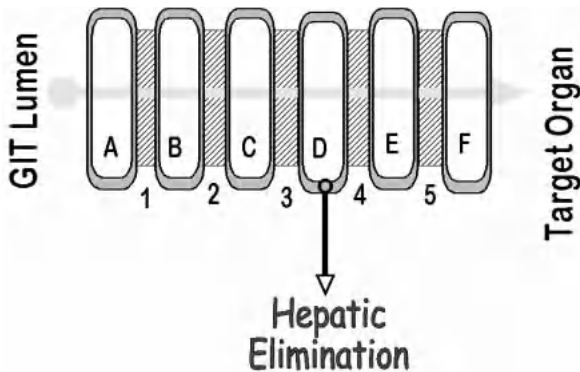


Figure 1–5 Barriers to intestinal absorption of a toxin. To reach the target organ, a toxin in the gastrointestinal (GIT) lumen must pass through cell membranes of an intestinal epithelial cell (A); interstitial fluid (1); membranes of capillary endothelial cells (B); plasma of the portal circulation (2); membranes of capillary endothelial cells (C); interstitial fluid (3); cell membranes of hepatocytes (D); interstitial fluid (4); membranes of capillary endothelial cells (E); plasma of the caudal vena cava and the systemic circulation (5); and membranes of capillary endothelial cells (F).

- Nonpolar (lipid-soluble) compounds are more readily absorbed than polar substances.
- General guidelines for polar toxin absorption are:
 - Weak acids are absorbed from the stomach.
 - Weak bases are absorbed from the small intestine.
- Any substance absorbed from the gastrointestinal tract first flows to the liver, also known as the first-pass effect.
 - detoxification
 - production of reactive metabolites
- Passive diffusion is the primary mechanism of absorption across epithelial cells of the gastrointestinal tract.
- Some toxins are absorbed by means of endogenous transport systems in the gastrointestinal tract (e.g., iron, thallium, cholecalciferol, and lead)
- Age differences in gastrointestinal absorption
 - Neonates have a poor gastrointestinal barrier.
- Species differences in gastrointestinal absorption
 - pH differences
 - ruminal pH—more alkaline environment
 - monogastrics pH—more acidic environment
 - salivary buffering due to large amount of saliva produced by ruminants
 - anatomic differences
 - Ruminants:** rumen serves as a reservoir, dilution of toxin within the rumen, protein binding, slower transit time
 - Monogastric species:** more rapid transit time

DERMAL ABSORPTION

- Dermal absorption is a common route of exposure to veterinary toxins.
- Skin is a good barrier because of
 - keratinization of the most superficial layer
 - avascular nature of epidermis
 - numerous layers of cells in epidermis

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- Dermal barrier is less effective following:
 - abrasion
 - hydration
 - exposure to organic solvents (carriers for some insecticides)
- Passive diffusion is the primary mechanism of toxin transport across skin.
- Stratum corneum is the rate-limiting layer for toxin absorption.
- Absorption through hair shaft and follicles is
 - more rapid than transdermal
 - less important quantitatively

RESPIRATORY ABSORPTION

- Passive diffusion is the primary mechanism of absorption in the respiratory tract.
- The respiratory system is the important route for noxious gases, such as
 - carbon monoxide
 - hydrogen sulfide
 - nitrogen dioxide
 - carbon dioxide
 - cyanide gas
- Absorption occurs only in the smaller airways and alveoli.
- At the level of the alveoli, there are
 - a tremendous surface area
 - close proximity to the vascular system
 - few barriers to absorption
- Factors influencing respiratory absorption
 - solubility
 - form (vapor or particulate)
 - particle size
- Particle size and respiratory deposition
 - >5 microns
impaction on the mucosa of the nasopharynx
 - 2–5 microns

deposited in the tracheobronchial tree

- <1 micron

flow to the alveoli

may be absorbed from the alveoli

Distribution

General

- Once a toxin has entered the body, it must reach the site of action.
- Distribution of toxins depends on the following factors:

Factors Affecting Distribution of Toxins

- Organ perfusion
 - Lipid solubility
 - Degree of protein binding
 - tissue proteins
 - plasma proteins
 - Tissue affinity of the toxin
 - Specialized barriers
-

Organ Perfusion

- The greater the perfusion (blood flow) the greater the possibility of toxin exposure to sensitive tissue.
- Highly perfused organs: kidneys, liver, brain, and heart
- Intermediate perfusion: skeletal muscle
- Low perfusion: adipose tissue, bone

Protein Binding

- The degree of protein binding is inversely proportional to the amount of free toxin.
- Toxin is generally inert when bound to plasma protein.
- A bound toxin cannot be filtered by the kidney.
- A protein-bound toxin can be displaced by another drug or toxin.

Tissue Affinity

- Some toxins have a predisposition to certain tissues.
- The toxin may accumulate in these tissues.
- Lead is similar to calcium and is concentrated in bone.
- Chlorinated hydrocarbon insecticides are more concentrated in adipose than in other tissue.

Specialized Barriers

Certain capillary beds have characteristics that prevent toxin distribution.

BLOOD-BRAIN BARRIER

- Acts as a substantial barrier to polar substances
- Prevents entry of toxins and drugs into the central nervous system
- Contains astrocytes, which surround the capillaries with tight junctions
- **example:** Ivermectin is generally a safe compound for mammals because it cannot cross the blood-brain barrier and affect neuronal γ -aminobutyric acid (GABA) receptors. The exception is collie-type dogs, which appear to have a less effective barrier and resulting increased susceptibility to ivermectin intoxication.

PLACENTAL BARRIER

- Comprises several layers of cells between the maternal and fetal circulation
- Species differences exist due to different placentation

Volume of Distribution

- Mathematical description of the volume of fluid in the body in which a toxin must be dissolved to equal the serum concentration.
- The apparent volume of distribution (Vd) may be more accurate, as follows:

Volume of Distribution (Vd)

$$Vd = \frac{\text{Amount of toxin in body}}{\text{Concentration in plasma}}$$

- V_d is often larger than body water volume
- V_d is not a physiologic parameter
- The term V_d also may be used for estimation of elimination mechanisms
 - If V_d is large (>5 L/kg),
plasma concentration is low
toxin is bound or concentrated in tissues
toxin is not amenable to dialysis
examples: digitalis, organochlorines, opiates
 - If V_d is small (< 1 L/kg),
plasma concentration is high
toxin is more accessible for dialysis
examples: ethanol, salicylate, theophylline

Elimination

Routes of Elimination

- urine
 - feces
 - bile
 - expired air
 - milk
 - saliva
-

General

- **Elimination:** the combination of toxin metabolism and excretion processes
- **Clearance:** volume of blood or plasma devoid of a toxin per unit time
- **Whole body clearance:** volume of blood or plasma devoid of a toxin by all elimination processes per unit time
- Clinically important routes of elimination are urinary and fecal

- Manipulation of pH or bulk flow can alter residence time of toxins.
- Supportive and antidotal therapies can alter these elimination processes.

Urinary Elimination

- Filtration
 - Unbound toxins with a molecular weight less than 60,000 are filtered.
- Tubular diffusion
 - Filtered toxins diffuse in the tubular portion of nephrons.
 - Lipid-soluble toxins diffuse from the tubular lumen toward the blood supply.
- pH manipulation in urine: the process of ion trapping
 - Weak acids are trapped in alkaline urine.
 - Weak bases are trapped in acidic urine.
- Tubular secretion
 - organic acids
 - organic bases
- Urinary clearance

Fecal Elimination

- Important route because of the common exposure of ingested toxins
- Fecal elimination due to lack of absorption
- Sum of
 - ingestion not absorption
 - biliary excretion (see later)
 - gastrointestinal secretion (salivary, pancreatic, and others)
- Increased elimination may be clinically possible owing to manipulation by
 - osmotic or saline cathartics
 - polyethylene glycol (whole-bowel irrigation)
 - activated charcoal

Biliary Elimination

- Diffusion is the primary mechanism.
- Route of elimination of larger molecular weight toxins
 - molecular weight greater than 325
 - **example:** ivermectin eliminated primarily through the biliary route
- Enterohepatic recycling
 - Some toxins are eliminated in bile.
 - Gastrointestinal bacteria cleave the conjugated sugar moiety.
 - The toxin is reabsorbed from the gastrointestinal lumen.
 - Toxin travels through the portal circulation to the liver.
 - The process may be repeated.

Milk Elimination

- May cause toxicosis in nursing animals.
- May be a public health concern.
 - **example:** tolerance levels of aflatoxin in milk destined for human consumption (<0.5 ppb)
 - Current dairy practices dilute milk from a single farm and thereby reduce the relative risk of human intoxication.
 - Most producers closely monitor the pastures of producing cows for potential toxins.
- Ion trapping possible because the pH of milk is lower than that of serum.
 - **example:** Tremetol from *Eupatorium rugosum* (white snakeroot) or *Isocoma wrightii* or *Haplopappus heterophyllus* (jimmy weed, ray-less goldenrod) can be passed from the dam to nursing offspring and to humans.
- The fat content of milk and colostrum may serve as an elimination route for lipid-soluble toxins.
 - **example:** Persistent toxins DDT (dichlorodiphenyltrichloroethane), PCB (polychlorinated biphenyl), and PBB (polybrominated biphenyl) are eliminated in the fat component of milk.

Respiratory Elimination

- Primary mechanism is diffusion.
- Gases are eliminated by this route.
- Rate of pulmonary elimination is inversely proportional to the solubility of the gas in blood.

Kinetics of Elimination

- Mathematical description of the processes involved in the removal of toxin from the body
- Limited utility in clinical toxicology for acute intoxication
- More important in chronic intoxication

Metabolism (Biotransformation) of Toxins

GENERAL

- The goal is to make a toxin (xenobiotic) more water soluble to enhance elimination.
- The liver is the primary organ involved in metabolism of toxins.
 - Most cells have metabolic capability.
 - The relative rates of detoxification systems vary
 - between individuals
 - within a species
 - between species
 - with physiologic status
- The results of biotransformation can be
 - a substance that is less toxic
example: ivermectin
 - a substance that is more toxic
example: parathion is metabolized to paraoxon
example: aflatoxin B₁ metabolized to aflatoxin B₁ epoxide
- Two major phases of biotransformation
 - phase I
break chemical bonds or remove active groups

produce a site on the compound for phase II processes

- phase II
conjugate
increase the water solubility and probability of elimination

PHASE I OF BIOTRANSFORMATION

- Cytochrome P450-mediated processes
 - P450 is a family of enzymes located in the endoplasmic reticulum.
 - Microsomes are the subcellular fraction that contains P450 after centrifugation.
 - The following chemical reactions are mediated by P450 enzymes:
 - oxidation
 - reduction
 - hydroxylation
 - dealkylation, especially for chemicals containing nitrogen, oxygen, or sulfur
 - epoxidation
 - desulfuration
 - sulfoxidation
- Non-P450-mediated processes

PHASE II OF BIOTRANSFORMATION

- Synthetic reactions
- Energy required
- Chemical processes
 - glucuronidation
 - most important conjugation process
 - rate limiting in cats
 - sulfation
 - glutathione conjugation
 - acetylation

- amino acid conjugation
- methylation

Ion Trapping

- After a compound is absorbed and equilibrated in plasma, the substance equilibrates at the site of action.
- Within the body many biologic membranes separate fluid compartments.
- These fluid compartments may have different pH values.
- The xenobiotic establishes an equilibrium at that membrane.
 - examples in veterinary medicine
 - mammary gland
 - pneumonic lungs
 - ascending and descending loop of the nephron
 - abscess

- mammary gland and milk

Epithelial tissue of the mammary gland presents a lipid barrier that separates the plasma (pH 7.4) from the milk (pH 6.5–6.8).

In cows with infectious mastitis, it is beneficial for the antimicrobial agent to reach the mammary tissue in sufficient quantity to effect bacteriostatic or bactericidal action.

The degree of ionization of the active ingredient in plasma and the pH differences between plasma and milk can greatly influence the relative concentration of active ingredient trapped in the milk.

Theoretical Equilibrium Concentration Ratio

- The theoretical equilibrium concentration ratio ($R_{x/y}$) explains the relative ratio of a drug or toxin between two compartments with different pH values (Figures 1–6 and 1–7).
- Compartments that can be examined with this relationship include
 - serum : milk
 - serum : saliva

<div style="border: 1px solid black; padding: 10px; margin-bottom: 10px;"> $R_{x/y} = \frac{1 + 10^{(pK_a - pH_x)}}{1 + 10^{(pK_a - pH_y)}}$ <p style="text-align: center;">or</p> $R_{x/y} = \frac{1 + \text{antilog}(pK_a - pH_x)}{1 + \text{antilog}(pK_a - pH_y)}$ </div> <p>(A) For an Acid</p>	<div style="border: 1px solid black; padding: 10px; margin-bottom: 10px;"> $R_{x/y} = \frac{1 + 10^{(pH_x - pK_a)}}{1 + 10^{(pH_y - pK_a)}}$ <p style="text-align: center;">or</p> $R_{x/y} = \frac{1 + \text{antilog}(pH_x - pK_a)}{1 + \text{antilog}(pH_y - pK_a)}$ </div> <p>(B) For a Base</p>
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Figure 1-6 (A) Theoretical equilibrium concentration ratio for an acid. (B) Theoretical equilibrium concentration ratio for a base.

$$R_{x/y} = \frac{1 + \text{antilog}(pH_x - pK_a)}{1 + \text{antilog}(pH_y - pK_a)}$$

$$R \text{ milk/plasma} = \frac{1 + \text{antilog}(6.8 - 2.7)}{1 + \text{antilog}(7.4 - 2.7)}$$

$$R \text{ milk/plasma} = \frac{1 + \text{antilog}(4.1)}{1 + \text{antilog}(4.7)}$$

$$R \text{ milk/plasma} = \frac{1 + 12589}{1 + 50118}$$

$$R \text{ milk/plasma} = \frac{12590}{50119}$$

$$R \text{ milk/plasma} \cong 0.25$$

Figure 1-7 Example of equilibrium across the mammary gland. Predict the concentration ratio (milk : plasma) for benzyl penicillin G (pKa 2.7) given that plasma pH is 7.4 and milk pH is 6.8.

Estimating Toxin Exposure

Pearson Square Ration Formulation Method

- A method to determine the relative concentration of a feedstuff in a final ration (Figures 1-8 and 1-9)
- Some guidelines:
 - Target concentration (e.g., toxin, crude protein, vitamin) must be intermediate to the concentration of each feedstuff.

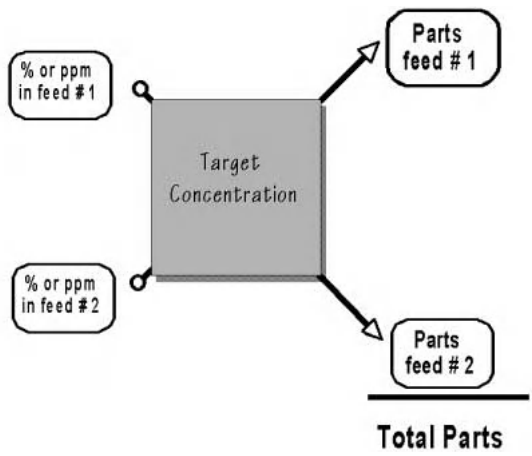
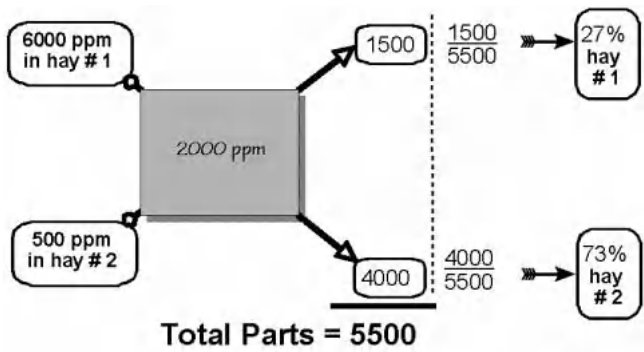


Figure 1–8 The Pearson square is a method for determining the composition of feedstuffs with different concentrations of a nutrient or toxin. The composition of each feedstuff is placed on the corners of the *left* side of the square. The target concentration is placed in the *center* of the square, and the *arrows* represent subtraction. The absolute value of the diagonal subtraction results in the parts of each feedstuff needed to achieve the target concentration.



Hay #1: $(0.27)(2000 \text{ lbs}) = 540 \text{ lbs of hay \#1}$
Hay #2: $(0.73)(2000 \text{ lbs}) = 1460 \text{ lbs of hay \#2}$

Figure 1–9 Example of a Pearson square. A producer has some hay with a tested nitrate concentration of 6000 ppm. He wants to feed this hay to his cattle. He plans to mix this hay with another source of hay (tested 500 ppm nitrate) to produce feed with a target concentration of 2000 ppm. What quantity of each source would be needed to make 1 ton of feed with the target concentration?

- Composition (dry matter or as fed) of feedstuffs must be the same.
- The differences between numbers must be used (negative numbers are ignored).
- Can be used to calculate the dilution of certain feedstuffs (e.g., high nitrate hay)

Estimating Toxin Intake from a Forage Exposure

- Used when chemicals or pesticides are applied to a forage source that animals may consume
- A common question or complaint posed to food-animal veterinarians
- Some assumptions
 - Forage intake during grazing is 3% of body weight per day.
 - All applied chemical adheres to the plant.

Memorize:

Forage Exposure to Toxin

1 pound/acre



7 mg/kg of body weight

Calculations Concerning Concentration

PARTS PER MILLION AND PARTS PER BILLION RELATIONSHIPS

- It is common to express the concentration of a toxin or drug in feed, water, or tissue residues in parts per million (ppm) or parts per billion (ppb).
- This often is the concentration expressed in analytical reports.
- The veterinarian must be able to translate this information into clinically useful data.
- One ppm is 1 part analyte (drug or toxin) per 1 million parts substance (feed, water, soil).
- An advantage of the metric system is that these relationships are readily apparent.
 - $1 \text{ ppm} = 1 \text{ mg/kg} = 1 \text{ }\mu\text{g/g}$

Memorize:

$$1 \text{ mg/kg} = 1 \text{ ppm}$$

- There is a direct correlation between ppm and percentage concentration.
- This relationship can be easily derived from the fact that 1 ppm equals 1 mg/kg.

$$1 \text{ ppm} = 1 \text{ mg/kg}$$

$$1 \text{ ppm} = 1 \text{ mg}/(1 \times 10^6 \text{ mg})$$

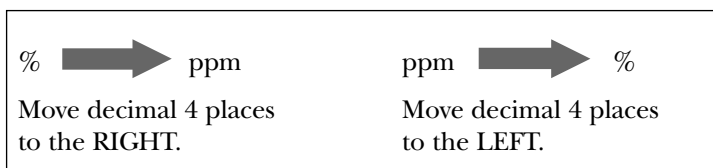
$$1 \text{ ppm} = 1/(1 \times 10^6)$$

$$1 \text{ ppm} = 0.000001$$

$$1 \text{ ppm} = 0.0001\%$$

- A veterinarian needs to know how to convert between the ppm and percentage as diagnostic reports may indicate that the substance in question is found in ppm or percentage concentrations.

Memorize:



Hint: ppm will always be *larger* than %

- The ppb concentration has a similar relationship to percentage as ppm.
- One ppb is 1 part analyte per 1 billion parts substance.
- $1 \text{ ppb} = 1 \text{ }\mu\text{g/kg}$

Example Calculations

- **Question:** A sample of cottonseed meal contains 0.25% gossypol. The recommended feeding concentration is ppm. What is the ppm concentration of gossypol for this sample?

- **Answer:** 2500 ppm gossypol
 - Use the guidelines to convert from percentage to ppm.
Move the decimal point four places to the right.
 $0.25\% = 2500 \text{ ppm}$
 - **Question:** A sample of cottonseed meal contains 0.25% gossypol. Determine the concentration of gossypol in milligrams per pound.
 - **Answer:** 5510 mg/lb
 - Convert percentage to ppm
2500 ppm
 - Convert ppm to mg/kg
 $1 \text{ ppm} = 1 \text{ mg/kg}$
2500 mg/kg of cottonseed meal
 - Convert kilograms to pounds
To convert kilograms to pounds multiply by 2.204
5510 mg gossypol/lb cottonseed meal
-

PERCENTAGE RELATIONSHIPS

- Percentage (weight/weight) or % (w/w)
 - Grams of substance per 100 grams of sample

$$\% \text{ (w/w)} = \frac{\text{grams of substance}}{\text{grams of sample}} \times 100$$

- Percentage (weight/volume) or % (w/v)
 - Grams of substance per 100 milliliters of liquid

$$\% \text{ (w/v)} = \frac{\text{grams of substance}}{100 \text{ ml of liquid}}$$

- **example:** *N*-Acetylcysteine, an antidote for acetaminophen intoxication, is available as a 10% or 20% solution. How many milligrams per milliliter are in each formulation?
 $10\% \text{ solution} = 10 \text{ g}/100 \text{ mL}$
 $10\% \text{ solution} = 0.1 \text{ g/mL}$
 $10\% \text{ solution} = 100 \text{ mg/mL}$
- 10% solution of *N*-acetylcysteine contains 100 mg/mL
- 20% solution contains 200 mg/mL
- Milligram percentage (mg%)
 - Milligrams of substance in 100 mL of solution.
 - A 12-mg% solution contains 12 mg/100 mL

2

Clinical Presentation and Diagnosis of Common Veterinary Toxicants: A Systems Approach

Grouping toxicants according to clinical presentation is a useful tool. This allows the clinician to keep toxins in mind when treating a patient. It is important to remember that patients do not read textbooks and may not present with classic signs. In a herd or flock of animals that are poisoned one animal may have mild clinical signs and another may have a more severe presentation. Some toxic agents, by the nature of their mechanism of action, alter the function of several different body systems and may produce multisystemic clinical signs. Several metals act in this manner, using a “shotgun” approach to altering normal physiologic processes rather than inhibiting a single enzyme or biochemical pathway. The pathophysiologic mechanisms of selected types of intoxication are included in this section. Pathophysiologic mechanisms also are described in the Mechanism of Action section for each toxin monograph later in the text.

Common Veterinary Neurotoxins ***Central Nervous System Toxicants***

TOXINS ASSOCIATED WITH SEIZURES

- Bromethalin
- Chocolate (methylxanthines)

- Lead
- Metaldehyde
- Organochlorine insecticides
- Pyrethrins and pyrethroids
- Strychnine
- Urea
- Water deprivation/sodium ion toxicosis
- Water hemlock (*Cicuta maculata*)

TOXINS ASSOCIATED WITH DEPRESSION

- Anticholinergic drugs
- Bluebonnets (*Lupinus* spp.)
- Ethylene glycol
- Ivermectin
- Jimsonweed (*Datura* spp.)
- Lead
- Locoweed (*Astragalus* and *Oxytropis* spp.)
- Marijuana (*Cannabis sativa*)
- Organophosphate insecticides
- White snake root (*Eupatorium rugosum*)
- Yellow star thistle (*Centaurea solstitialis*)

Peripheral Nervous System Toxicants

TOXINS ASSOCIATED WITH WEAKNESS

- Blue-green algae anatoxin-a
- Botulism
- Larkspur (*Delphinium* sp.)
- Tick paralysis

Common Veterinary Gastrointestinal Toxins

Toxins Associated with Salivation

- Blue-green algae anatoxin-a
- Carbamates

- Organophosphorus insecticides
- Plants with insoluble oxalate crystals
 - family Araceae
 - family Euphorbiaceae
- Pyrethroids
- Sflaframine
- *Bufo* toads
- Corrosives

Toxins Associated with Gastritis or Gastroenteritis

- Aspirin
- Arsenic
- Lead
- Ibuprofen
- Naproxen
- Oak (*Quercus* spp.) or acorn toxicosis

Pathophysiology of Emesis

- Caused by a number of chemicals and toxins (Figure 2–1)
- Used for gastric decontamination
 - See Chapter 5, “Methods of Gastrointestinal Decontamination for Veterinary Patients.”
- Clinical signs
 - retching
 - hypersalivation
 - anxiety
 - emesis
- Important control areas of emesis in the medulla of the brain stem
 - emetic center
 - near the floor of the fourth ventricle
 - in the medulla of the brain stem
 - chemoreceptor trigger zone (CRTZ)
 - in the area postrema

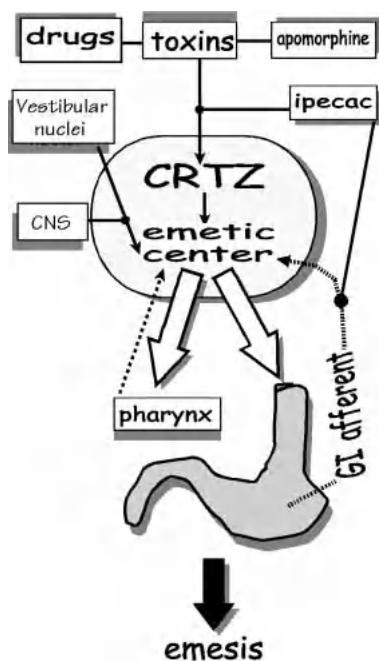


Figure 2-1 The pathophysiology of emesis. The inputs to the emetic center arise from drugs and toxins acting through the chemoreceptor trigger zone (CRTZ), higher central nervous system centers, and directly from the mucosa of the gastrointestinal tract and pharynx. The emetic center integrates the input and is responsible for sending the signal for the muscular contractions associated with emesis, as well as the coordinated efforts to close the glottis, thereby protecting the airway.

outside the blood-brain barrier

receives input from systemic circulation and cerebrospinal fluid

BASIC MECHANISM OF EMESIS

- Afferent input to the emetic center (vomitive center)
 - CRTZ
 - humoral input
 - peripheral input
 - pharyngeal mucosa

irritation of gastrointestinal mucosa

damage to gastrointestinal mucosa

vagal and splanchnic input

central (brain) input: direct cerebral activation and vestibular centers

- Efferent outflow from the emetic center (emesis)
 - efferent outflow to
 - diaphragm
 - salivary gland
 - esophagus
 - cranial nerves
 - common emetic pathway
 - deep inspiration
 - closure of glottis
 - opening of upper esophageal sphincter
 - entrance to nasopharynx covered by epiglottis
 - strong diaphragmatic contractions
 - contraction of abdominal muscles
 - opening of the lower esophageal sphincter
 - forceful ejection of gastrointestinal contents

CHEMORECEPTOR TRIGGER ZONE

- One of the sites of action of emetic drugs
 - apomorphine
 - ipecac
- Stimulation of CRTZ causes release of
 - dopamine
 - histamine
 - norepinephrine
 - serotonin
- These neurotransmitters stimulate the vomiting center—a rationale for use of antiemetic agents.

Common Veterinary Toxins Affecting the Circulatory System

Toxins Affecting the Heart

- Digitalis-like effects (cardiac glycosides)
 - *Digitalis* spp.
 - *Nerium oleander*
 - *Rhododendron* spp.
 - toad (*Bufo* spp.) intoxication
- Cardiomyopathy
 - gossypol
 - ionophores

Toxins or Drugs Associated with Tachycardia

- Amphetamine
- Blister beetles
- Caffeine
- Chocolate (theobromine)
- Cocaine
- Cyanide
- Ephedrine, pseudoephedrine
- Metaldehyde
- Monensin (in horses)
- Nitrate
- Organophosphorus insecticides
- Phencyclidine hydrochloride (PCP)
- Theophylline
- White snakeroot

Sympathomimetic agents also can cause agitation and excitement.

Toxins or Drugs Associated with Bradycardia

- α -Adrenergic antagonists (xylazine)
- *Bufo* toad ingestion

- Calcium channel antagonists
- Carbamates
- Digitalis
- Membrane depressant drugs
 - β -blockers
 - encainide
 - procainamide
 - quinidine
 - tricyclic antidepressants
- Organophosphorus insecticides
- Physostigmine

Toxins Associated with Hemolysis

- Copper
- Red maple (*Acer rubrum*)
- Zinc

Toxins or Drugs Capable of Producing Methemoglobin in Veterinary Medicine

- Acetaminophen
- Benzocaine
- Chlorates
- Lidocaine
- Methylene blue
- Nitrates
- Nitrites
- Onions (*N*-propyl disulfide)
- Red maple (*Acer rubrum*)
- Zinc

CLINICAL SIGNS

- Cyanosis
- Dyspnea
- Dark brown or chocolate-colored blood

PATHOPHYSIOLOGIC FEATURES OF METHEMOGLOBIN

- Methemoglobin is an oxidized form of hemoglobin (Figure 2–2).
- The iron in the heme portion of the hemoglobin molecule is oxidized from the ferrous (Fe^{++}) to the ferric (Fe^{+++}) state.
- Exposure to a toxin or drug causes oxidation of hemoglobin to form methemoglobin, which is called methemoglobinemia.

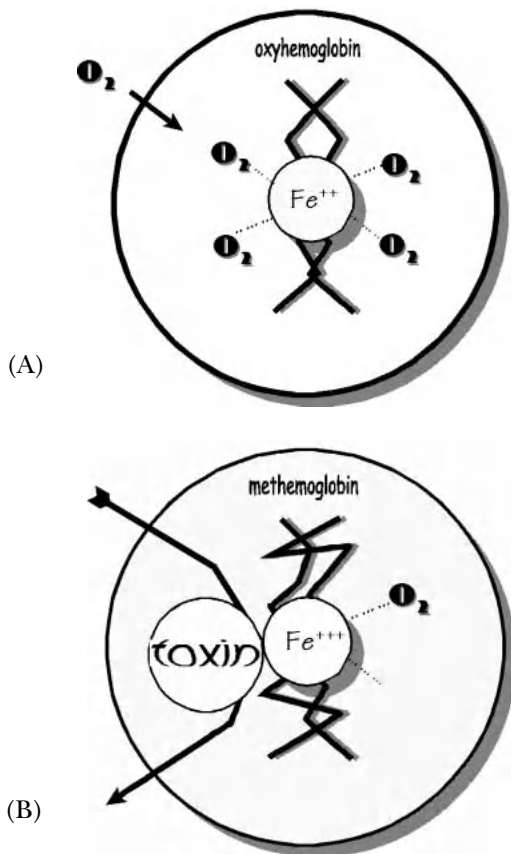


Figure 2–2 The pathophysiology of methemoglobin formation. (A) A normal red blood cell can carry a large amount of oxygen. Each hemoglobin molecule may bind as many as four oxygen molecules. Note iron is in the ferrous (Fe^{++}) state. (B) After exposure to an oxidizing toxin, the tertiary structure of hemoglobin is altered. Note iron is in the ferric (Fe^{+++}) state. This changes the conformation of the oxygen-binding sites. The results are reduced oxygen-binding capacity and formation of a different species of hemoglobin—methemoglobin.

Toxins Associated with Increased Bleeding

- Anticoagulant rodenticides
- Bracken fern (*Pteridium* spp.)
- Moldy sweetclover (*Melilotus* spp.)
- Snake venom, especially rattlesnake

PATHOPHYSIOLOGY OF HEMOSTASIS

- Liver-derived coagulation factors circulating in the serum
- Complex coordination of different pathways to achieve a clot (Figure 2–3)
- intrinsic pathway
- extrinsic pathway
- common pathway

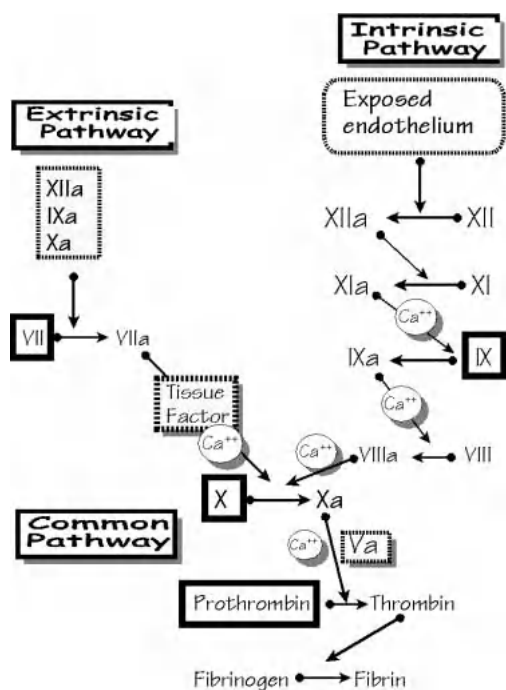


Figure 2–3 Formation of fibrin and blood clot. Schema shows intrinsic, extrinsic, and common pathways. The vitamin K–dependent factors are outlined by a thick line.

- Evaluation and diagnosis
 - prothrombin time (PT)
older name one-stage prothrombin time (OSPT)
used for measuring extrinsic and common pathways
factors VII, X, V, II and fibrinogen
 - activated partial thromboplastin time (aPTT)
used for measuring intrinsic and common pathways
factors XII, XI, IX, VIII, X, V, II and fibrinogen
 - proteins induced by vitamin K antagonists (PIVKA)
sensitive to deficiencies of factors II, VII, IX, and X
prolonged with ingestion of anticoagulant rodenticides
- Anticoagulants
 - vitamin K–dependent factors II, VII, IX, X
 - prolonged activated clotting time (ACT), PIVKA, PT, and PTT
 - normal platelet count

Common Veterinary Toxins Affecting the Musculoskeletal System

Toxins Associated with Myopathy

- Gossypol
- Ionophores: monensin, lasalocid, salinomycin
- Sennas (*Cassia* spp.) intoxication
- *Thermopsis montana* intoxication
- Vitamin E: selenium deficiency

Toxins Associated with Lameness

- Black walnut (*Juglans nigrum*)
- Ergot alkaloids (fescue)
- Fluoride
- Selenium
- Sorghum
- Vitamin D–containing plants

Common Veterinary Reproductive Toxins

Toxins Associated with Infertility

- Gossypol: infertility among males
- Zearalenone

Toxins Capable of Inducing Abortion

- Broomweed (*Gutierrezia* or *Xanthocephalum* spp.)
- Locoweed (*Astragalus* spp.)
- Pine needles from Western or Ponderosa pines (*Pinus ponderosa*), dried or fresh pine needles; consumption associated with vulvar edema
- Prostaglandins
- Sumpweed (*Iva angustifolia*)

Toxins Capable of Causing Teratogenesis

- Bluebonnets (*Lupinus* spp.)
- Poison hemlock (*Conium maculatum*)
- Skunk cabbage (*Veratrum californicum*); consumption by ewe on day 14 of gestation causes cyclopia in the lamb
- Sorghum
- Therapeutic agents
 - prednisone
 - vitamin A
- Tobacco (*Nicotiana tabacum*)

Common Veterinary Toxins Affecting the Skin

Photosensitization Syndromes in Veterinary Medicine

PRIMARY PHOTOSENSITIZATION

- Plants
 - **toxin:** furocoumarin
 - Umbelliferae family: celery, parsnip, parsley
 - bishop's flower (*Ammi majus*)
 - Dutchman's breeches (*Dicentra cucullaria*)

- **toxin:** hypericin
St. John's wort (*Hypericum perforatum*)
- **toxin:** fagopyrin
buckwheat (*Fagopyrum esculentum*)
- **toxin:** perloine
perennial rye grass (*Lolium perenne*)
- **toxin:** unknown
clover (*Trifolium* spp.)
oats (*Avena sativa*)
rape (*Brassica napus*)
alfalfa (*Medicago* spp.)
- Drugs and chemicals
 - phenothiazine
 - sulfonamides
 - tetracyclines

SECONDARY (HEPATOGENOUS) PHOTSENSITIZATION

- Plants
 - **toxin:** pyrrolizidine alkaloids
echium, salvation Jane (*Echium* spp.)
heliotrope (*Heliotropium* spp.)
hound's tongue (*Cynoglossum officinale*)
ragwort, groundsel (*Senecio* spp.)
rattlebox (*Crotalaria* spp.)
 - **toxin:** saponins
agave, lechuguilla (*Agave lecheguilla*)
 - **toxin:** triterpenes
lantana (*Lantana camara*)
 - **toxin:** unknown
kochia, fireweed, Mexican burning bush (*Kochia scoparia*)
sacahuiste (*Nolina texana*)
kleingrass (*Panicum coloratum*)
panic grass (*Panicum* spp.)

- Drugs and chemicals
 - carbon tetrachloride
 - copper
 - iron
- Mycotoxins
 - Sporodesmin (*Pithomyces chartarum*)
 - Tricothecenes (*Fusarium* spp.)
 - Aflatoxin (*Aspergillus* spp.)

Primary Photosensitivity

GENERAL

- Caused by
 - members of the Umbelliferae family (celery, parsnip, parsley)
 - St. John's wort (*Hypericum perforatum*)
 - buckwheat (*Fagopyrum esculentum*)
 - perennial rye grass (*Lolium perenne*)

PATHOPHYSIOLOGY

The foregoing plants contain pigments called *furocoumarins* that can cause photodermatitis directly without metabolic activation.

Secondary Photosensitivity

GENERAL

- Hepatogenous, bighead in sheep
- Produced by many plants and toxins that act on the liver
- Hepatic damage precedes dermal signs

PATHOPHYSIOLOGY

- Sequela of liver damage
 - decreased hepatic function
 - decreased bilirubin conjugation
- A primary function of the liver of herbivores is to degrade and remove the photodynamic pigments of plants, especially chlorophyll.

- Phylloerythrin is one such pigment that is formed by the ruminal microbial breakdown of chlorophyll.
- After an insult to the liver, phylloerythrin is absorbed and enters the systemic circulation, where it eventually travels to the dermal capillary beds.
- In dermal capillaries, phylloerythrin is exposed to ultraviolet light and is activated to a higher energy state.
- Phylloerythrin is not connected to an electron transport system to generate energy.
- The activated pigments transfer their electrons to the surrounding tissues (epidermal cells) and generate free radicals.
- The process is more pronounced in the lighter, nonpigmented areas of the animal (e.g., white patches of holstein cattle) and in areas that receive more sunlight (dorsum, ears, face).
- Free-radical damage produces gross lesions that progress through the following:
 - erythema
 - edema
 - pruritus
 - vesicle formation and ulceration
 - necrosis

Toxins Affecting the Hair

- Copper
- Molybdenum
- Selenium

Common Veterinary Toxins Affecting the Eyes

Toxins Associated with Mydriasis

Mydriasis is dilatation of the pupil.

- Antihistamines
- Atropine
- Ivermectin
- Lysergic acid diethylamide (LSD)

- Lead
- Marijuana
- Plants with atropine-like properties (*Datura*)
- Tricyclic antidepressants

Toxins Associated with Miosis

Miosis is contraction of the pupil.

- Carbamates
- Nicotine
- Opiates
- Organophosphorus insecticides
- Physostigmine

Common Veterinary Nephrotoxins

Toxins Affecting the Kidneys

PLANTS

- Cocklebur (*Xanthium* spp.)
- Oak or acorn (*Quercus* spp.)
- Oxalate-containing plants
 - beets (*Beta vulgaris*)
 - dock (*Rumex* spp.)
 - fireweed (*Kochia scoparia*)
 - halogeton (*Halogeton glomeratus*)
- Pigweed (*Amaranthus* spp.)

THERAPEUTIC AGENTS

- Acetaminophen
- Aminoglycosides
- Amphotericin B
- Nonsteroidal antiinflammatory drugs
 - aspirin
 - phenylbutazone

- ibuprofen
- indomethacin
- naproxen
- Polymyxin B
- Sulfonamides
- Thiacetarsemide

METALS

- Arsenic
- Copper
- Lead
- Zinc

ENDOGENOUS NEPHROTOXINS

- Hemoglobin (hemolysis)
- Myoglobin (rhabdomyolysis)

MISCELLANEOUS

- Cholecalciferol rodenticides
- Citrinin
- Ethylene glycol
- Ochratoxin

Toxins Affecting the Urinary Bladder

- Bracken fern (*Pteridium* spp.)
- Cantharidin (blister beetle)
- Cyclophosphamide
- Sorghum cystitis

General

- The kidneys are a major excretory organ and as such are exposed to toxins excreted in the urine.
- The renal system is susceptible to the effects of toxins because of
 - blood flow (20% to 25% of cardiac output)

- metabolic activity of cells of the renal system
 - energy demands
 - drug-metabolizing ability
- large surface area of the glomerular endothelial cells
- secretory function of the kidneys
- reabsorption by the kidneys
 - reabsorb 99% of water
 - concentration of some toxins

Mechanisms of Renal Intoxication

GLOMERULAR DYSFUNCTION (ALTERATION IN FILTRATION)

- Decreased renal blood flow due to renin-angiotensin system–stimulated vasoconstriction, as by nonsteroidal antiinflammatory drugs
- Blockage of tubular lumen
 - casts
 - increased pressure within the lumen, which decreases the net flux of filtration across the glomerular capillary bed
- **examples**
 - myoglobin
 - hemoglobin

TUBULAR DYSFUNCTION

- Direct cytotoxicity
 - toxin may damage the tubular epithelial cells
- **Examples**
 - amphotericin B
 - aminoglycosides

Tests of Renal Function

CLINICAL LABORATORY

- Blood urea nitrogen
 - indicator of damage to renal tissue
 - occurs only after substantial nephron loss (>70%)
- Serum creatinine also an indicator of renal damage

- Urinalysis
 - elevated sodium concentration
 - glycosuria
 - proteinuria
 - urine casts
 - enzyuria
 - alkaline phosphatase
 - lactate dehydrogenase

CLEARANCE

- Estimate of glomerular function (Figure 2–4)
- Inulin
 - filtered by glomerulus
 - not bound by proteins
- Creatinine
 - endogenous by-product of protein metabolism
 - not as accurate as inulin

Clinical Presentation

- Acute renal failure
 - nausea
 - vomiting
 - azotemia
 - dehydration
 - polyuria
 - bleeding in gastrointestinal tract
- Chronic renal failure

$$C_x = \frac{\text{urine concentration (mg / mL)} * \text{urine volume (mL / min)}}{\text{plasma concentration (mg / mL)}}$$

Figure 2–4 Clearance equation.

- hypertension
stimulation of renin-angiotensin-aldosterone system
retention of sodium and water
- hypocalcemia
- anemia
decreased erythropoietin

Common Veterinary Hepatotoxins

Hepatotoxic Agents

PLANTS

- Agave (*Agave lecheguilla*)
- Bitterweed (*Hymenoxys* spp.)
- Blue-green algae
- Cocklebur (*Xanthium strumarium*)
- Cycad palm (*Cycas* and *Zamia* spp.)
- Fireweed (*Kochia scoparia*)
- Lantana (*Lantana camara*)
- Lily of the valley (*Convallaria majalis*)
- Mushrooms (*Amanita* spp.)
- Pyrrolizidine alkaloid-containing plants
- Sneezeweed (*Helenium* spp.)
- White snakeroot (*Eupatorium rugosum*)

THERAPEUTIC AGENTS

- Acetaminophen
- Diazepam
- Iron
- Halothane
- Mebendazole
- Phenobarbital
- Phenytoin
- Thiacetarsemide

MYCOTOXINS

- Aflatoxins
- Fumonisin
- Sporidesmin

METALS

- Arsenic
- Copper
- Iron
- Phosphorus
- Zinc

HOUSEHOLD PRODUCTS

- Pennyroyal oil
- Phenol, phenolics
- Pine oil

General

- The liver is positioned to detoxify blood from the gastrointestinal tract.
 - Most of the hepatic blood supply is portal blood.
- The liver detoxifies most xenobiotics before they enter the systemic circulation.
 - first-pass effect
 - greatest concentration of cytochrome P450 is in the liverThe liver is exposed to reactive intermediate metabolites.
- Xenobiotics are metabolized to more water-soluble compounds.
- Some toxins are excreted in the bile.
- The liver has an immense reserve capacity and regenerative ability.
 - decreased liver function not noted until 75% of hepatic mass is diminished

Mechanisms of Hepatic Intoxication**HEPATIC FAILURE**

- Cytotoxic effect

- **Examples**

- *Amanita* mushrooms
- phenolics
- copper intoxication
- Damage associated with reactive metabolite

- **Examples**

- acetaminophen in dogs
- pyrrolizidine alkaloid-containing plants

CHOLESTASIS

- Damage to the bile canaliculi or epithelial cells of the bile ducts
- Decrease in production and secretion of bile
- Increase in bilirubin and bile acids
- **Examples**
 - aflatoxin
 - lantana

Tests of Hepatic Function

CLINICAL LABORATORY

- Liver function tests
 - alanine aminotransferase (ALT)
 - alkaline phosphatase (ALP or AP)
 - aspartate aminotransferase (AST)
 - γ -glutamyl-transferase (GGT)
 - sorbitol dehydrogenase (SDH)
- Serum bilirubin
- Bile acids
- Other tests of hepatic function
 - serum albumin
generally performed for chronic conditions
 - coagulation
coagulation factors are produced in the liver

CLINICAL PRESENTATION

- By time of onset of clinical signs
 - acute hepatic failure
 - chronic hepatic failure
- Clinical signs
 - anorexia
 - depression
 - coma
 - vomiting
 - icterus, jaundice

Common Veterinary Respiratory Toxins***Respiratory Irritants***

- Ammonia
- Hydrogen sulfide

Ventilatory Muscle Paralysis

- Botulism
- Neuromuscular junction blockers
- Organophosphorus insecticides
- Snake envenomation
- Strychnine
- Tetanus

Respiratory Center Depression

- Barbiturates
- Ethylene glycol
- Hypnotics
- Opiates and opioids
- Sedatives
- Tricyclic antidepressants

Pneumonia

- Crude oil
- 3-Methyl indole
- Paraquat

Cellular Hypoxia

- Carbon monoxide
- Cyanide
- Hydrogen sulfide
- Methemoglobinemia
- Sulfhemoglobin

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3

Pathophysiology of Selected Mechanisms

γ -Aminobutyric Acid–Mediated Chloride Channel

- γ -Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system of vertebrates (Figure 3–1).
- The GABA-mediated chloride channel is the site of action of many drugs and toxins.
- Insect GABA receptors are present in the periphery at the neuromuscular junction.
- Mammalian receptors are protected by the blood-brain barrier.
- Ivermectin acts as an agonist of GABA receptors.
- Diazepam and barbiturates potentiate the binding actions of GABA.
- Picrotoxin is the classic antagonist of the GABA receptor.
- Binding of GABA to the receptor increases chloride flux into neurons.
- Hyperpolarization of postsynaptic neurons decreases neuronal activity.

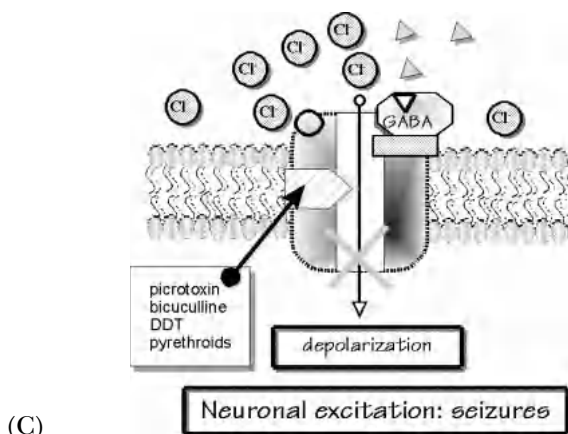
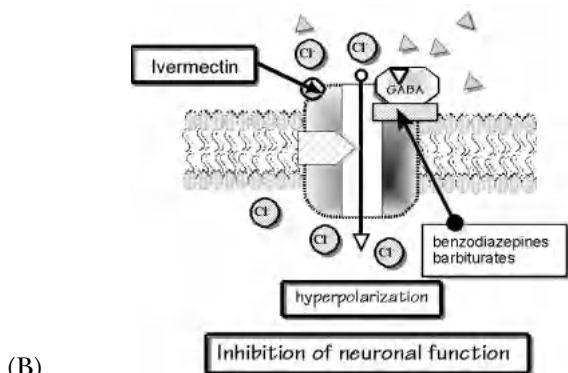
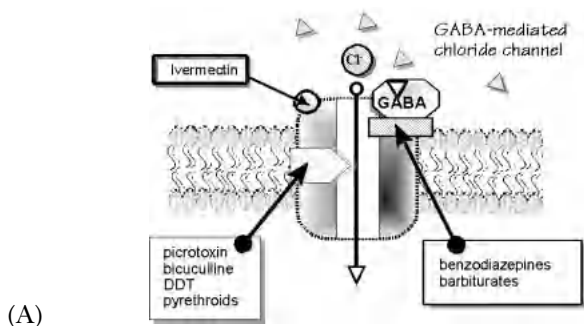


Figure 3–1 Pathophysiologic mechanism of the γ -aminobutyric acid (GABA)-mediated chloride channel. (A) Overview of the GABA-mediated chloride channel with binding sites for various drugs and toxins. (B) Drugs and toxins that act as agonists for the channel and increase chloride conductance and hyperpolarization. (C) Drugs and toxins that act as antagonists for the channel and cause depolarization, removal of inhibition, and seizures.

Toxin-Induced Hyperthermia

Clinical Presentation

- Increased body temperature in absence of infection
- Body temperature is markedly elevated.
- Panting
- Dehydration

Toxins Capable of Uncoupling Oxidative Phosphorylation

- Arsenicals
- Bromethalin
- Dinitrophenol (dinoseb) (Figure 3–2)
- Pentachlorophenol (Figure 3–3)
- Salicylates

Oxidative Phosphorylation

- Protons are translocated across the mitochondrial membrane from the matrix to the intermembrane space as a result of electron

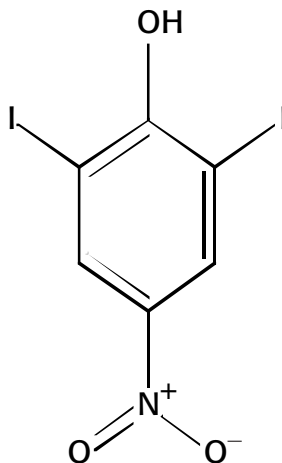


Figure 3–2 Chemical structure of dinitrophenol.

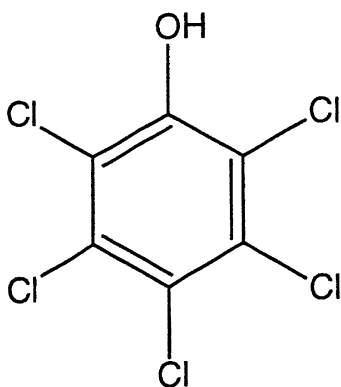
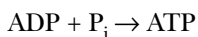


Figure 3–3 Chemical structure of pentachlorophenol.

transport due to formation of the reduced form of nicotinamide adenine dinucleotide (NADH) in oxidative reactions (Figure 3–4).

- The result is generation of a proton gradient.
- Adenosine triphosphate (ATP) synthase is a large protein complex. It has a proton channel that allows re-entry of protons.
- ATP synthesis is driven by the resulting current of protons flowing down their concentration gradient:



Management of Hyperthermia

- Increase heat loss.
 - Spray animal with cool water.
 - Place fans to blow over the animal.

Mechanisms of Cell Death

General

- Regardless of the etiologic factor, there is commonality in cellular death.
- In the early stages, many of these processes are reversible.
- Cellular targets of the processes of cell death

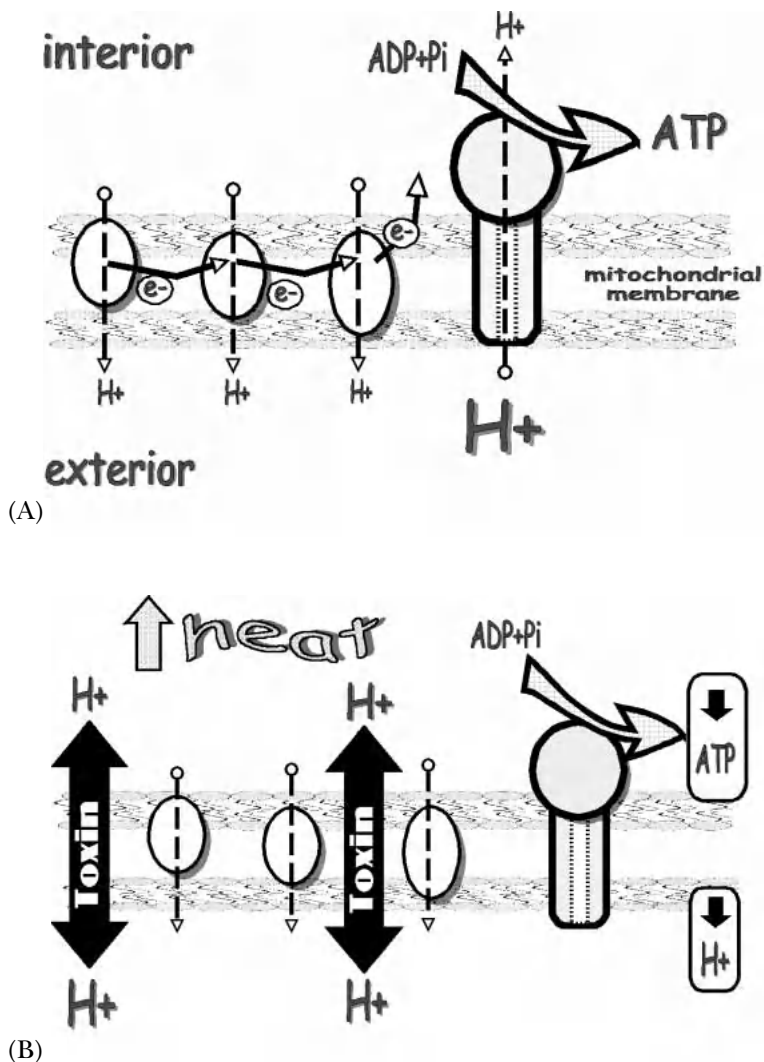


Figure 3-4 (A) The process of oxidative phosphorylation that occurs within the mitochondria. The production of adenosine triphosphate (ATP) is directly linked to and uses a proton gradient that has been generated in response to electron transport after oxidation of nicotinamide adenine dinucleotide (NADH). The proton gradient provides the power to link a high-energy phosphate (P_i) to adenosine diphosphate with the resulting ATP. (B) Mechanism of action of toxins capable of producing hyperthermia. The toxin inserts itself into the mitochondrial membrane. Most of these toxins then serve as a shuttle for protons. The protons are transported down the concentration gradient. Oxidation of NADH continues without linking the energy of oxidation to electron transport. The result is heat generation and decreased ATP production.

- ionic homeostasis (cell membrane)
- aerobic respiration (mitochondria)
- protein synthesis (nucleus and endoplasmic reticulum)
- deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (nucleus)
- Mechanisms or processes of cell death
 - ATP depletion by altering aerobic or oxidative metabolism
 - production of oxygen-derived free radicals
 - alteration of intracellular calcium concentration
 - irreversible damage to the mitochondria
- Many of the foregoing processes lead to final common pathways of cell death:
 - necrosis
 - apoptosis
- An understanding of the mechanism of toxin action leading to cell death is important.
 - The medical professional has greater rationale for choosing a course of therapy.
 - With the paucity of true antidotes in veterinary medicine, greater knowledge of pathophysiology is important.
 - The mechanisms of toxin action and cell death are not restricted to toxicology.

They are involved in infectious disease, endocrinopathy, cancer, and other disorders.

The processes described are an introduction to the pathophysiology of cell death. The most commonly accepted aspects of these processes are discussed. This is an ever evolving area of science, so it is important to keep current (Figures 3–5 and 3–6).

Calcium-Mediated Cell Death

- A common final pathway for many toxins (Figure 3–7)
- The tight regulation of intracellular calcium is responsible for many normal physiologic mechanisms:
 - release of neurotransmitters

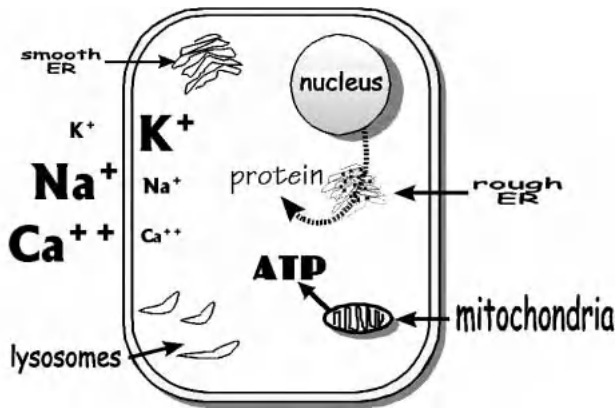


Figure 3–5 Fully functional cell. The cell membrane is an effective barrier that maintains ionic homeostasis. The concentrations of sodium and calcium are higher outside the cell membrane, and concentration of potassium is higher inside the cell. The nucleus is sending messenger RNA to the rough endoplasmic reticulum to produce proteins. The mitochondria are compact and produce ATP to fuel protein synthesis and the ATPases responsible for maintaining the ionic gradients.

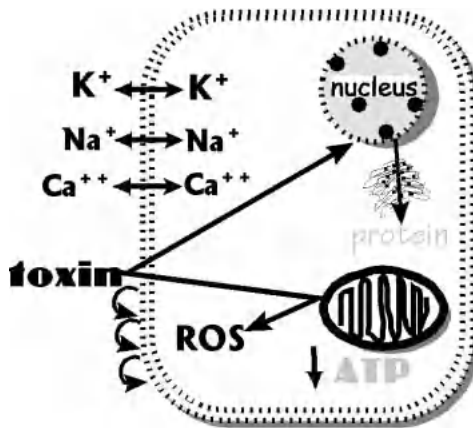


Figure 3–6 Dysfunctional and dying cell. This hypothetical cell has been exposed to a toxin. The toxin has altered the structure and function of the cell membrane preventing the production of ionic gradients (note intramembrane gaps). The toxin has directly and indirectly (by means of cations) induced changes in the structure of the nuclear envelope and has diminished protein synthesis. The toxin has acted directly and indirectly (cations) on the mitochondria to decrease production of ATP (note swelling of mitochondria). The toxin has induced production of reactive oxygen species (ROS). This has increased the permeability of the mitochondria and a chain reaction of peroxidation within the cell membrane.

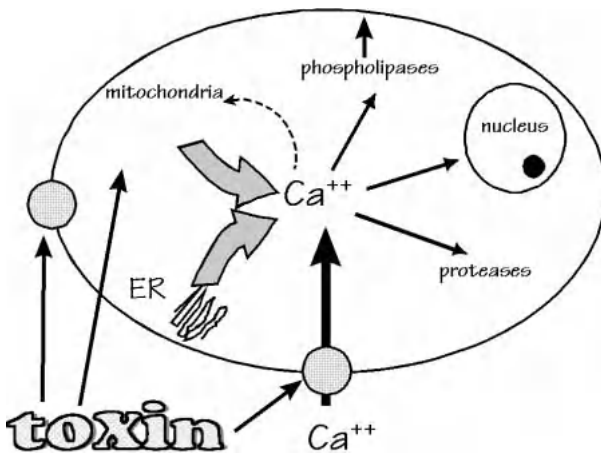


Figure 3-7 Mechanism of calcium-mediated cell death. A toxin interacts with a cell and disrupts calcium homeostasis. Calcium may enter through a calcium channel or calcium-sodium exchanger. The cell attempts to adapt by accumulating calcium in the mitochondria and endoplasmic reticulum. As more calcium enters the cytoplasm, it activates calcium-dependant enzymes in the cell. These enzymes then degrade the structural integrity of the cell.

- skeletal muscle contraction
- normal cardiac contraction
- Calcium also serves as a cellular trigger that leads to cell death, for example
 - excitatory neurotransmitter glutamate, which induces apoptosis and necrosis by stimulating massive calcium influx
 - calcium activation of proteases
 - caspases
 - calpains
 - calcium activation of oxygen free radical-generating enzyme systems
 - nitric oxide synthase
 - damage to DNA, cellular proteins, and membranes
 - other free radicals include the reactive oxygen species
 - superoxide
 - hydrogen peroxide
 - hydroxyl radical

Apoptosis and Necrosis

General

- There are two types of cell death—apoptosis and necrosis.
- They represent ends of the spectrum of cell death.
- This represents a final common pathway that may share signals
 - apoptosis or necrosis may be induced by
 - reactive oxygen species
 - alteration of DNA or chromatin
 - elevation of intracellular calcium

Apoptosis

- Programmed cell death
 - normal physiologic process
 - tightly regulated
 - mediated by many factors, including toxins
 - controlled by many genes or gene products
 - causes the following:
 - cell shrinkage
 - condensation of chromatin
 - formation of apoptotic bodies
 - densely packed fragments of the cell
 - phagocytosis of apoptotic bodies without inflammation

REGULATORY COMPONENTS

- *bcl-2* (B-cell lymphoma-leukemia-2-gene)
 - an antiapoptosis protein located in
 - outer mitochondrial membrane
 - nuclear membrane
 - endoplasmic reticulum membrane
 - prevents most but not all forms of apoptosis
- Stimuli capable of inducing apoptosis
 - Bax
 - related to *bcl-2*

stimulates rather than inhibits apoptosis

- *c-myc* oncogene
may induce apoptosis
if combined with *bcl2* may promote cell survival
- p53
- Effectors of the apoptosis pathway
 - caspases

APOPTOSIS PATHWAY

- Trigger (toxin)
- Activation of a second-messenger system
 - gene transcripts
 - increased intracellular calcium
 - activation of calcium-dependent enzymes
- Activation of an apoptosis promoter
 - Bax
 - p53
- Increased permeability of mitochondrial membrane
 - mitochondrial depolarization
- Cytoplasmic release of cytochrome *c*
- Activation of multiple capsases
- Increased activity of
 - proteases (cell shrinkage)
 - endonucleases (DNA fragmentation)
- Engulfment by phagocytes

Necrosis

- Another end of the spectrum of cell death
- Not regulated
- A point of no return
 - Injured cells attempt to preserve the nucleus and cell membrane.
 - When adaptations can no longer occur, the cell begins the necrotic process.

- Similar to apoptosis in
 - signals (many including toxins)
 - calcium-mediated processes effecting cellular changes
 - central role of the mitochondria in both processes
- Differs from apoptosis
 - cell swelling
 - fragmented nucleus
 - inflammation
 - rupture of cell membrane
 - leakage of intracellular components

Pathophysiology of Free Radical Generation

- A free radical is a species of an element or compound that has an unpaired electron in the outer shell or orbital.
- Free radicals are produced in response to metabolism.

TYPES (SPECIES) OF COMMON FREE RADICALS

- Superoxide anions
- Hydrogen peroxide
- Peroxides
- Hydroxyl radicals

FATE OF FREE RADICALS

- Half-life of a free radical may range from a nanosecond to a millisecond.
- Free radicals are highly reactive species with electron instability that causes the generation of new free radicals.
- If a free radical interacts with another free radical, an inert species is produced that is no longer reactive.

RESULTS OF FREE RADICAL PRODUCTION

- Lipid peroxidation of membranes
- Cleavage of DNA
- Destruction of enzymes or enzyme systems

ENDOGENOUS FREE RADICAL SCAVENGERS

- Glutathione
- Superoxide dismutase
- Catalase

TOXINS THAT GENERATE FREE RADICALS

See Figures 3–8 through 3–14.

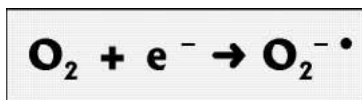


Figure 3–8 Pathway of generation of a superoxide anion.

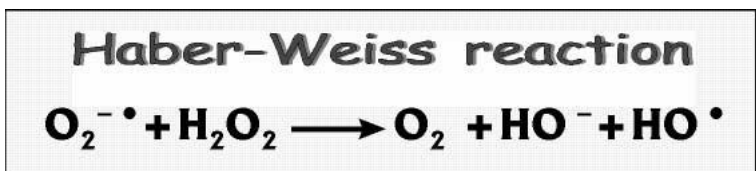


Figure 3–9 The Haber-Weiss pathway for production of hydroxyl radicals.



Figure 3–10 Reaction catalyzed by catalase enzyme whereby hydrogen peroxide is detoxified with the production of water and oxygen.

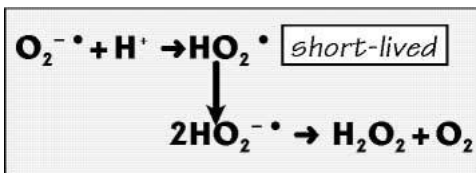


Figure 3–11 Production of hydrogen peroxide reactive oxygen species. The hydroperoxyl radical is a short-lived radical that forms hydrogen peroxide and oxygen.



Figure 3-12 Reaction catalyzed by superoxide dismutase (SOD). This enzyme reduces the reactivity of the superoxide anion by forming hydrogen peroxide and oxygen.

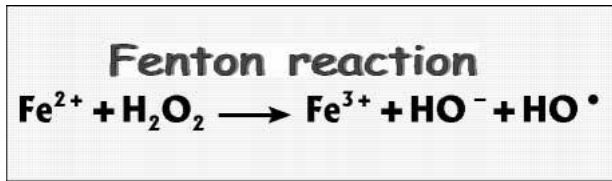


Figure 3-13 Fenton reaction. Interaction of hydrogen peroxide and ferrous iron mediates production of ferric iron and reactive ions.

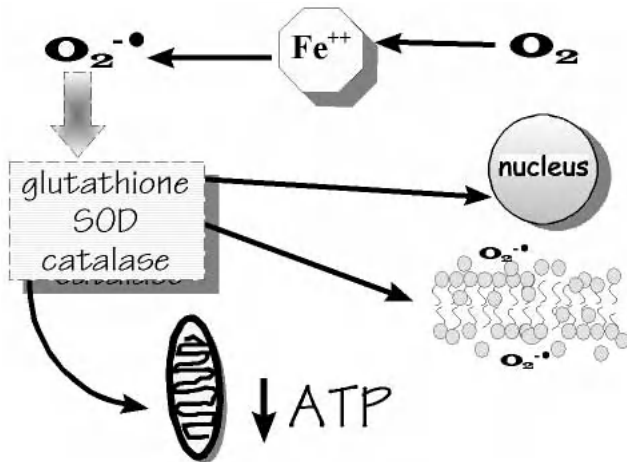


Figure 3-14 Reactive oxygen species damage to cells. Oxygen gains an electron and is transformed to a free radical. The radical is then subjected to one of the endogenous antioxidant systems—glutathione, superoxide dismutase (SOD), or catalase. If the antioxidant capacity is diminished, the radical can interact with functional and structural macromolecules of the cell. The radical can act on the mitochondria, disrupt oxidative phosphorylation, and decrease ATP production. The radical can interact with DNA to prevent protein synthesis. The radical also can instigate a chain reaction of radical generation in the cell membrane, disrupting membrane integrity and ionic homeostasis.

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4

Alphabetical Listing of Common Veterinary Toxins

Acetaminophen

General

- The chemical structure of acetaminophen is shown in Figure 4–1.
- Many well-intentioned owners assume that if acetaminophen is safe to give their infants, it must be safe for their pets.
- Cats should never be given acetaminophen because they lack sufficient glucuronyl transferase to detoxify the reactive metabolites that can cause cellular damage.

Source

- Acetaminophen and acetaminophen-containing combinations are found in many over-the-counter products used by humans.

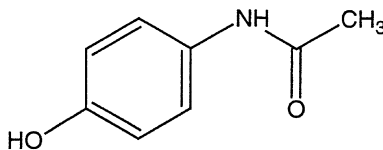


Figure 4–1 Chemical structure of acetaminophen.

- The products are used to manage a variety of ailments, such as colds, headaches, and sinus problems.

Species

- Cats are extremely sensitive; dogs also have been poisoned.

Clinical Signs

- Two syndromes—methemoglobinemia in cats, acute hepatic necrosis in dogs

CATS

- Cyanosis
- Methemoglobinemia
- Dyspnea
- Depression
- Edema of the paws and face

DOGS

- Signs associated with acute centrilobular hepatic necrosis:
 - Vomiting
 - Anorexia
 - Abdominal pain
 - Shock

Toxicity

- Greater risk of intoxication with repeated dosing
- Cats: >60 mg/kg
- Dogs: >200 mg/kg

Mechanism of Action

- After absorption, metabolism occurs through the cytochrome P450 system.
- Reactive intermediates are generated.
 - Reactive intermediates are rendered inert by glucuronidation and sulfation (phase II processes).

- Cats are deficient in glucuronyl transferase activity.
- Overdose can overwhelm the phase II processes.
- Reactive metabolites interact with glutathione and become inactivated.
- As glutathione concentrations decrease (<30% of normal), reactive metabolites interact with cellular macromolecules.
 - hemoglobin
 - hepatic endothelial cells
- Cytotoxicity and cell death occur, and clinical signs appear.

Diagnosis

- History of exposure
- Clinical signs
- Serum acetaminophen concentrations can be analyzed at many hospitals, but most animals have symptoms and require treatment.

Treatment

- Gastrointestinal decontamination
 - if the animal is relatively stable (e.g., no respiratory distress)
 - emesis
 - activated charcoal
 - cathartic
- Promote excretion of acetaminophen.
- Correct methemoglobinemia and provide supportive care.
- Acetylcysteine therapy to regenerate glutathione (Figure 4–2)
 - initial loading dose: 280 mg/kg orally or IV (slow bolus)
 - subsequent dosing: 70 mg/kg orally every 6 hours for 3 days
 - See Chapter 5 for information about antidotes.
- Reduce methemoglobinemia.
 - ascorbic acid for cats: 20 mg/kg orally
 - methylene blue
 - one dose: 1.5 mg/kg IV reduces methemoglobin concentration without inducing formation of Heinz bodies
 - second dose: induces formation of Heinz bodies

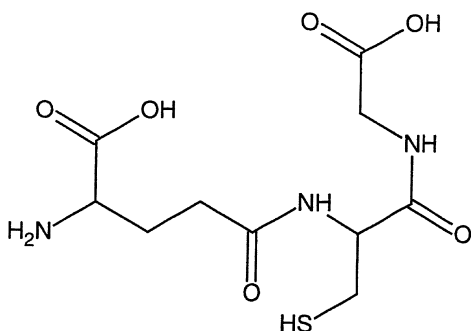


Figure 4-2 Chemical structure of glutathione.

- Reduce production of reactive metabolites.
 - Cimetidine and acetylcysteine have been shown to reduce hepatic damage in rats with acetaminophen intoxication.
 - Cimetidine is a cytochrome P450 inhibitor and may reduce the generation of reactive metabolites from acetaminophen.
 - The usual dose of cimetidine is 10 mg/kg IV or orally every 6 hours.
- Supportive therapy
 - oxygen therapy if patient is cyanotic
 - cage rest
 - fluid therapy

References

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- Savides MC, Oehme FW, Nash SL, et al. The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. *Toxicol Appl Pharmacol.* 1984;74:26–34.
- Speeg KV Jr, Mitchell MC, Maldonado AL. Additive protection of cimetidine and *N*-acetylcysteine treatment against acetaminophen-induced hepatic necrosis in the rat. *J Pharmacol Exp Ther.* 1985;234:550–554.

Acute Bovine Pulmonary Edema and Emphysema (ABPE, AIP, 3-Methyl Indole)

General

- This disease can occur when animals are moved from dry, marginal grazing areas to lush, green pastures.
- Adaptation of ruminal microflora to the new feedstuff is the primary cause.
- The syndrome is noticed within 4–10 days after change to a new pasture and affects mature animals.

Source

- Lush pastures that contain high concentrations of the amino acid L-tryptophan.
- The syndrome also may be caused by perilla mint (*Perilla frutescens*), which contains perilla ketones, and moldy sweet potatoes, which contain 4-ipomenol.

Species

- Cattle and other ruminants, horses

Clinical Signs

- Presentation similar to that of shipping fever
- Dyspnea
- Tachypnea
- Lethargy
- Depression

- Sudden death
- Animals in good body condition
- Coughing generally not part of this syndrome
- Gross necropsy and histopathologic findings
 - interstitial emphysema and pulmonary edema
 - gas trapped in the subcutaneous tissues and mediastinum
 - lungs congested and rubbery and fail to collapse
 - caudal lung lobes more commonly affected
 - alveolar edema
 - eosinophilic hyaline membranes
 - proliferation of type II pneumocytes

Mechanism of Action

- L-tryptophan metabolized by ruminal microbes to 3-methylindole (3-MI)
 - 3-MI is absorbed from the ruminal wall and enters the systemic circulation.
 - In the lungs, 3-MI is further metabolized by the mixed-function oxidases (MFO) in the lungs.

MFO are present in type I pneumocytes and Clara cells.

Metabolism produces a highly reactive metabolite.

Metabolite is toxic where it is formed.

Reactive metabolite binds with macromolecules of the lung.

The cells of the lung are damaged.
- Perilla ketones and 4-ipomenol also are metabolized by the MFO in the lungs and react locally with macromolecules in the lungs.

Diagnosis

- History of exposure to the plants causing problems
- Clinical and pathologic signs

Differential Diagnosis

- Allergic alveolitis

- Bovine respiratory syncytial virus
- Paraquat intoxication
- Parasitic bronchitis (*Dictyocaulus viviparus*)
- Petroleum intoxication
- Shipping fever

Treatment

SYMPTOMATIC THERAPY

- Reduction of stress: Limit movement of animals.
- Flunixin meglumine: Antiprostaglandin therapy.

PREVENTION

- Pasture management: Limit sudden introduction of hungry, unadapted animals to lush, green pastures.
 - Offer hay or supplements.
 - Limit grazing.
 - These steps are labor intensive.
- Polyether antibiotic supplementation
 - Monensin (Rumensin) or lasalocid (Bovatec)
 - alter ruminal microflora
 - decrease production of 3-MI
 - decrease reactive metabolites generated in the lungs
 - must be in feed for a day or two before exposure to pasture

References

- Kerr LA, Johnson BJ, Burrows GE. Intoxication of cattle by *Perilla frutescens* (purple mint). *Vet Hum Toxicol.* 1986;28:412–416.
- Kerr LA, Linnabary RD. A review of interstitial pneumonia in cattle. *Vet Hum Toxicol.* 1989;31:247–254.
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Aflatoxin (Aflatoxicosis)

General

- The chemical structure of aflatoxin is shown in Figure 4–3.
- Toxicosis is more commonly associated with ingestion of corn, peanuts, and cottonseed meal.
- The causative fungal organism is common in the environment.
- Corn and peanuts can become infected in the field, during transport, or during storage.
- Conditions favoring aflatoxin production are warm weather ($>86^{\circ}\text{F}$; $>30^{\circ}\text{C}$), high relative humidity, and high moisture of the grain.
- Any factor that damages the corn kernels (drought, insect damage) can predispose to production of aflatoxin.
- The diagnosis of aflatoxicosis can be difficult because several organ systems can be affected.
- There are U.S. Food and Drug Administration action levels for aflatoxin in human food, including milk.
 - Milk should contain less than 0.5 ppb aflatoxin M_1 .
 - Corn and cottonseed meal that is to be fed to dairy cattle should contain less than 20 ppb aflatoxin.
 - Information concerning aflatoxin action levels is found in the FDA Compliance Policy Guides (http://www.fda.gov/ora/compliance_ref/cpg; CPG 527.400 and CPG 683.100).

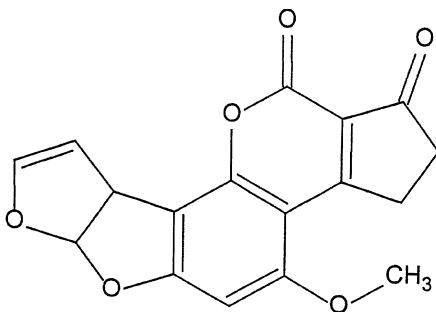


Figure 4–3 Chemical structure of aflatoxin B_1 .

Source

- A group of closely related chemicals produced as a by-product of fungal growth
- Produced by *Aspergillus flavus* and *Aspergillus parasiticus*
- Designated aflatoxin B₁, B₂, G₁, G₂; after ingestion aflatoxin M₁ and M₂ may be found in milk.

Species

- Poultry, cattle, sheep, swine; although all species are susceptible

Clinical Signs

- Hepatotoxicity is the most well-defined syndrome of aflatoxicosis in most species.
- Other syndromes are less well defined.

HEPATOTOXICITY

- Anorexia
- Decreased growth rate
- Decreased feed efficiency
- Decreased production (weight gain, milk production)
- Icterus
- Lesions
 - acute hepatic necrosis and hemorrhage
 - pale liver
 - bile duct hyperplasia
 - karyomegaly

OTHER SYNDROMES

- Immunotoxicity
- Carcinogenesis

Toxicity

- LD50 ranges from 0.5 to 10 mg/kg body weight
- Increased aflatoxin concentration in broken grain (corn screenings)

- Young animals are more sensitive than older animals.
- In general, monogastric animals are more sensitive than ruminants.

Mechanism of Action

- Aflatoxin B₁ is the most potent inducer of toxicosis.
- Aflatoxin B₁ is metabolized by the hepatic microsomal mixed function oxidases.
 - Produces several metabolites.
 - Some of the metabolites are epoxides.
 - The epoxides are highly reactive intermediates.

Epoxides seek chemical stability.

To become stable, the epoxide must interact with an endogenous compound.

Epoxides of aflatoxin B₁ interact with RNA, DNA, and cellular proteins.

The combination of the epoxide and DNA or RNA produces an adduct.

The adduct cannot be read to produce messenger RNA or protein.

Protein synthesis is inhibited.

- Induction of hepatic carcinoma is a more complex and less understood process.

Diagnosis

- History of consumption of suspect feedstuffs
- Clinical signs
- Clinical pathology
 - increased serum concentrations of hepatic enzymes: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase
 - decreased serum albumin concentration
 - decreased albumin to globulin ratio
 - increased serum bilirubin concentration
- Histopathology

- bile duct hyperplasia
- centrilobular necrosis
- Black-light screening (Wood's lamp)
 - moldy corn may have bright greenish-yellow fluorescence (BGYF)
 - only suggests the possibility of aflatoxin contamination
 - kojic acid
 - by-product of fungal growth
 - may be produced under environmental conditions that favor *Aspergillus* spp.
 - fluorescent product responsible for BGYF
- Chemical analysis
 - the best method to make a definitive diagnosis
 - thin-layer chromatography
 - gas chromatography
 - liquid chromatography
 - mass spectrometry
- Samples
 - animal
 - milk
 - urine
 - liver
 - kidney
 - feed
 - corn
 - cottonseed meal

Treatment

- No specific antidote
- Supportive and symptomatic
 - Discontinue the suspect feed.
 - Feed a high-quality source of protein.
- Hydrated sodium calcium aluminosilicate

- Used as an anticaking agent
- Is recognized by the FDA as safe when used for this designated purpose
 - may reduce the residues of aflatoxin in affected animals
 - at this time, hydrated sodium calcium aluminosilicate is not approved by the FDA as a binding agent for mycotoxins

References

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Allium (Onion Intoxication)

General

- Ingestion of wild onions is not a common source of intoxication, but it can cause an offensive odor to the milk of dairy cows.
- Cattle often are fed cull onions in areas where onions are cultivated.

Source

- The genus *Allium* includes onions and garlic.

Species

- Cattle, dogs, horses, sheep; goats are the least sensitive
- Dogs can be poisoned by eating onions or a concentrated source, such as dehydrated onions.

- Cats have been poisoned after consuming baby food that contains dehydrated onions.

Clinical Signs

- Signs of an acute hemolytic event
- Weakness
- Tachypnea
- Tachycardia
- Dark urine
- Icterus
- Onion odor of breath
- Clinical pathology
 - decreased packed cell volume
 - hemoglobinemia, hemoglobinuria
 - Heinz body anemia
 - possibly methemoglobinemia

Toxicity

- In experiments
 - Dogs weighing 10–12 kg fed 200 g boiled onions were intoxicated.
 - Dogs fed 5.5 g/kg dehydrated onions were intoxicated.

Mechanism of Action

- The toxin is an oxidant that acts on erythrocytes.

TOXIC PRINCIPLES

- *n*-Propyl disulfide is most commonly reported.
- Onions and garlic also contain *S*-methylcysteine sulfoxide, which in the rumen is transformed into dimethyl disulfide.

MECHANISMS

- *n*-Propyl disulfide acts directly on erythrocytes and hemoglobin to induce oxidative stress.
 - Oxidation of erythrocytes produces denatured hemoglobin.
 - Heinz bodies are erythrocyte intracellular inclusions of hemoglobin.

- Erythrocyte glutathione is decreased.
- Disulfides may reduce the activity of thiol enzyme systems in erythrocytes
- Disulfides also may affect the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH).
- reduced activity of
 coenzyme A
 coenzyme A reductase

Diagnosis

- History of exposure and consumption of onions
- Clinical signs
 - Acute hemolytic anemia
 - Clinical pathologic alterations
 - decreased packed cell volume
 - increased number of Heinz bodies
- Odor of onions on breath

Treatment

- Symptomatic
- Blood transfusion if anemia is severe
- Fluid therapy to correct hypovolemia and shock
- Saline diuresis with sodium bicarbonate to reduce potential hemoglobin-associated damage to renal tubules

Prevention

- Cull onions fed to cattle should be chopped and thoroughly mixed in the ration.
- Cattle may acquire a taste preference for onions and consume onions over other components of the ration.

References

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Amitraz

General

- The chemical structure of amitraz is shown in Figure 4–4.
- Amitraz is a formamidine insecticide used as an insecticide and ascaricide.
- The formulations are dips, impregnated flea collars, and liquid for sprays.
- The indications for use are demodectic mange and ticks.

Source

- Mitaban liquid concentrate contains approximately 20% amitraz dissolved in an organic solvent carrier.
- Preventive tick collars for dogs are impregnated with amitraz.

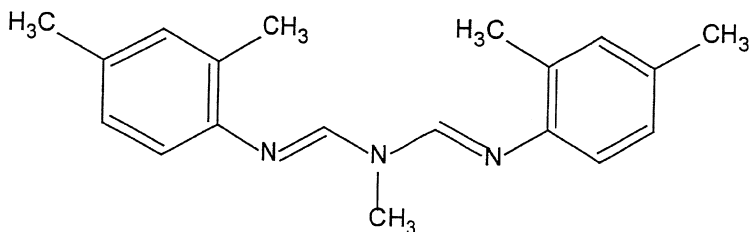


Figure 4–4 Chemical structure of amitraz.

Species

- Dogs, cats, swine, and horses

Clinical Signs

- Sedation/depression
- Bradycardia
- Mydriasis, miosis
- Polyuria
- Hypothermia
- Hyperglycemia

Toxicity

- Dog: LD50 = 100 mg/kg
- Dog: clinical signs (depression) at 1 mg/kg

Mechanism of Action

- α_2 -Adrenergic agonist activity
- Other possible mechanisms
 - monoamine oxidase inhibitor
 - increased calcium influx through voltage-gated calcium channels

Díagnosis

- History of exposure
- Clinical signs
- Clinical pathology
 - increased blood glucose
 - increased urine glucose
- Chemical analysis
 - gas chromatography of fat, liver, skin

Treatment***Decontamination*****DERMAL EXPOSURE**

- Wash the animal to remove any additional insecticide.

- Use a mild detergent.
- Persons washing the animal should wear gloves.

ORAL EXPOSURE

- Activated charcoal and sorbitol cathartic
- Emetic therapy should be used judiciously because
 - animals may have altered mental status
 - hydrocarbon solvents in the amitraz products
- Enterotomy may be needed to remove segments of ingested collar

Reversal of α_2 -Adrenergic Effects

- Yohimbine 1 mg/kg IV
- Atipamezole
- Atropine to reverse bradycardia can induce arrhythmia, gastrointestinal ileus

Symptomatic and Supportive

- Monitor body temperature
- Blankets or heating pads
- Monitor heart rate and blood pressure

Prognosis

- Good with mild signs

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Anticoagulant Rodenticides

General

- A large group of compounds available as pellets, tracking powders, and baits.
- Many of these products are available to the public, and consumption by nontarget species can cause poisoning.
- The original compound, warfarin, was developed after it was observed that cattle that consumed moldy sweet clover had increased bleeding.
- Fungal metabolism of coumarin in the plant produced dicoumarol, which is the toxic agent.
- The name *warfarin* was coined by the research group that discovered this property and pays tribute to the Wisconsin Alumni Research Foundation and the chemical suffix of *coumarin*.

Species

- Mainly dogs and cats
- All species susceptible; pigs are quite sensitive to warfarin.

Source

- Moldy sweet clover (*Melilotus* spp.)
 - Rodenticides
 - Multiple feeding, first generation
Warfarin (Figure 4–5) (e.g., Final)
Pindone (e.g., Pival, Pivalyn)
 - Single feeding, first generation
Diphacinone (Ramik[®], Ditrac[®])
Chlorophacinone (e.g., Rozol[®])
 - Single feeding, second generation
Brodifacoum (e.g., Talon, Havoc, d-Con)
Bromadiolone (e.g., Maki, Contrac)
- Another possible source is consumption of poisoned mice or rats.

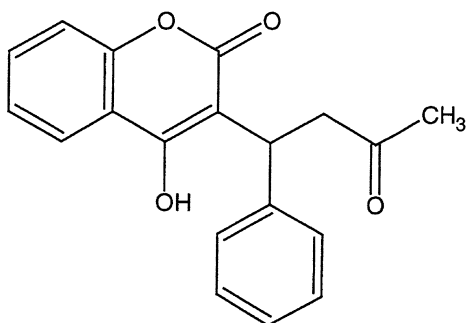


Figure 4-5 Chemical structure of warfarin.

Clinical Signs

- Overt hemorrhage
- Hematoma
- Melena
- Epistaxis
- Increased bruising
- Dyspnea (pleural hemorrhage)
- Pale mucous membranes
- Lethargy
- Swollen joints
- Sudden death
- Lesions
 - blood in body cavities
 - hemorrhage

Toxicity

- Toxic dose is reduced with multiple feedings.
- Intoxication in swine is potentiated by concurrent administration of sulfanilamide.

ACUTE TOXICITY IN DOGS

- Warfarin 20–300 mg/kg
- Brodifacoum 0.2–4 mg/kg
- Bromadiolone 11–15 mg/kg
- Diphacinone 0.9–8 mg/kg (Figure 4–6)

ACUTE TOXICITY IN CATS

- Warfarin 5–30 mg/kg
- Brodifacoum 25 mg/kg
- Bromadiolone >25 mg/kg
- Diphacinone 0.3 mg/kg

Mechanism of Action

- Inhibition of vitamin K₁ epoxide reductase
 - enzyme involved in the recycling of vitamin K
 - essential cofactor in some of the coagulation factors
- Vitamin K–dependent coagulation factors II, VII, IX, and X
 - Active vitamin K₁ serves as a carboxyl group donor for the coagulation factors.
 - This allows the factors to bind calcium during coagulation.
 - Factor VII has the shortest half-life (approximately 6 hours).

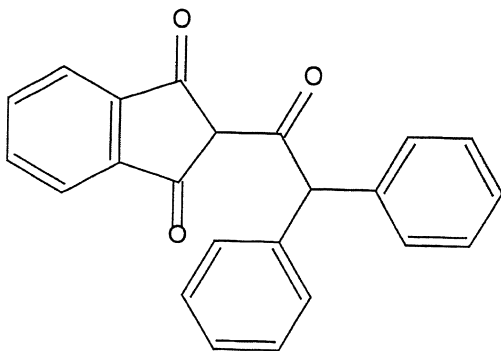


Figure 4–6 Chemical structure of diphacinone.

Diagnosis

- Clinical signs
- History of exposure to anticoagulant rodenticides
- Laboratory testing: citrated blood
 - decreased packed cell volume
 - prolonged activated clotting time (intrinsic pathway)
 - prolonged partial thromboplastin time (intrinsic pathway)
 - prolonged prothrombin time (extrinsic pathway)
 - sample from healthy dog needed for comparison
 - clotting times 25% longer than normal suggest poisoning
- Normal platelets and fibrin degradation products
- Response to therapy
 - generally within 24–48 hours of initiation of therapy
- Chemical analysis of vomitus, blood, bait, or liver
 - Refrigerate blood, vomitus.
 - Freeze liver.

Treatment

RECENT SUSPECTED OR OBSERVED INGESTION WITHOUT CLINICAL SIGNS

- Conduct gastric decontamination (induce emesis, administer activated charcoal and cathartic).
- Observe animal closely for clinical signs in the next week.

TRANSFUSION OF BLOOD OR CLOTTING FACTORS

- If packed cell volume is less than 15% and animal has severe bleeding
 - 10–20 mL/kg body weight fresh whole blood
 - 9 mL/kg body weight fresh plasma

VITAMIN K₁ (PHYTONADIONE) THERAPY

- Exogenous vitamin K₁ for carboxylation of factors II, VII, IX, and X
- Doses:
 - dogs and cats: 2.5–5.0 mg/kg orally or subcutaneously

- cattle, horses, swine, and sheep: 0.5–2.5 mg/kg IM
- Dosing guidelines
 - greater absorption after oral administration, if animal can tolerate this method of dosing
 - if animal is vomiting, use subcutaneous route for 2 or 3 days, then switch to oral administration
 - divide the subcutaneous dose and inject into several sites
 - use the smallest-gauge needle possible
 - do not give IM or IV owing to risk of anaphylaxis
 - vitamin K₃ is ineffective and should not be used
- Duration of vitamin K₁ therapy
 - 3–4 weeks to ensure protection from the longer-acting agents
- Monitoring therapy
 - repeat measurement of prothrombin time 2–5 days after cessation of vitamin K₁ therapy
 - improvement in clotting function should occur within 12 hours

OWNER EDUCATION

- When sending animal home with vitamin K₁ tablets or capsules, inform owner to continue therapy until clotting test results are normal.
- Restrict animal's activity during therapy to prevent trauma.
- Observe the animal closely for clinical signs.
- Educate owners about proper placement of baits.

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Arsenic (Inorganic and Organic)

General

- Arsenic poisoning is less common now owing to decreased use of arsenic-containing pesticides.
- There are two distinct clinical syndromes of intoxication due to specific forms of arsenic
 - inorganic, aliphatic, and trivalent organic arsenicals
 - phenylarsonic compounds

Source

INORGANIC

- Arsenic trioxide
 - herbicides
 - exhaust from iron smelters
 - wood preservatives
 - oil field waste products
- Pentavalent and trivalent form
 - salts, arsenates, and arsenites (pesticides)
 - defoliants

ORGANIC

- Thiacetarsemide (heartworm adulticide)
- Herbicides
 - monosodium methanearsonate (MSMA)
 - disodium methanearsonate (DMSA)
- Phenylarsonic compounds
 - arsanilic acid
 - 3-nitro, 4-hydroxyphenylarsonic acid (3-nitro)

Species

- All species
- Inorganic and organic: cattle, horses, and dogs more commonly poisoned
- Phenylarsonics: mainly swine and poultry

Toxicity

- Trivalent forms (arsenite) are 5–10 times more toxic than the pentavalent forms.
- Trivalent forms are excreted through the biliary system.
- Pentavalent forms are eliminated through the kidney.
- General toxic oral dose of sodium arsenite for most species is 1–25 mg/kg of body weight.
- Thiacetarsemide has a narrow therapeutic index in dogs.
 - therapeutic dose of 2.2 mg/kg twice a day every 2 days
 - intoxication can be found at therapeutic doses
- Phenylarsonics
 - 250 ppm over several days causes intoxication in swine

Mechanism of Action

- Trivalent form of arsenic is thought to be the cause of intoxication.
- Arsenic acts on and binds sulfhydryl groups within cells.
 - disrupts and inhibits sulfhydryl-containing enzymes of aerobic metabolism
 - tissues most severely affected include gastrointestinal tract, kidney, liver, and lungs
- Capillaries of the gastrointestinal tract are highly sensitive to arsenic.
 - capillary damage
 - dilation
 - transudation and decreased blood perfusion to the splanchnic tissues
 - resulting in decreased systemic blood volume and shock

- In the kidneys, arsenic acts on the capillaries of the cortex and causes dilation.
 - transudation of plasma
 - tubular degeneration
 - renal casts in the urine
- Phenylarsonics have an unknown mechanism of action.

Clinical Signs

ACUTE INTOXICATION

- High morbidity and mortality
- Gastrointestinal pain
- Colic
- Diarrhea
- Vomiting
- Dehydration
- Weak pulse
- Ruminal atony
- Prostration

SUBACUTE INTOXICATION

- Watery bloody diarrhea
- Depression
- Dehydration
- Anuria

THIACETARSEMIDE INTOXICATION

- Anorexia
- Vomiting
- Lethargy
- Fever
- Diarrhea
- Urinary casts

PHENYLARSONIC INTOXICATION

- Peripheral neuropathy with low mortality
- Ataxia and incoordination
- Blindness
- “Dog sitting” of swine
- Paralysis
- Recumbency
- Animals continue to eat

Diagnosis

- Clinical signs of intoxication
- History of exposure
- Identification of potential sources of arsenic
 - often difficult until after chemical identification
- Chemical analysis of arsenic in kidney, liver, or stomach contents
 - Normal renal and hepatic arsenic concentrations are <1 ppm.
 - Intoxicated animals have renal and hepatic arsenic concentrations >3 ppm.
 - Arsenic concentrations >2 ppm in stomach contents or urine suggest arsenic intoxication.
- Phenylarsonic samples
 - peripheral nerves, such as optic nerves for histopathologic examination
 - complete feed

Treatment**RECENT EXPOSURE WITH NO CLINICAL SIGNS**

- Decontamination (emesis if applicable, activated charcoal)
- Gastrointestinal protective agents (kaolin, pectin)

ANIMALS WITH CLINICAL SIGNS

- Aggressive fluid therapy (shock doses)
- Chelation
 - small animal: IV disodium methanearsonate, 2,3 dimercapto-1-propanesulfonic acid, possibly D-penicillamine, or thioctic acid

- large animal: oral thioctic acid and possibly British anti-Lewisite (dimercaprol), sodium thiosulfate
- Provide other sources of sulfhydryl groups
 - cysteine, acetylcysteine, and glutathione have been shown to protect rodents from arsenic intoxication
- Antibiotics for secondary bacterial infection, especially of the gastrointestinal tract.
- Monitoring of renal and hepatic function

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Black Walnut (*Juglans nigra*)

General

- Black walnut is used in the manufacture of furniture, and the shavings are sold as bedding material.
- Shavings can contain only a small percentage of black walnut and still cause laminitis.
- Several horses in a herd generally are affected.

Source

- Black walnut wood shavings are used as bedding for horses.
- Intoxication is more prevalent with fresh shavings.
- The black walnut tree grows from the northeastern United States to eastern Texas.

Species

- Horses and other equids

Clinical Signs

- Laminitis occurring within 8 hours after introduction of the bedding material
- Edema of the legs (stocking up)
- Anorexia and depression
- Increases in the following values:
 - heart rate
 - respiratory rate
 - body temperatures
 - coronary band and hoof temperature
- Pounding digital pulses

Toxicity

- As little as 5% of the bedding material from black walnut shavings can cause laminitis.
- All portions of the tree can cause the syndrome.

Mechanism of Action

- The toxic principle is not known.
- Juglone once was believed to be involved because it was found in high concentrations in the hull of the nut.
- Aqueous extracts of the heartwood, which contains no juglone, consistently induced laminitis.
- The pathogenesis is not completely understood but is believed to be similar to that of other causes of acute laminitis.

- Black walnut shavings or aqueous extracts induce alterations in the hemodynamics of blood flow to the hoof.
- Overall, blood flow to the foot is increased and perfusion to the hoof is decreased.
- In vitro studies have shown that an aqueous extract of black walnut shavings does not directly cause vasoconstriction of isolated equine digital artery preparations but does enhance the vasoconstriction induced by administration of epinephrine potentiated by hydrocortisone.

Diagnosis

- Sudden onset of clinical signs associated with new bedding material
- Acute laminitis in several horses at the same time
- Radiographs of the feet show the severity of laminitis.

Treatment

- Begin treatment immediately.
- Remove all horses from the bedding, and remove the bedding.
- Wash legs with mild detergent to remove any remaining residues.
- Conduct gastrointestinal decontamination with mineral oil.
- Administer symptomatic therapy to control pain.
- Place affected animals in sand stalls for relief of pain.

References

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Bluebonnets or Lupines (*Lupinus* spp.)

General

- A common plant intoxication in the western United States
- Many species of nontoxic lupines

Source

EXAMPLES OF POISONOUS LUPINES

- Big Bend lupine (*Lupinus leucopsis*)
- Douglas spurred lupine (*L. laxiflorus*)
- Kellogg's spurred lupine (*L. caudatus*)
- Silky lupine (*L. sericeus*)
- Silvery lupine (*L. argenteus*)
- Woolly-leaved lupine (*Lupinus leucophyllus*)

Species

- Acute intoxication and death more common in sheep
- Greater potential for teratogenesis in cattle

Clinical Signs

ACUTE

- Primarily affect sheep
- Sudden death
- Nervousness
- Depression
- Severe dyspnea, snoring
- Ataxia
- Convulsions
- Coma

CROOKED CALF SYNDROME

- Plant consumed on days 40–70 of gestation
- Limbs (primarily forelimbs) twisted or bowed
- Arthrogryposis

- Scoliosis of thoracic or cervical vertebrae
- Cleft palate

Toxicity

- Ingestion of 1% of body weight of plant can induce intoxication.
- All portions of the plant are toxic.

Mechanism of Action

TOXIC PRINCIPLES

- Quinolizidine alkaloids
 - lupinine
produces nicotinic effects
acute effects on sheep
 - anagryne produces teratogenic effects
- Piperidine alkaloids (teratogenic effects)
 - ammodendrine
 - *N*-methyl ammodendrine
 - *N*-acetyl hystrine

MECHANISM

- Decreased movement of the fetus in utero is caused by maternal consumption of the plant.
- Decreased movement is associated with the occurrence of crooked calves.

Diagnosis

- Clinical signs
- Evidence of consumption of the plant material
 - can be difficult for teratogenic effects

Treatment

- Gastrointestinal decontamination
- Symptomatic: control seizures
- Prevention is most important.

- Restrict access to plant material.
- Herbicide therapy may not be economical.

References

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Blue-Green Algae (Cyanobacteria)

General

- Intoxication by blue-green algae can be difficult to diagnose owing to the variety of toxins produced.
- Intoxication is most commonly observed in the summer during rapid growth of algae—the bloom.
- Other factors that can precipitate an episode of intoxication include windy weather that concentrates the floating bloom to one side of a body of water and drainage of fertilized fields into ponds.

Source

- Several species of Cyanobacteria
 - *Anabaena flos-aquae*
 - *Anabaena spiroides*
 - *Microcystis aeruginosa*

Species

- Dogs, cattle, swine, and waterfowl

Clinical Signs

- Ataxia
- Anorexia

- Muscle tremors
- Recumbency
- Dehydration
- Diarrhea (possibly bloody)
- Ruminal atony
- Hepatotoxicity, fulminate hepatic failure
- Clinical pathology
 - hepatic injury (microcystins)
 - increased serum concentrations of alkaline phosphatase, γ -glutamyl transferase, aspartate transaminase, and lactate dehydrogenase
- Necropsy findings
 - liver enlarged, friable, discolored, or congested
- Histopathologic findings
 - hepatocyte necrosis, dissociation, or degeneration

Mechanism of Action

- Several toxins affect vertebrates.
- Hepatotoxic peptides (cyclic peptides)
 - inhibition of protein phosphatase 1 and 2A
increased concentration of cytosolic phosphoprotein
activation of intracellular protein kinase
 - increase in production of hepatic reactive oxygen species and lipid peroxidation
 - some toxins decrease sulfhydryl content of cytoskeleton
- Neurotoxin
 - anatoxin-a(s)
 - nicotinic agonist
- Peripheral-acting anticholinesterase
- Sodium channel antagonist
- Endotoxin (lipopolysaccharide)

Diagnosis

- History of exposure to water containing algae
- Presence of clinical signs

- Clinical pathology
 - elevated liver enzymes
 - inhibition of acetylcholinesterase activity
- Microscopic evaluation of water or stomach contents for cyanobacteria
- Chemical analysis
 - High-pressure liquid chromatography detection of algal toxins
- Intraperitoneal injection of suspect material into mice

Treatment

- Activated charcoal
- Procaine penicillin
- Glucose
- Calcium and magnesium gluconate

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Botulism

General

- Intoxication due to ingestion of a preformed toxin
- Also called *limber neck* (avian) and *shaker foal syndrome* (horses).
- In waterfowl, associated with consumption of rotten vegetation in shallow feeding areas and can appear as an epidemic
- In cattle, associated with the habit of eating bones or consuming partially decomposed carcasses (improperly ensiled poultry litter, contaminated hay)
- In carnivores due to eating carrion but the disease is not common in dogs and cats.

Source

- *Clostridium botulinum*, an anaerobic, gram-positive, spore-forming rod that produces a series of potent neurotoxins
- Seven types—A, B, C, D, E, F, and G—based on the antigenic specificity of the toxin produced by each strain
- Types A, B, E, and F more commonly associated with botulism in humans
- Botulism toxin C cause of disease in most species, type D in cattle, and type B in horses
- Botulism toxin (BoTox) used for cosmetic purposes in humans to paralyze mimetic muscles involved with frowning

Species

- Wild birds, poultry, cattle, horses, but all species susceptible

Clinical Signs

- Progressive neuromuscular weakness
- No specific gross signs or histopathologic lesions in animals that die

MOST SPECIES

- Myasthenia gravis–like signs
- Progressive ataxia from hind limbs to cranial nerves
- Depression
- Mydriasis
- Recumbency
- Death usually due to respiratory paralysis

HORSES

- Weakness of the tongue
- Difficulty eating or swallowing liquids
- Muscular tremors
- Decreased tail tone
- Ptosis

CATTLE

- Decreased ruminal motility
- Hypersalivation
- Decreased masticatory muscle tone

Toxicity

- One of the most lethal substances, natural or synthetic
- The lethal dose for a mouse is 4×10^7 molecules.
- Only nanogram amounts of toxin must escape destruction in intestines to induce clinical disease.

Mechanism of Action

- Botulinum toxin decreases acetylcholine release at peripheral cholinergic synapses, especially the neuromuscular junction.
- Botulism toxin is composed of heavy and light chains.
- Light chains inhibit acetylcholine release.
 - zinc-dependent proteolysis of components of the synaptic vesicle
 - light chains are metalloendoproteases or metalloproteases
- Protein targets of the botulism toxin
 - vesicle-associated membrane protein (VAMP) or synaptobrevin—an integral protein in synaptic vesicles
 - soluble *N*-ethylmaleimide-sensitive factor attached protein (SNAP-25)—a membrane protein
 - syntaxin—a membrane protein
- Several of these processes are regulated by calcium.
- Cleavage of synaptic vesicle and cell membrane proteins disrupts the normal synaptic excitation-secretion coupling.
- Acetylcholine is not released in response to depolarization of the axon terminal.

Diagnosis

- Often difficult
- Clinical signs
- Detection of toxin
 - suspect feed; tissues or serum of affected animals injected into mice
 - test performed at few laboratories
 - less toxin in horse serum than serum from other species
 - suspect material fed to susceptible species
 - enzyme-linked immunosorbent assay for toxin
- Culture of the tissues of affected animals

Treatment

- Gastric decontamination with activated charcoal and cathartic

- Antitoxin therapy
 - better results early in the disease
- Antimicrobial therapy
 - Penicillin intravenous or intramuscular can reduce number of reproducing organisms in the tissues of horses and dogs.
 - *Oral penicillin and aminoglycosides by all routes of administration are contraindicated.*
- Supportive therapy
 - Keep animals warm, hydrated on padded bedding.
 - Administer oxygen to severely affected animals.

Prevention

- Administer vaccine.
- Remove all carcasses or feedstuffs contaminated with carcasses.
- Ensure correct mineral nutrition because deficiencies can predispose cattle to consume bones.

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Bracken Fern (*Pteridium aquilinum*; Older Name *Pteris aquilina*)

General

- Different syndromes in horses and cattle
- In horses, thiamine deficiency and a neurologic syndrome
- Cattle less sensitive owing to the thiamine production by the ruminal microflora

Source

- Thiaminase in bracken fern—greater concentrations in the rhizome than the leaves or stem
- Grows throughout the United States in poor soil and in moist areas
- Intoxication more common during times of the year when other forage sources are poor or not available (late summer or drought)
- Can be incorporated into hay as a source of poisoning
- Contains other substances, such as ptaquiloside, that cause disease in cattle

OTHER SOURCES OF THIAMINASE

- *Equisetum arvense* (horsetail)
 - Hay with 20% horsetail can induce disease in horses.
- *Marsilea drummondii* (Nardoo, southern cross)
 - Australian plant with 100 times more thiaminase than bracken fern
- Internal organs of carp species of fish
 - cause of Chastek paralysis in mink

Species

- Horses more commonly affected with the neurologic syndrome
- Cattle more commonly affected with bone marrow depression and enzootic hematuria (tumors of the urinary bladder)
- Pigs and sheep reluctant to consume bracken fern

Clinical Signs

HORSES

- Generally after a month of eating the plant
- Weight loss with normal appetite
- Incoordination
- Ataxia
- Recumbency
- Death within a few days without treatment

CATTLE

- Generally after long-term consumption of the plant
- Elevated body temperature
- Weight loss
- Anemia
- Bloody discharges from orifices
- Hematuria
- At necropsy, hemorrhages in most body organs, abomasal ulcers
- High mortality (>80%) associated with clinical disease

Toxicity

- Hay containing 20% bracken fern causes disease in horses within 1 month

Mechanism of Action

- Two or more principal toxins: thiaminase and ptaquiloside more commonly associated with poisoning
- Other potential carcinogens in bracken fern: tannin, quercetin, shikimic acid, prunasin, kaemferol

THIAMINASE

- Thiamine (vitamin B₁) is an essential cofactor in decarboxylation reactions.
- Thiaminase cleaves thiamine into a pyrimidine and a thiazole group.

- Conversion of pyruvate to acetyl coenzyme A and oxidation of α -ketoglutarate to succinyl coenzyme A are inhibited.
- Aerobic metabolism is decreased, and less adenosine triphosphate is produced.
- Elevation of pyruvate concentration can alter neuronal function.

PTAQUILOSIDE

- In alkaline conditions, the glucose moiety is lost. The result is an intermediate containing a highly reactive cyclopropyl ring capable of reacting with cellular macromolecules.
- DNA may be alkylated at N3 of adenines and N7 of guanines.
- These alkylations may cause mismatch repair, which leads to induction of protooncogenes such as *H-ras*.
- There is concern that ptaquiloside may be transferred in milk and be a carcinogen in humans.

Diagnosis

- History of exposure
- Clinical signs
- Decreased serum thiamine concentration
- Decreased erythrocyte transketolase activity
- Elevated serum pyruvate concentration
- Elevated serum lactate concentration

Treatment and Prevention**HORSES**

- Thiamine (vitamin B₁)
 - 0.5–5 mg/kg IV, subcutaneously, IM, or orally
 - IM injection can cause muscle soreness and tenderness
 - may be necessary to repeat therapy for several days
 - horses should exhibit normal behavior in 1 or 2 days

CATTLE

- Blood transfusion up to 4 L
- Broad-spectrum antibiotics

- Indications of severe bone marrow depression (leukocyte count $<2000/\text{mm}^3$ or platelets $<100,000/\mu\text{L}$) suggest a poor prognosis.
- DL-batyl alcohol: suggested in older literature to stimulate bone marrow, not considered to be an effective treatment
- Removal of animals from the pasture
- Deep plowing, aggressive pasture management, or herbicides to control fern

References

- Shahin M, Moore MR, Worrall S, et al. H-ras activation is an early event in the ptaquiloside-induced carcinogenesis: comparison of acute and chronic toxicity in rats. *Biochem Biophys Res Commun.* 1998;250:491–497.
- Shahin M, Smith BL, Prakash AS. Bracken carcinogens in the human diet. *Mutat Res.* 1999;443:69–79.
- Smith BL, Seawright AA. Bracken fern (*Pteridium* spp.) carcinogenicity and human health: a brief review. *Nat Toxins.* 1995;3:1–5.

Bromethalin

General

- The chemical structure of bromethalin is shown in Figure 4–7.
- Bromethalin is a rodenticide packaged as a pelleted, grain-based bait containing 0.01% (100 ppm) of the substance.
- The bait pellets are impregnated with a green water-soluble dye.

Source

- Brand names of bromethalin rodenticides
 - Vengeance
 - Assault
 - Trounce

Species

- Dogs, primarily, and cats

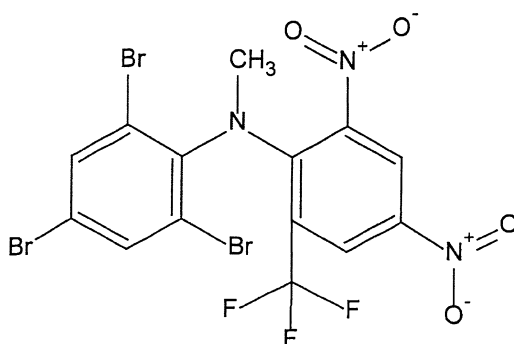


Figure 4-7 Chemical structure of bromethalin.

Clinical Signs

- Onset after a large dose can be 2 to 4 hours after ingestion; however, the more typical onset is 8 to 12 hours.
- Tremors
- Hyperexcitability
- Seizures
- Hindlimb hyperreflexia
- Paralysis
- Depression
- Prostration
- Death

Toxicity

- See Figure 4-8.
- Lower doses can cause a chronic syndrome with a delayed onset of signs.

DOGS

- Minimal toxic dose = 1.67 mg/kg
- Minimal lethal dose = 2.5 mg/kg
- LD₅₀ = 4.7 mg/kg

CATS

- Toxicosis experimentally induced with 1.5 mg/kg
- LD50 = 1.8 mg/kg

Mechanism of Action

- Bromethalin uncouples oxidative phosphorylation in mitochondria of the central nervous system.
- The greatest toxic effects occur in the white matter.
- Uncoupling of oxidative phosphorylation leads to
 - decreased production of adenosine triphosphate
 - decreased sodium–potassium–adenosine triphosphatase activity
 - development of intramyelinic fluid-filled vacuoles, which increases intracerebral pressure and causes cerebral edema
 - increased pressure on neurons, which decreases neural conduction and causes paralysis and death
- The metabolite of bromethalin, desmethyl-bromethalin, is more potent as an uncoupler of oxidative phosphorylation than is the parent compound.

A single throw pack of bromethalin is 1.5 oz and contains 100 ppm bromethalin.

$$x \text{ mg bromethalin} = \left(\frac{28.375 \text{ mg}}{1 \text{ oz}} \right) (1.5 \text{ oz}) (100 \text{ ppm})$$

$$x \text{ mg bromethalin} = \left(\frac{28.375 \text{ mg}}{1 \text{ oz}} \right) (1.5 \text{ oz}) \left(\frac{100 \text{ mg}}{\text{kg}} \right)$$

$$x \text{ mg bromethalin} = \left(\frac{28.375 \text{ mg}}{1 \text{ oz}} \right) (1.5 \text{ oz}) \left(\frac{1 \text{ kg}}{1000 \text{ mg}} \right) \left(\frac{100 \text{ mg}}{\text{kg}} \right)$$

$$x \text{ mg bromethalin} = 4.26$$

A single pack could cause intoxication in a small dog or cat (< 6 pounds).

Figure 4–8 Risk of intoxication with bromethalin.

Diagnosis

- Clinical signs, especially cerebral edema and hindlimb paralysis
- History of possible exposure to bromethalin
- Chemical analysis of
 - vomitus or stomach contents
 - bait
 - kidney, liver, fat, and brain tissue at necropsy to ascertain exposure
- Histopathologic examination of brain
 - diffuse white matter spongiosis, which indicates intramyelinic vacuolation

Treatment

- No specific antidote
- Activated charcoal
 - repeated dosage may be necessary because of enterohepatic recycling of bromethalin
 - continue for several days
 - Emesis; used judiciously because emesis can induce a seizure in a poisoned animal
- Reduction of cerebral edema
 - osmotic diuretics (mannitol)
 - glucocorticoids
 - may be needed for several days
 - may not reverse the symptoms

References

- Dorman DC, Simon J, Harlin KA, et al. Diagnosis of bromethalin toxicosis in the dog. *J Vet Diagn Invest.* 1990;2:123–128.
- Dorman DC, Zachary JF, Buck WB. Neuropathologic findings of bromethalin toxicosis in the cat. *Vet Pathol.* 1992;29:139–144.

Bufo (Toad Poisoning)

Source

- *Bufo marinus*, a toad originally from Puerto Rico that was introduced to Hawaii and the southern United States

Species

- Dogs

Clinical Signs

- Salivation
- Tachypnea
- Emesis
- Diarrhea
- Cyanosis
- Convulsions

Toxicity

- Lethal oral dose used experimentally described as the total contents of both parotid glands from one toad
- 100 mg crude bufotoxin for a dog weighing 9–14 kg

Mechanism of Action

- The toxic principles are a mixture of substances from the parotid glands of the toad.
- Parotid glands from *Bufo* toads contain
 - bufotoxins, bufagins
cardiac glycosides
digitalis-like effect
ventricular fibrillation
 - bufotenines
oxytocic action
 - Other components:
epinephrine, cholesterol, ergosterol, and serotonin

Diagnosis

- History of biting or eating a toad
 - important because the clinical syndrome is not specific
 - several diseases and intoxications with similar manifestations
 - must consider this potential poison when examining a dog with these cardiac effects
- Excessive salivation
- Cardiac clinical signs

Treatment

- Decontamination
 - Wash mouth with copious amounts of running water.
- Antidotal therapy
 - no specific antidote
 - centered on preventing ventricular fibrillation
 - propranolol 5.0 mg/kg IV rapid bolus
repeat dose by same route in 20 minutes, if necessary
 - Anesthetize.
Administer pentobarbital.
Intubate.
 - Wash oral mucous membranes again.
 - Monitor electrocardiogram.
 - Provide supportive therapy with fluids.
- Use caution in using β -adrenergic blockers to treat older dogs with cardiac or respiratory disease.

References

- Otani A, Palumbo N, Read G. Pharmacodynamics and treatment of mammals poisoned by *Bufo marinus* toxin. *Am J Vet Res.* 1969;30:1865–1872.
- Palumbo NE, Perri S, Read G. Experimental induction and treatment of toad poisoning in the dog. *J Am Vet Med Assoc.* 1975; 167:1000–1005.

Cantharidin Intoxication (Blister Beetle Poisoning)

General

- The chemical structure is shown in Figure 4–9.
- Toxicosis occurs when horses ingest alfalfa hay contaminated with blister beetles.
- Beetles concentrate in alfalfa fields during blooming to feed on pollen and plant nectar.
- Swarms of beetles numbering in the thousands occur at mating.
- Beetles are caught in the hay because of the single-pass method of hay preservation—cut, crimp, and swath at the same time.

Source

- Beetles are from the family Meloidae. Blister beetles (*Epicauta* spp.) range from the southwestern United States to the East Coast.
- Cantharidin is believed to protect insects from predation; it is present in hemolymph and gonads of the beetles.
- The cantharidin content of the beetles ranges from 1% to 5% of dry weight.
- Male beetles have the highest concentration of cantharidin and transfer toxin to females during copulation.

Species

- More common in horses
- Ruminants occasionally poisoned

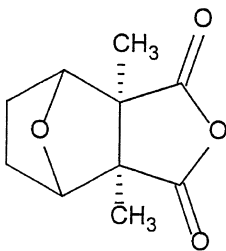


Figure 4–9 Chemical structure of cantharidin.

Clinical Signs

- Shock and death
- Oral ulceration
- Colic
- Tachypnea and tachycardia
- Anorexia
- Sweating
- Soft stools
- Dysuria
- Synchronous diaphragmatic flutter

CLINICAL PATHOLOGY

- Hypocalcemia
- Hypomagnesemia
- Hypoproteinemia
- Hematuria
- Elevated packed cell volume
- Hyposthenuria (urine specific gravity, 1.003–1.006)
- Increased creatine kinase concentration

NECROPSY AND HISTOPATHOLOGIC FINDINGS

- Acantholysis of the gastrointestinal tract (esophagus and nonglandular portion of stomach) and urinary bladder
- Gastritis and enterocolitis characterized by mucosal hyperemia, hemorrhage, ulceration, and edema
- Hemorrhagic and ulcerative cystitis

Toxicity

- Toxicity caused by dried beetles varies because of varying concentrations of cantharidin in beetles.
- As little as 4–6 g of dried beetles can be fatal.
- Minimal lethal dose for horses is less than 1 mg cantharidin per kilogram body weight.
- In experiments, 450–720 µg/kg orally caused clinical signs and death in horses.

Mechanism of Action

- Cantharidin, a bicyclic terpenoid, is rapidly absorbed from the gastrointestinal tract and excreted in urine.
- Cantharidin is a vesicant and a mucosal irritant that can cause ulcers of the mouth and urinary bladder that result in colic in horses.
- Phosphatase 2A is inhibited.
 - Phosphatase 2A is involved in:
 - control of cell proliferation
 - activity of membrane-associated channels and receptors
 - modulation of protein kinases
 - modulation of phosphatases
- The mechanism of hypocalcemia is not known but is thought to be responsible for synchronous diaphragmatic flutter.

Diagnosis

- History of alfalfa hay consumption
- Visual inspection of hay for beetles
- Clinical signs
- Gross and microscopic lesions
- Chemical analysis for cantharidin
 - High-pressure liquid chromatography and gas chromatography–mass spectrometry
 - Call diagnostic laboratory for possibility of analysis—tests are uncommonly performed and not available at all laboratories.
 - Stomach contents, urine, or serum

Treatment

- No specific antidote
- Removal of alfalfa or suspect feed
- Gastrointestinal decontamination: activated charcoal, mineral oil
- Symptomatic therapy
 - fluid therapy for dehydration and diuresis
 - analgesics

- broad-spectrum antibiotics
- calcium replacement (if warranted)

References

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- Schmitz DG. Cantharidin toxicosis in horses. *J Vet Intern Med*. 1989;3:208–215.

Carbon Monoxide

- See *Noxious Gases*.

Cardiac Glycosides (Digitalis Intoxication)

General

- Intoxication by the cardiac glycosides can occur after exposure to several plants, toads (see *Bufo Poisoning*), or therapeutic agents.
- Digitalis is a mixture of active ingredients from the dried leaves of *Digitalis purpurea*.
- These agents have traditionally been associated with cardiovascular signs; however, some species of *Asclepias* can produce neurotoxicosis.

Sources

- *Bufo* toads
- Digitalis
- Digoxin
- Foxglove (*Digitalis* spp.)
- Lily of the valley (*Convallaria majalis*)
- Milkweeds (*Asclepias* spp.)
- Oleander (*Nerium oleander*)
- *Rhododendron* spp.

Species

- All species susceptible
- Cats more sensitive than dogs
- Livestock poisoned after consumption of range plants

Clinical Signs

GENERAL

- Weakness

GASTROINTESTINAL

- Nausea
- Vomiting
- Diarrhea
- Decreased body weight

CARDIOVASCULAR

- Decreased heart rate (sinus bradycardia)
- Second- and third-degree heart block
- Ventricular tachycardia

CLINICAL PATHOLOGY

- Elevated serum potassium concentration

TOXICITY

- Due to the differences in concentration of toxic principle, the toxic dose is variable.
- Most animals consume the plants when forage is scarce.

Mechanism of Action

- Cardiac glycosides inhibit sodium–potassium–adenosine triphosphatase pump of cell membranes of excitable tissues.
 - elevated extracellular potassium concentration
 - elevated intracellular sodium triggered by sodium for calcium exchange at the cell membrane
 - increased intracellular calcium concentration

other resins in the sap (e.g., galitoxin) may contribute to intoxication

Diagnosis

- History of exposure to plant or drugs
- Clinical signs
- Chemical confirmation or serum digoxin concentration
 - rarely performed in veterinary medicine
 - not beneficial in the treatment of an animal with clinical signs

Treatment

GASTROINTESTINAL DECONTAMINATION

- Activated charcoal
 - repeated dosing to prevent enterohepatic recycling
- Cathartic
- Emesis after recent ingestion (dogs and cats)
 - Animal may have vomited the material.

SUPPORTIVE AND SYMPTOMATIC THERAPY

- Monitor cardiac function by means of electrocardiogram for small animals.
- Manage bradycardia with atropine.
- Correct hyperkalemia.
 - sodium bicarbonate
 - glucose and insulin
 - increase amount of potassium entering into cells
 - possibly monitor serum potassium concentration
- Management of arrhythmias
 - lidocaine
 - phenytoin
- Oxygen therapy

FOR LARGE ANIMALS

- Treatment may not be practical.
 - sudden death

- expense of therapy
- Remove from the source of toxin (pasture).
- Provide alternative feed sources.

References

- Hamlin RL. Clinical toxicology of cardiovascular drugs. *Vet Clin North Am Small Anim Pract.* 1990;20:469–481.
- Maixent JM, Charlemagne D, de la Chapelle B, et al. Two Na,K-ATPase isoenzymes in canine cardiac myocytes: molecular basis of inotropic and toxic effects of digitalis. *J Biol Chem.* 1987; 262:6842–6848.
- Moxley RA, Schneider NR, Steinegger DH, et al. Apparent toxicosis associated with lily-of-the-valley (*Convallaria majalis*) ingestion in a dog. *J Am Vet Med Assoc.* 1989;195:485–487.
- Rosen MR. Cellular electrophysiology of digitalis toxicity. *J Am Coll Cardiol.* 1985;5:22A–34A.

Chocolate Poisoning (Theobromine)

General

- The chemical structures of caffeine and theobromine are shown in Figures 4–10 and 4–11.
- Chocolate intoxication is more common in dogs, perhaps because they have a taste preference or indiscriminate eating habits.
- Although this can be a problem at any time, risk of poisoning increases during holidays associated with candy—Halloween, Easter, Christmas.
- Diarrhea is a common problem after dogs eat chocolate.
- Dogs do not seem to dislike the bitter taste of unsweetened chocolate.

Source

- Theobromine (3,7-dimethylxanthine)
 - Present in chocolate, cocoa, soft drinks, and tea
- Theobromine, caffeine, and theophylline are all naturally occurring molecules (the methylxanthines) found in plants, foods, beverages, and several human and veterinary medications.

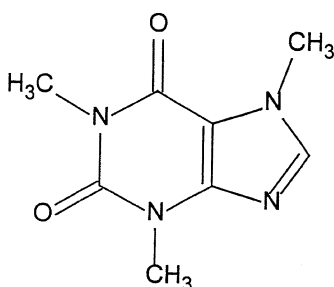


Figure 4-10 Chemical structure of caffeine.

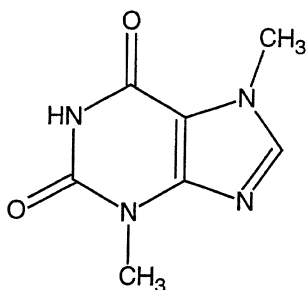


Figure 4-11 Chemical structure of theobromine.

- Theobromine is obtained from the plant *Theobroma cacao* and does not grow naturally within the United States.
- Theobromine is present in chocolate, cocoa beans, cocoa bean hulls, cola, and tea.
- Milk chocolate used in candy is obtained from seeds of *Theobroma cacao* after fermentation and roasting.

Species

- Dogs most often, but there are reports of intoxication in cattle and horses caused by consumption of cocoa bedding materials.

Clinical Signs

- Vomiting
- Diarrhea
- Increased urination

- Tachycardia
- Arrhythmia
- Restlessness
- Ataxia
- Seizures

Toxicity

- Lethal range for dogs: 100–250 mg/kg
- LD50 of caffeine and theobromine in dogs and cats: 100–200 mg/kg
- LD50 for theophylline: 300 mg/kg (dogs) and 700 mg/kg (cats)
- Serious illness can occur at lower doses depending on the age, physiologic condition, and concurrent treatment of the animal.
- Concentration of theobromine in various products:
 - white chocolate: 0.25 mg per 28 g (1 ounce)
 - unsweetened (baking) chocolate: 390–450 mg per 28 g
 - milk chocolate: 44–60 mg per 28 g
 - hot chocolate mix: 13 mg theobromine per 28 g
 - cocoa meal: 300–900 mg per 28 g
 - cocoa hulls: 300–1200 mg per 28 g
- Relative risk
 - The following amounts of the following substances may cause problems:
 - 7 g (0.25 oz) baking chocolate per kilogram body weight
 - 56 g (2 oz) of milk chocolate per kilogram body weight
 - 11.2 kg (400 oz) of white chocolate per kilogram body weight

Mechanism of Action

- Stimulation of the central nervous system and cardiac muscle
- Inhibition of cyclic adenosine monophosphate
 - increase in intracellular calcium
 - decrease in sequestration of calcium
- Increased contractility of cardiac muscle

Diagnosis

- Clinical signs
- History of exposure to chocolate or cocoa products

Treatment

- No specific antidote for theobromine intoxication
- Gastrointestinal decontamination
 - emesis and possible gastric lavage to treat a small dog
 - activated charcoal
 - cathartic agent
- Symptomatic and supportive therapy
 - respiratory
 - cardiovascular
 - control arrhythmias
 - correct acid-base disturbances
 - correct electrolyte abnormalities
 - central nervous system
 - diazepam for excitation or seizures

References

- Glauber A, Blumenthal PH. Chocolate poisoning in the dog. *J Am Anim Hosp Assoc*. 1983;19:246–248.
- Owens JG, Dorman DC. Drug poisoning in small animals. *Vet Med*. 1997;92:149–156.
- Tarka SM Jr. The toxicology of cocoa and methylxanthines: a review of the literature. *Crit Rev Toxicol*. 1982;9:275–312.

Cholecalciferol

General

- The chemical structure of cholecalciferol is shown in Figure 4–12.
- Cholecalciferol-containing rodenticides are used to control mice and rats.

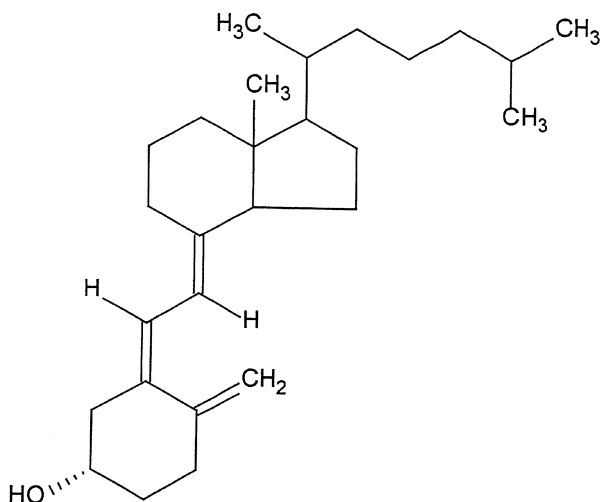


Figure 4-12 Chemical structure of cholecalciferol.

- Rodents usually die within 2 days after ingestion and do not appear to show bait shyness.
- Intoxication with these types of rodenticides is more common in dogs because of their indiscriminate eating habits.
 - Young male cats seem to share this predilection.
- Cholecalciferol-containing rodenticides increase absorption and serum concentration of calcium and phosphorus.

Source

CHOLECALCIFEROL

- More common trade names of cholecalciferol-containing rodenticides:
 - Quintox
 - Rampage
 - Ortho Mouse-B-Gone
 - Ortho Rat-B-Gone

VITAMIN D-CONTAINING MULTIVITAMINS

- Feed-grade or dietary sources of vitamin D

- added to the rations of food-producing animals
- given to dairy cattle to reduce the incidence of postparturient hypocalcemia (milk fever)

CALCINOGENIC PLANTS

- See *Differential Diagnosis*.

Toxicity

GENERAL

- 1 IU vitamin D is equivalent to 25 nanogram cholecalciferol
- One throw-pack of rodenticide (30 g) is formulated with 0.075% cholecalciferol as the active ingredient.
- This pack represents 900,000 IU of cholecalciferol, or 10,000 times the daily requirement for the dog.

DOGS

- Toxic doses after ingesting bait products range from 0.5 mg/kg to 20 mg/kg.
- Death has been reported after ingestion of 4.5 mg/kg.
- The oral LD50 of the technical material is 88 mg/kg.

CATS

- Reported to be more susceptible to cholecalciferol than are dogs.

SWINE

- Poisoned after 48 hours of consumption of a diet containing 473,000 IU/kg (11.8 mg/kg or 11.8 ppm) vitamin D.

HORSES

- Two horses receiving 12,000–13,000 IU/kg per day cholecalciferol for 30 days developed signs of intoxication.

Clinical Signs

- Signs usually appear within 12–36 hours after ingestion.
 - initially: anorexia, depression, vomiting, muscle weakness, and constipation
 - later: hypertension, polyuria, and polydipsia
 - pain elicited during renal palpation

- mineralization of cardiac and renal tissues and eventual organ failure
- Signs are not specific for cholecalciferol intoxication but occur with other causes of elevated serum calcium (e.g., neoplasia).
- Clinical pathology
 - elevated serum calcium concentration: greater than 11 mg/dL for an adult animal
Hypercalcemia (12.0 to 18.3 mg/dL) has occurred in cats after consumption of cholecalciferol.
 - elevation in serum phosphorus concentration before elevation in serum calcium concentration
 - Other alterations include azotemia, hyperproteinemia, proteinuria, glycosuria, and urine specific gravity of 1.002–1.006.
 - elevated serum 25-hydroxy and 1,25-dihydroxy cholecalciferol concentrations
 - elevated serum calcium, which can cause cardiac arrhythmia

Mechanism of Action

CHOLECALCIFEROL INCREASES SERUM CALCIUM CONCENTRATION

- Increasing gastrointestinal absorption of phosphorus and calcium
- Increasing osteoclastic resorption
- Increasing distal renal tubular reabsorption of calcium

NORMAL FUNCTION OF VITAMIN D

- After exposure to sunlight epidermal cells produce cholecalciferol (vitamin D₃)
- Cholecalciferol is bound to a serum vitamin D-binding protein and transported to the liver.
- Cholecalciferol is enzymatically converted to 25-OH-D₃, which is transported to the kidneys.
- 25-OH-D₃ is enzymatically converted to 1,25-dihydroxy-D₃, the active form of vitamin D.
- 1,25-Dihydroxy-D₃ acts on the small intestine to increase the transport of calcium and phosphorus from the lumen of the gastrointestinal tract into intestinal cells.

- 1,25-Dihydroxy-D₃ also stimulates osteoclastic proliferation and resorption of bone.
- 1,25-Dihydroxy-D₃ acts on the cells of the renal distal tubular cells and increases calcium reabsorption.

Diagnosis

- History of exposure to cholecalciferol and clinical signs
- Elevated serum calcium or phosphorus concentration
- Calcification of tissues as evidenced at ultrasonography or radiography.
- In later stages, as calcification of tissues occurs, pain on palpation of the kidneys
- Elevated serum concentration of 25-hydroxy or 1,25-dihydroxy cholecalciferol

Differential Diagnosis of Elevation in Serum Calcium Concentration

- Ingestion of calcinogenic plants
 - *Solanum malacoxalon*
 - *Solanum torvum*
 - *Cestrum diurnum*
 - *Trisetum flavescens*
- Overdose of vitamin D supplements
- Neoplastic hypercalcemia, especially lymphoma
- Overdose of calcipotriol (antipsoriasis vitamin D analogue)
- Pseudohyperparathyroidism
- Primary hyperparathyroidism

Treatment

GASTROINTESTINAL DECONTAMINATION

- Emesis followed by administration of activated charcoal and cathartic
- Of greatest benefit less than 4 hours after ingestion

REDUCTION OF SERUM CALCIUM CONCENTRATIONS IN AN ANIMAL WITH CLINICAL SIGNS

- Measure baseline serum calcium and subsequent calcium concentrations to monitor the effectiveness of therapy.
- Initiate fluid therapy with normal saline solution 0.9% NaCl IV.
- Administer concurrent furosemide diuretic therapy.
- Administer glucocorticoid to increase urine calcium elimination.
- Administer calcitonin (salmon calcitonin).
 - reduces calcium absorption from the gastrointestinal tract
- Provide low-calcium diet.
- Minimize exposure to sunlight to reduce production of activated vitamin D.
- Continue therapy until serum calcium concentrations return to and stay within normal limits for 72 hours after discontinuation of drugs.

SYMPTOMATIC TREATMENT

- Address organ dysfunction.
 - renal: increased blood urea nitrogen concentration
 - cardiac: possible arrhythmias

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Coal Tar

- See *Phenolics and Coal Tars*.

Cocklebur (*Xanthium strumarium*)

Source

- *Xanthium strumarium*, the cocklebur, grows throughout the United States.
- The dicotyledon stage (two leaves) has the greatest potential for intoxication.
- Animals have been poisoned by eating the burs, especially in hay.
- The plant is an annual that grows in sandy soil that commonly floods, as on riverbanks.
- Other species of *Xanthium* also can cause disease.

Species

- Cattle, sheep, and swine primarily

Clinical Signs

- Clinical presentation of severe hypoglycemia
- Sudden death
- Hyperexcitability

- Anorexia
- Incoordination and ataxia
- Coma
- Convulsions
- Gross lesions
 - ascites
 - edema of the gallbladder
 - gastrointestinal congestion
 - firm, pale liver with a mottled hemorrhagic pattern on cut surface
- Histopathologic lesions
 - marked centrolobular hepatic necrosis
 - gastroenteritis
 - renal tubular necrosis

Toxicity

- Cattle: 1.8% of body weight
- Swine: 2% of body weight
- Sheep: >2.0% of body weight

Mechanism of Action

- Carboxyatractyloside is the toxic principle.
 - diterpene glycoside
 - inhibits carrier-mediated exchange of adenosine diphosphate and adenosine triphosphate across the mitochondrial membranes

Diagnosis

- Evidence of animals grazing the dicotyledons
- Dicotyledons or burs in the ruminal and stomach contents
- Clinical signs
- Gross necropsy findings
- Histopathologic findings
- Chemical analysis of rumen and stomach content for carboxyatractyloside

Treatment

- Removal from source of plants
- Symptomatic therapy
 - fluids
 - glucose
 - seizure control

References

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Copper

General

- Copper and molybdenum are intimately related.
- Chronic copper toxicosis has a component of molybdenum deficiency.
- Molybdenum intoxication manifests as a copper deficiency.
- See *Molybdenum (Teart Scours, Peat Scours)*.
- There is an interaction between sulfur and copper and molybdenum.

Source

- Copper-containing fungicides and algicides (copper sulfate)
- Anthelmintics
- Dietary supplementation
 - calculation errors
 - sheep fed rations formulated for cattle

- Contamination from mining operations
- Poultry litter

Species

- Sheep most sensitive, goats more resistant, cattle, swine
- Poultry relatively resistant
 - Poultry rations can contain high concentrations of copper.
- Copper intoxication in dogs usually related to breed disposition to copper storage disease (Bedlington terriers)

Clinical Signs

- Syndromes due to hemolytic crisis

CHRONIC TOXICOSIS

- Weakness
- Pale mucous membranes
- Anorexia
- Hemoglobinuria, hemoglobinemia
- Icterus

ACUTE TOXICOSIS

- Signs of chronic syndrome
- Gastrointestinal pain
- Nausea, vomiting
- Colic
- Diarrhea
- Shock

GROSS AND HISTOPATHOLOGIC FINDINGS

- Enlarged, gun metal-colored (bluish-black) kidneys
- Red-colored urine (from hemoglobin)
- Icterus
- Distention of gallbladder
- Cytoplasmic vacuolation of hepatocytes
- Hepatic necrosis

- Renal tubular necrosis
- Hemoglobin within renal tubules

Toxicity

ACUTE TOXICITY

- Sheep: 20–50 mg/kg
- Adult cattle: 200–800 mg/kg
- Calves: 40–100 mg/kg

CHRONIC TOXICITY

- Sheep: 1.5 g per ewe per day

COPPER AND MOLYBDENUM

- 6:1 to 10:1 copper to molybdenum ratio ideal for cattle

COMPLICATIONS

- Minerals and micronutrients in addition to molybdenum
 - High dietary or water concentrations of sulfur, zinc, or iron can reduce the toxicity of copper by decreasing absorption or increasing excretion.
- Stress, such as transportation or shows, can precipitate acute onset of clinical signs of chronic intoxication in sheep.
- Ingestion of hepatotoxic plants, those containing pyrrolizidine alkaloids, can potentiate copper toxicosis.

Mechanism of Action

NORMAL COPPER MOVEMENT IN MAMMALIAN CELLS

- Copper is absorbed from the gastrointestinal tract.
 - Most mammals absorb copper from the small intestine.
 - Sheep also absorb copper from the large intestine.
 - Younger animals absorb more copper than do older animals.
- Copper is bound to a serum protein—albumin or transcuprin.
- Most absorbed copper is initially transported to the liver and kidneys.
- Divalent copper (Cu^{2+}) is reduced to monovalent copper (Cu^+) with glutathione.

- Cu^+ is partitioned into the following intracellular compartments:
 copper-containing enzymes: superoxide dismutase, cytochrome *c* oxidase, lysyl oxidase, dopamine monoxidase, and others
 copper-requiring proteins: ceruloplasmin
 secreted into the bile
 for most species, more copper results in greater biliary excretion
 copper–adenosine triphosphatase (ATPase) pumps or secretion
 of copper-containing vesicles
 sheep have decreased excretory function than other species
 sequestered (see later)
- Cu^+ is incorporated into ceruloplasmin
 Ceruloplasmin is the main transporting protein for copper.
 Ceruloplasmin is secreted into the systemic circulation.
- Copper transported through ceruloplasmin is available to all cells.
- Copper is transported into many cells by means of copper-ATPase pumps.

PATHOGENIC ACCUMULATION OF COPPER

- The foregoing processes are not abnormal; the degree to which they occur, especially in sheep, is abnormal.
- Metallothionein
 - Cu^+ is incorporated into metallothionein in cytosol.
 - Cu^+ induces upregulation and synthesis of metallothionein.
 sequestration
 - Cu^+ is pumped with copper-ATPase into various organelles.
 mitochondria
 Golgi apparatus
 lysosomes—extensive proliferation of lysosomes can occur
 nucleus
 Kupffer's cells
 accumulated copper visualized microscopically with specialized stains
- pumped for storage regulation of intracellular concentrations and possibly future excretion

- accumulation of copper occurs at the expense of other hepatic functions
 - increased release of liver-specific enzymes
 - not correlated with elevated serum copper concentration
- The liver attains the maximal accumulation of copper and releases it.
 - trigger can be stress, such as shipping
 - dramatically increased serum copper concentrations
 - induction of a hemolytic crisis

Diagnosis

- Clinical signs
- Clinical pathology
 - increased serum bilirubin concentration
 - hemoglobinemia
 - hemoglobinuria
 - Increased serum concentration of liver enzymes (lactate dehydrogenase, aspartate aminotransferase, sorbitol dehydrogenase)
 - can be used to predict animals at greatest risk.
- Necropsy and histopathologic findings
- Copper analysis by means of atomic absorption
 - liver: >150 ppm wet weight
 - kidney: >15 ppm
 - serum: >0.7–1.3 ppm
 - serum concentration not useful before onset of clinical signs
 - rapid increase in serum concentration 1–3 days before hemolytic crisis
 - feed: >25 ppm copper and little or no molybdenum
 - feces, especially in acute intoxication

Treatment

- Low morbidity, high mortality.

SYMPTOMATIC THERAPY

- Fluids

CHELATION THERAPY

- Dogs
 - D-penicillamine
 - ascorbic acid increases copper excretion
- Chelation too expensive for treating a flock of sheep

PREVENTION

- Administer ammonium or sodium molybdate 50 to 500 mg/kg per day in feed.
- Maintain 6:1 copper to molybdenum ratio in sheep rations.

References

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Corrosives

General

- Corrosive agents are common in the house.

Source

ACIDS

- Hydrochloric acid
 - bleach, toilet bowl cleaner (e.g., Lysol, Sno Bol), drain cleaner

- Sulfuric acid
 - drain cleaner (e.g., Drano, Mister Plumber), automobile batteries
- Acetic acid
 - permanent wave neutralizers, photographic stop bath, disinfectants
- Oxalic acid
 - tanning compounds (e.g., for taxidermy), disinfectants, household bleach, antirust polish
- Phosphoric acid
 - metal cleaner, toilet bowl cleaner, rustproofing agents, disinfectants
- Sodium bisulfite
 - swimming pool cleaner, toilet bowl cleaner (e.g., Sani-Flush)

ALKALIS

- Sodium or calcium hypochlorite
 - bleach (e.g., Clorox, Purex)
- Sodium or potassium hydroxide
 - lye, oven cleaner
- Calcium hydroxide
 - lime
- Ammonia (>5%)
 - window cleaner, floor cleaner
- Calcium oxide
 - unslaked lime

Species

- Dogs and cats primarily

Clinical Signs**ORAL EXPOSURE**

- Salivation
- Nausea, vomiting, retching
- Respiratory distress

- Ulcerations of oral mucosa

OCULAR EXPOSURE

- Blepharospasm
- Lacrimation
- Ocular pain

DERMAL EXPOSURE

- Chemical burn
- Erosion or sloughing of epithelium

Mechanism of Action

ACID INJURY

- Acid comes into contact with water (mucosa)
- Acid releases hydronium (H^+) ions
 - desiccation of surface proteins
 - coagulative necrosis with eschar formation
- Coagulation and eschar are thought to limit the extent of injury.

ALKALI INJURY

- After exposure to alkali
 - liquefactive necrosis
 - saponification of cell membrane fatty acids
 - loss of membrane integrity
- Continued action of alkali on cell membranes
 - continued damage
- Longer duration of exposure and stronger alkali solutions
 - increased risk of full-thickness burns and ulceration
 - esophageal rupture
 - corneal sloughing

COMBINATION OF CLEANING PRODUCTS

- Increased risk of intoxication
- Bleach plus acid produces chlorine gas
- Bleach plus ammonia produces chloramine gas

Diagnosis

- History of exposure
- Clinical signs

Treatment

DECONTAMINATION

- Oral exposure
 - Dilute with small amounts of milk or water.
 - Do not attempt neutralization.
highly exergonic reactions
further damage to esophagus
 - Do not induce emesis.
esophagus weakened
 - Do not administer activated charcoal.
- Ocular exposure
 - Flush eye with saline solution.
minimum of 20 minutes
direct stream into folds of conjunctiva
 - Perform ophthalmic examination.
determine degree of corneal damage
- Dermal exposure
 - Flush skin with saline solution to dilute the agent.
minimum of 20 minutes

SYMPTOMATIC AND SUPPORTIVE THERAPY

- Withhold food and water by mouth.
- Administer antibiotics.
- Manage dermal exposure as a burn.

Reference

Kore AM, Kiesche-Nesselrodt A. Toxicology of household cleaning products and disinfectants. *Vet Clin North Am Small Anim Pract.* 1990;20(2):525–537.

Cyanide

General

- Cultivated plants become toxic after rapid growth following stress, such as heat, a dry period, cold weather, or physical trauma.
- Young, actively growing plants pose the greatest risk.
- Risk of intoxication increases with nitrogen fertilization.

Source

- Plants that contain cyanide
 - in leaves, flowers, or seeds
 - bound as complex glycoside
- Small animals rarely are intoxicated with cyanide containing-pesticides; a more common source is smoke inhalation during a house fire.

CYANOGENIC PLANTS

- Common ornamental plants
 - apple (*Malus* spp.)
 - cherry, plum, peach (*Prunus* spp.)
 - photina, red leaf (*Photina* spp.)
 - heavenly bamboo, nandina (*Nandina* spp.)
 - elderberry (*Sambucus* spp.)
 - mountain mahogany (*Cercocarpus* spp.)
- Common cultivated or pasture plants
 - clover (*Trifolium* spp.)
 - corn, maize (*Zea mays*)
 - sudan, sorghum, Johnson grass, Columbus grass (*Sorghum* spp.)
 - trefoil (*Lotus* spp.)
 - manna grass (*Glyceria* spp.)

Species

- Cattle, sheep, and horses predominantly

Clinical Signs

- Rapid onset, within 30 minutes of ingestion
- Polypnea
- Weakness
- Trembling
- Recumbency
- Dyspnea
- Multiple attempts to urinate
- Apnea and bradycardia
- Terminal convulsions
- If animal survives the first hour, prognosis for recovery improves.

Mechanism of Action

- Toxic principles, depending on the plant, are cyanogenic glycosides (Figure 4–13).
 - amygdalin, dhurrin, prunasin
- Within the plant, the glycoside and β -glycosidase enzymes are partitioned.
 - Physical damage to the leaf breaks down this barrier and allows the cyanogenic glycoside and β -glycosidase to interact.
 - The glycosidase cleaves the sugar moiety from the cyanogenic glycoside and liberates hydrogen cyanide.
 - This can occur during mastication or in the rumen, which is a favorable environment for hydrolysis of the glycoside.
- The cyanide is absorbed and enters the systemic circulation.
- Cyanide interacts with the ferric (Fe^{3+}) ion of cytochrome oxidase.
 - This creates a stable complex.

Diagnosis

- Access to cyanogenic plants
- Clinical signs
- Response to therapy
- Chemical analysis for cyanide

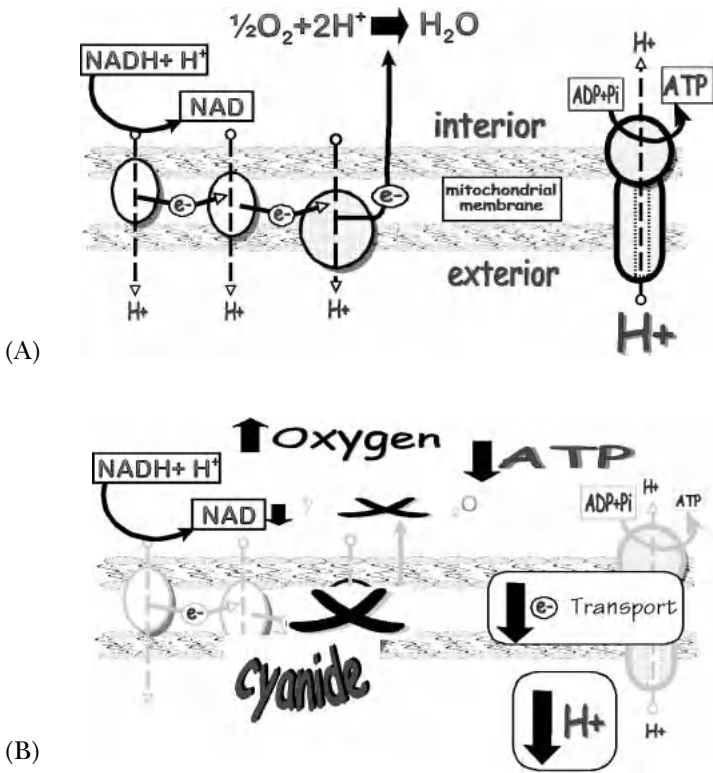


Figure 4-13 Mechanism of action of cyanide at the mitochondria. (A) Normally functioning mitochondria in which the production of an electron gradient across the inner mitochondrial membrane serves as the force to produce adenosine triphosphate (ATP) through proton-driven ATPase. (B) When cyanide enters a cell, it inhibits membrane-bound cytochromes, which prevents the flow of electrons, use of oxygen in oxidative phosphorylation, and ultimately production of ATP.

- Procedure is difficult and tedious.
- Hydrogen cyanide is volatile and often produces false-negative results.
- Suspect feed, ruminal contents, tissues can be collected.
Keep cold in airtight container.
A pH >10.0 may be needed to prevent loss of cyanide.

Picrate Test

- Picrate test can be done in the field to determine the risk potential of a suspect forage.
- Most diagnostic laboratories can rapidly and economically analyze forage samples for cyanide and provide quantitative or semiquantitative values for the veterinarian.

Treatment

- Disease often progresses too rapidly for therapeutic intervention.

SODIUM THIOSULFATE

- Dose
 - cattle: 0.5 g/kg body weight IV
Use a 30%–40% (weight/volume) solution.
Give rapidly using a 12–14 gauge needle.
 - horses: 30–40 mg/kg body weight IV
Use a 20% solution.
Pretreat with 16 mg/kg sodium nitrite IV.
Use as a source of exogenous sulfur.
- Sodium thiosulfate increases the detoxification of cyanide by rhodanese.
Rhodanese is thiosulfate cyanide sulfurtransferase.
It converts cyanide to nontoxic thiocyanate.
- Thiocyanate is excreted in the urine.

SODIUM NITRITE

- Sodium nitrite can be used to induce methemoglobinemia.
- Cyanide has greater affinity for methemoglobin iron than for cytochrome oxidase.
- Cyanomethemoglobinemia is generated.
- Thiosulfate can be used to detoxify the cyanide.
- In cattle there is no benefit to using sodium nitrite over sodium thiosulfate alone.
- Use of sodium nitrite poses the following risks:

- induced methemoglobinemia
- incorrect diagnosis (animal has nitrate poisoning, giving sodium nitrite will produce a more severe disease)

PREVENTION

- Observe animals closely for the first hour after introduction to a sorghum or sudan grass pasture with actively growing plants.
- When it is several feet high, forage becomes less a hazard.
- Submit representative forage samples to diagnostic laboratory for cyanide testing before placing animals in the pasture

Forage Cyanide Interpretation and Recommendations

Cyanide in forage (ppm)	Interpretation
0–500	Very low to minimal risk of intoxication
500–750	Moderate risk of intoxication
750–1000	Marked risk of intoxication
>1000	Do not allow animals to consume forage

References

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Death Camas (*Zigadenus* spp.)

General

- Several species in the genus *Zigadenus* can cause intoxication.

- All portions of these onion-like perennials are toxic, although they are considered unpalatable. Intoxication usually occurs in the spring when no other forage is available.
- These plants can produce a solid stand in a field or pasture.

Source

- Nuttall's camas (*Z. nuttallii*)—Southern Great Plains eastward to Tennessee
- Death camas (*Z. venenosus*)—western United States
- White camas (*Z. elegans*)—western United States
- Northern camas (*Z. glaucus*)—northeast United States
- Southern camas (*Z. glaberrimus*)—southeastern United States
- Black camas or crow poison (*Z. densus*)—southeastern coastal areas

Species

- Sheep (more commonly), cattle, and horses

Clinical Signs

- Sudden death
- Hypersalivation
- Vomiting
- Muscle weakness
- Incoordination
- Tremors
- Dyspnea
- Cyanosis
- Bradycardia early, then tachycardia

Toxicity

- Sheep: consumption of 0.2% of body weight in plant material can induce clinical signs.

Mechanism of Action

- Toxic principle is veratrum-type alkaloids.

- The toxic principle acts on the sodium channel.
- The veratrum-type alkaloids increase sodium conductance in excitable tissues.
- This causes increased repetitive firing from minor stimuli.
- Vagal afferent fibers and their endings are sensitive to the alkaloid.
 - increased afferent input
 - vasodilatation
 - hypotension and bradycardia
- Areas of respiratory and vomiting center afferent fibers are stimulated.
 - increased afferent input to these areas
 - respiratory depression caused by pulmonary stretch receptors
 - vomiting

Diagnosis

- Clinical signs
- Identification of the plant or evidence of grazing in the pasture

Treatment

- Symptomatic
- Atropine for relief of cardiovascular signs
- Sympathomimetic agents to help reverse hypotension

References

Heilpern KL. *Zigadenus* poisoning. *Ann Emerg Med.* 1995;25:259–262.
Panter KE, Ralphs MH, Smart RA, et al. Death camas poisoning in sheep: a case report. *Vet Hum Toxicol.* 1987;29:45–48.

Ethylene Glycol

Source

- Automobile antifreeze, rust remover

Species

- Dogs, cats most often

Clinical Signs

- Three clinical stages of ethylene glycol intoxication

CENTRAL NERVOUS SYSTEM

- 1–2 hours after ingestion
- Polyuria, polydipsia in some cases
- Depression
- Stupor
- Ataxia

CARDIOVASCULAR, PULMONARY

- 12–24 hours after ingestion
- Tachycardia or bradycardia
- Tachypnea

RENAL

- 12–72 hours after ingestion
- Oliguric acute renal failure
- Polyuria
- Crystalluria
- Dehydration
- Vomiting

Toxicity

- Cats: 2–4 mL/kg undiluted antifreeze
- Dogs: 4–5 mL/kg undiluted antifreeze

Mechanism of Action

- Rapidly absorbed from the gastrointestinal tract
- Crosses the blood-brain barrier
 - central nervous system depression
- Excreted in urine to a large extent
- Metabolized in liver by alcohol dehydrogenase
 - glycoaldehyde
 - glycolic acid

- glyoxylic acid
- oxalic acid
- Acidic metabolites of ethylene glycol
 - cause metabolic acidosis
 - Glycolic acid is a major contributor to acidosis.
 - Metabolites can inhibit enzymes of the tricarboxylic acid cycle.
- Calcium oxalate crystals
 - Oxalic acid binds to serum calcium.
 - Crystals are present in the microvasculature and renal tubules.

Diagnosis

- History of exposure
- Clinical signs
- Clinical pathology
 - increased anion gap (>25 mEq/L)
 - increased serum osmolality
 - metabolic acidosis
 - increased serum blood urea nitrogen concentration
 - crystalluria (oxalate, hippurate)
 - isothermia (urine specific gravity, 1.008–1.012)
- Chemical analysis of ethylene glycol
 - not performed at all laboratories
 - time to obtain results too long for the test to be of benefit
- Ultrasonography
 - helpful but not pathognomonic
 - increased echo signal from the kidney
 - halo sign—increased renal cortical echogenicity
 - signs associated with renal failure indicate poor prognosis

Treatment

- If animal has been observed ingesting ethylene glycol and has mild clinical signs
 - perform gastrointestinal decontamination with emetic, activated charcoal, cathartic (saline or sorbitol)

- When clinical signs are severe
 - administer fluid therapy to correct dehydration
 - provide specific antidotal therapy
 - prevent metabolism of ethylene glycol
 - inhibit alcohol dehydrogenase with ethanol or fomepizole
 - correct metabolic acidosis
 - sodium bicarbonate
- Provide ethanol or fomepizole therapy for 48–72 hours.
- Fomepizole is not effective, or approved, for cats.
- Monitor urinary pH; maintain pH between 7.0 and 7.5.

References

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Fescue (*Festuca Arundinacea*, Tall Fescue)

General

- Tall fescue is a commonly grown forage grass.
- Fescue has the following desirable factors:
 - overwinters
 - provides good yields
 - grown in a variety of soils and environmental conditions
- Tall fescue is grown mainly in the midwestern and southeastern parts of the United States.

Source

- Tall fescue infected with an endophyte *Neotyphodium coenophialum* (also called *Acremonium coenophialum*)
- Alkaloid mycotoxins ergovaline, ergosine, and ergonine (Figure 4–14), which are produced by the endophyte and are thought to be responsible for intoxication

Species

- Cattle and horses more commonly, but all herbivores susceptible

Clinical Signs

- Several syndromes are associated with fescue intoxication.
- Many signs overlap.
- Most horses have only the agalactia syndrome.

FESCUE FOOT

- Occurs most often in late fall and winter
- Reduced weight gain or loss of condition
- Rough hair coat
- Lameness
- Hyperemia and swelling of the coronary band
- Sloughing of the hoof or tail

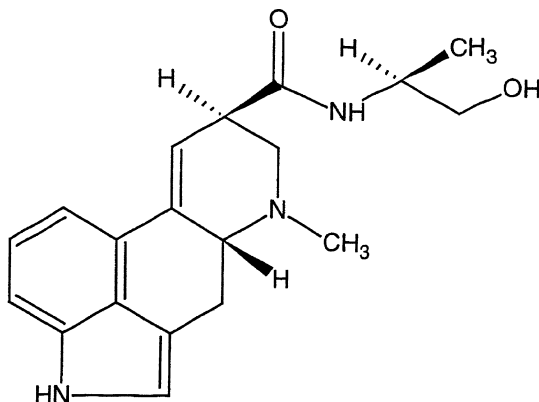


Figure 4–14 Chemical structure of ergonovine.

SUMMER SLUMP OR SUMMER SYNDROME

- Reduced performance during the heat of the summer
- Most common syndrome accounting for the greatest economic losses
- Elevated body temperature
- Increased respiratory rate
- Excessive salivation
- Seeking of shade or water
- Rough hair coat, reduced weight gain, reduced feed intake

FAT NECROSIS

- Hardened masses of fat within the abdominal cavity
- Elevated body temperature
- Rough hair coat

AGALACTIA

- More common in mares than cows
- Reduction of milk production
- Thickened placenta
- Weak foals

Mechanism of Action

AGALACTIA

- Mares and cows consuming infected fescue have marked decreases in serum prolactin concentration.
- Depressed prolactin concentration occurs within 3 or 4 days after feeding.

MECHANISMS OF INTOXICATION

- As the percentage of endophyte-infected fescue plants increases, consumption of the forage decreases.
- Ergot alkaloids have powerful vasoconstrictive effects.
 - possibly restricted blood flow to internal organs
- Restricted blood flow to peripheral tissue and thermal (cold) stress may cause local hypoxia and necrosis of the hoof and tip of tail.

- diminished blood flow to the skin during heat stress, reduced heat loss in cattle that consume endophyte-infected fescue
- Animals that ingest endophyte-infected fescue have greater response to endotoxin.
- Injection of prazosin, an α_1 -adrenergic antagonist, reduces body temperatures and increases weight gain in endophyte-fed, heat-stressed rats.

Diagnosis

- History of grazing on tall fescue
- Clinical signs
- Identification of endophyte-infected fescue
 - direct visualization with microscopic examination
 - enzyme-linked immunosorbent assay
 - high-pressure liquid chromatography of plant or rumen fluid
- History of the pasture; most producers are aware of this recurrent problem.

Treatment and Prevention

REPRODUCTIVE

- Do not allow pregnant mares access to tall fescue pastures after 300 days of gestation.
- Monitor mares near parturition to assist with delivery, if necessary.
- Supplement foals with milk replacement and ensure they receive adequate colostrum.
- Treat pregnant mares with dopamine antagonists (domperidone, sulpiride) to maintain serum prolactin concentration.

MANAGEMENT OF FESCUE PASTURE

- Maintain the plants in the vegetative state, rapidly growing.
- Mow or bale the pasture during the summer.
- Pasture susceptible animals only in the spring and fall.
- Plant legumes with fescue.
- Rotate animals frequently to areas of new growth.
- Reseed with endophyte-free seed—an expensive option.
- Treat with fungicide (sterol inhibitors)—expensive.

POSSIBLE FUTURE THERAPIES

- Domperidone (Equidone)
 - dopamine antagonist for agalactia in mares grazing on fescue
 - not yet commercially available
 - experimental license for use to treat mares before and after birth
 - mare treated 10 days before foaling
 - can be used to manage agalactia after foaling, the dose must be doubled
 - oral formulation
 - must contact Equi-Tox (864-646-6443; equitox@innova.net)
- Immunization against the alkaloids produced by the endophyte
- Several groups are examining this possibility.

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Fluoride Intoxication**General**

- Acute fluorosis in dogs is uncommon because of a reduction in use of fluoride-containing pesticides.

- Fluorosis is most common in herbivores as chronic intoxication.
- Fluorosis occurs in older animals (breeding beef cows and dairy cattle) more commonly than in younger animals.

Source

- Consumption of plants or soil contaminated with fluoride from industrial operations (smelter plants, fertilizer manufacturing)
- Rock phosphate contaminated with fluoride
- Water containing fluoride

Species

- All species susceptible
- Herbivores at greatest risk of chronic fluorosis
- Cattle and sheep affected more often than horses

Clinical Signs

- Enamel hypoplasia
- Mottled or stained teeth
- Excessive dental wear
- Lameness
- Exostosis of the diaphysis or metaphysis of weight-bearing bones

Toxicity

- The form is important to the availability of fluoride.
 - sodium fluoride—greatest fluoride absorption
 - rock phosphate—moderate absorption
 - dicalcium phosphate—lowest absorption

Mechanism of Action

- Fluoride is absorbed and alters production of the bony matrix.
- Fluoride has an affinity for calcium.
 - can replace the hydroxyl groups in the hydroxyapatite of bone
 - Low concentration increases bone density and strength.

- Higher concentration causes formation of weaker bones and teeth.

Diagnosis

- Clinical signs
- History of exposure
- Chemical analysis for fluoride
 - urinary concentration
 - >15 ppm indicates possible intoxication
 - bone (mandible) concentration compatible with poisoning
 - >6000 ppm (cattle)
 - >11,000 ppm (sheep)
 - complete ration should be
 - <30 ppm (cattle)
 - <60 ppm (sheep)
 - on a dry matter basis
 - water should contain <5 ppm fluoride

Treatment

- No specific therapy for chronic fluorosis.
- In areas with elevated fluoride water content, diet should be low in fluoride.
- Supplementation with sources of aluminum, calcium carbonate, and defluorinated phosphate may decrease fluoride absorption and enhance excretion.

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Fumonisin Intoxication

General

- Equine leukoencephalomalacia (ELEM), blind staggers, corn stalk disease, moldy corn poisoning, porcine pulmonary edema (PPE)
- In horses, fumonisin intoxication is expressed as two clinical syndromes—hepatotoxic and neurotoxic.
- Either or both of these syndromes can be present in a group of horses.
- Hepatotoxic syndrome requires a longer duration of ingestion to cause damage to the liver and usually has a clinical course of 7–10 days between onset of clinical signs and death.
- Neurotoxic syndrome manifests clinically with a shorter duration and only 2–3 days before the onset of clinical signs and death.

Source

- Corn that has been infected with *Fusarium monilliforme* or *Fusarium proliferatum* and has produced the mycotoxin fumonisin.
- Fumonisin exists in at least three different forms: fumonisin B1, B2, and B3.
- Fumonisin B1 is recognized as the most important of the three forms of this mycotoxin.
- Climatic conditions that predispose corn to the growth of *Fusarium* species and increase the likelihood of fumonisin generation include drought during the middle of the growing season followed by an early, wet fall.
- Management factors that predispose animals to fumonisin intoxication include feeding corn screenings and pasturing horses on corn stalks.
- In addition to corn, other cereal grains that can be infected include sorghum, millet, and oats.

Species

- Horses and pigs are more commonly affected.
- Cattle seem to be more resistant than horses and pigs to the toxic effects of fumonisin.
- Poultry, rabbits, and rats have been poisoned experimentally.

- Fumonisin may be a carcinogen.

Clinical Signs

HORSES

- Neurotoxic syndrome
 - anorexia
 - depression
 - ataxia
 - blindness
 - head pressing
 - stupor
 - terminal convulsions

SWINE

- Acute pulmonary edema
 - dyspnea
 - cyanosis
 - death

HORSES AND SWINE

- Hepatotoxic syndrome
 - icterus
 - edema of the extremities
 - elevated liver enzyme concentrations
 - coma

Toxicity

- Horses: feed concentration >10 ppm
- Swine: feed concentration >50 ppm

Mechanism of Action

- Fumonisin is a potent inhibitor of sphingosine and sphinganine N-acetyltransferases.
- Inhibition of these enzymes causes accumulation of sphinganine, a metabolic intermediate of the sphingolipids.

- Accumulated sphinganine is present in the tissues, blood, and urine of poisoned animals.
- Sphinganine decreases production of cell membrane sphingolipids that are critical at attachment sites for extracellular proteins for cell to cell communication and membrane structure.
- This can disrupt the normal barrier function of endothelial cells and can cause edema and hemorrhage.
- The sphinganine to sphingosine ratio increases.

Diagnosis

- Clinical signs
- Cerebrospinal fluid analysis
 - increased concentration of myelin basic protein (>14 ng/mL; normal value, <2.0 ng/mL)
 - cytologic findings suggestive of chronic inflammation
- Chemical analysis of feed for fumonisin
 - Submit representative samples of feed to a veterinary diagnostic laboratory.
- Histopathology
 - horses: leukoencephalomalacia
 - swine: pulmonary edema (interstitial and interlobar), increased fluid in the thoracic cavity
- Fungal culture is not indicated because *Fusarium* spp. will grow from most corn samples.

Treatment

- Immediately remove the suspect feed for all animals on the farm.
- Provide supportive care to all animals with even slight clinical signs.

Prognosis

- Recovery is extremely rare after the onset of clinical signs.
- Even if recovery occurs, there is permanent neurologic damage.
- Swine that survive may have decreased weight gains and feed efficiency.
- Swine may be predisposed to respiratory infections.

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Gossypol

General

- The chemical structure of gossypol is shown in Figure 4–15.
- Gossypol intoxication may be expressed as a chronic syndrome as the toxin accumulates in tissues.

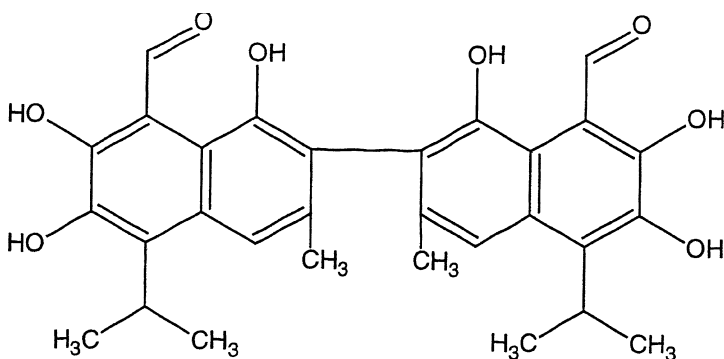


Figure 4-15 Chemical structure of gossypol.

- Different processing methods can alter gossypol content of cottonseed meal.
- In older screw-press methods, use of pressure to extract oil generated heat, which caused the gossypol to be bound to proteins and decreased the free fraction.
- Total solvent extraction of cottonseeds to collect oil is a more efficient process but produces meal with a greater gossypol content.
- In a newer process, the use of heat before solvent extraction ensures high oil extraction and lower free gossypol concentration.
- Free gossypol can be bound to iron, protein, or amino acids.
- In the rumen, some free gossypol is bound and unavailable for absorption.
- Gossypol fed to laying hens can discolor the egg yolks.

Source

- Seeds and meal derived from cotton (*Gossypium* spp.)
- Gossypol is a polyphenolic pigment in the glands of the seeds.
- The gossypol content of different cotton varieties varies greatly.
- Gossypol exists as free and bound forms in cottonseed meal.
- The free form is the toxic component.

Species

- Young cattle and sheep are more susceptible than older ruminants.
- All monogastric species are susceptible.

- Swine diets are regulated to contain less than 0.01% free gossypol.

Clinical Signs

- Sudden death of apparently healthy animals
- Anorexia
- Depression
- Weakness
- Edema and jugular venous distention
- Respiratory symptoms similar to those of shipping fever that are unresponsive to antibiotic therapy
 - dyspnea
 - labored breathing, known as thumping in swine
- Decreased fertility

CLINICAL PATHOLOGIC FINDINGS

- Increased serum concentration of:
 - lactate dehydrogenase
 - sorbitol dehydrogenase
 - γ -glutamyltransferase
 - aspartate aminotransferase

GROSS NECROPSY AND HISTOPATHOLOGIC FINDINGS

- Peritoneal, pericardial, and pleural fluid accumulation
- Generalized edema
- Heart pale, enlarged (dilated), streaked
- Myocardial necrosis
- Liver enlarged and friable with distinct lobular pattern
- Centrilobular hepatic congestion and necrosis
- Pale skeletal muscles, edematous abomasal mucosa, red tinge to urine

Toxicity

FREE GOSSYPOL CONCENTRATION

- Swine: >0.02% gossypol in diet
- Calves: >0.02% gossypol in diet

Mechanism of Action

- Gossypol is a primarily a cardiotoxic agent that may affect the liver secondarily.
- The precise mechanism of action is not well understood.
- Gossypol has been shown in experiments to
 - disrupt communication between cells at gap junctions
 - generate reactive oxygen species
 - elevate intracellular calcium concentration
 - depolarize mitochondrial membranes
 - increase proton membrane permeability
 - inhibit protein kinase C activity
 - induce apoptosis of spermatocytes

Diagnosis

- History of cottonseed meal or whole cottonseeds in the diet
- Clinical signs: sudden death, chronic dyspnea
- Gross necropsy and histopathologic signs
- Chemical analysis of feedstuffs for gossypol

DIFFERENTIAL DIAGNOSIS OF GOSSYPOL INTOXICATION

- *Asclepias* spp. (milkweed)
- *Cassia* spp. (coffee senna)
- *Eupatorium rugosum* (white snakeroot)
- *Lantana camara* (lantana)
- Monensin toxicosis
- *Pteridium aquilinum* (bracken fern)
- Vitamin A and selenium toxicosis

Treatment

- No specific treatment
- Remove suspect feedstuff and replace with soybean meal-based protein source.
- Minimize stress (stress may precipitate sudden death).

- Deaths may continue for several weeks after removal of cottonseed meal.

Prevention

GENERAL FEEDING GUIDELINES

- Use a certified laboratory to quantitate gossypol concentration in all bulk shipments of cottonseed meal.
- Alternate protein sources.
- Increase iron, protein, or calcium in the diet to bind free gossypol and reduce the risk of intoxication.

SPECIFIC RECOMMENDATIONS FOR FEEDING GOSSYPOL-CONTAINING RATIONS

- Swine
 - <0.01% Gossypol
- Calves and lambs younger than 8 weeks
 - do not feed untested rations that contain cottonseed meal
- Young breeding bulls
 - whole cottonseed: less than 10% of the ration
 - solvent extracted cottonseed meal: 5% of the ration
 - screw-press extracted or expander-processed cottonseed meal: up to 15% of the ration
- Adult beef cattle
 - whole cottonseed: 4–6 lb (1.8–2.7 kg) per head per day
 - solvent-extracted cottonseed meal: 2 lb (0.9 kg) per head per day
 - screw-press–extracted or expander-processed cottonseed meal: 4 lb (1.8 kg) per head per day

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Herbicides

General

- When used as directed, most herbicides are not a significant risk to animals.
- The assumption of the general public is that if a chemical is powerful enough to turn the entire yard brown, it must be able to harm the family dog.
- Herbicides encompass a large group of diverse chemicals.
 - See *Arsenic (Inorganic and Organic)*.
 - See *Organophosphorus and Carbamate Intoxication*.
- Risks of intoxication after herbicide treatment:
 - increased palatability of poisonous plants
 - presence of hydrocarbon-based carriers
 - ingestion of herbicide from storage tanks

- use of paraquat for malicious poisoning
- Most herbicides that once posed a threat have been
 - discontinued
 - reformulated (diluted)
- reclassified as restricted use pesticides (RUP) not available to the general public

Source

- Plant growth regulators
 - 2,4-D (Formula 40, Weedar 64)
 - dicamba (Banvel, Clarity)
- Disrupters of cell membranes
 - paraquat (several generic)
- Plant amino acid synthesis inhibitors
 - glyphosate (Roundup)
 - chlorimuron (Classic)
- Photosynthesis inhibitors
 - atrazine (numerous generics)
 - bentazon (Basagran)
 - bromoxynil (Buctril)
- Seedling growth inhibitors
 - EPTC (Eptam)
 - pendimethalin (Prowl, Pre-M, Pendulum)
 - trifluralin (Treflan, Tri-4, Trific)

Species

- Dogs, cattle, and horses

Clinical Signs

- Nonspecific gastrointestinal syndrome
 - nausea, vomiting
 - diarrhea
 - anorexia

- Syndrome attributed to phenoxy herbicides (2,4-D)
 - tremors
 - muscular weakness
 - myotonia
- Syndrome attributed to dipyridyl herbicides (paraquat)
 - respiratory signs: increased respiration rate, cyanosis
 - long-term exposure causing pulmonary fibrosis

Toxicity

- Paraquat: LD50 2–25 mg/kg in dogs
- 2,4-D: myotonia at doses >8.8 mg/kg

Mechanism of Action

- Most herbicides act on plant-specific biochemical pathways.
- 2,4-D is reported to uncouple oxidative phosphorylation.
- Paraquat is metabolized in the lungs and produces free radicals.
 - Free radicals damage the parenchyma of the lungs.

Diagnosis

- History of exposure to a concentrated source of herbicides
- Clinical signs
- Exclusion of other possible causes

Treatment

DECONTAMINATION

- Activated charcoal
- Clay adsorbent for paraquat
- Ocular decontamination
- Dermal decontamination

SUPPORTIVE AND SYMPTOMATIC

- Fluid therapy
- High-quality diet
- Antioxidant therapy for paraquat

Prognosis

- 2,4-D: good prognosis if therapy is initiated quickly
- Paraquat: guarded prognosis after onset of clinical signs

References

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Hydrogen Sulfide

- See *Noxious Gases*.

Insoluble Oxalate-Containing Plants

General

- A common group of house plants

Source

- Plants containing insoluble oxalates:
 - Anthurium (*Anthurium* spp.)
 - Arrowhead vine, Nephthytis (*Syngonium podophyllum*)
 - Begonia (*Begonia rex*)

- Caladium (*Caladium bicolor* and *Xanthosoma* spp.)
- Calla lily (*Zantedeschia* spp.)
- Devil's ivy, Marble queen, Porthos (*Scindapsus aureus*)
- Dieffenbachia, Dumbcane (*Dieffenbachia* spp.)
- Dragon root (*Arisaema* spp.)
- Elephant ear (*Alacasia* spp. or *Colocasia* spp.)
- Jack-in-the-pulpit (*Arisaema* spp.)
- Philodendron, heartleaf (*Philodendron* spp.)
- Skunk cabbage (*Symplocarpus foetidus*)
- Spathiphyllum (*Spathiphyllum* spp.)

Species

- All species are susceptible
- Since these are generally houseplants, more common in dogs and cats
- A common plant intoxication in children

Clinical Signs

- Hypersalivation
- Edema and redness of the oral mucosa
- Dysphagia
- Difficulty swallowing
- Shaking of the head
- Rubbing the face
- Swelling of the face or throat

Toxicity

- A nibble or two may not cause severe problems.
- Animals that graze on these plants are more likely to have signs.
- Most pets will ignore these plants following a single encounter.

Mechanism of Action

- Calcium oxalate crystals are shaped like double-pointed spears.
- The crystals are stored in plant cells that propel or “inject” the crystals.

- Crystals are propelled into the mucosa of the mouth.
- generally in response to grazing
- Crystals are called raphides.
- The plant cells are called idioblasts.
- Some of these plants also contain proteolytic enzymes.
 - Enzymes trigger the release of kinins and histamines.
 - These serve to increase swelling of the oral mucosa.

Diagnosis

- History of exposure to one of the plants listed above
- Clinical signs
- Examination of the oral cavity
 - swelling of the tongue, need to evaluate the pharynx
 - If excessive swelling there may be restriction of the airway.
- If lacrimation is noted, an ophthalmic examination is necessary.
 - Crystals may cause corneal ulcerations.

Treatment

- Provide supportive therapy.
 - first aid: rinse the mouth and offer cool water
 - possibly antihistamines
- If signs progress then more intensive therapy is necessary.
 - possibly oxygen therapy
- Prevention of intoxication
 - Inform pet owners of the types of plants that may cause this problem.
 - Plant grass seed in a pot to provide the pet a nontoxic alternative grazing material.

References

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Ionophores (Lasalocid, Monensin, and Salinomycin)

General

- Ionophores are produced by saprophytic fungi, predominantly *Streptomyces* spp. used as anticoccidial and growth promoting feed additives.
- Other uses of these agents include:
 - reduction of bloat and acidosis
 - prevention of tryptophan-induced atypical bovine pulmonary emphysema
- The carboxylic ionophores are open-chained oxygenated heterocyclic rings with a single terminal carboxyl group of moderate molecular weight (200-2000).
- Ionophores form lipid-soluble complexes with polar cations (K⁺, Na⁺, Ca²⁺, and Mg²⁺).
- The ionophores have a diverse antibacterial spectrum.

Source

Ionophore	Trade Name	Manufacturer	Species
Monensin (Figure 4–16)	Rumensin	Elanco	Beef cattle Goats
	Elancoban, Coban		Broiler chickens, Turkeys
Salinomycin	Sacox	Hoechst-Roussel	Broiler chickens
	Bio-Cox	Roche	Broiler chickens
Lasalocid	Avatec	Roche	Broiler chickens
	Bovatec		Beef cattle Sheep
Narasin	Monteban	Elanco	Broiler chickens
Laidlomycin propionate potassium	Cattlyst	Roche	Beef cattle

Conditions Surrounding Toxicosis

- The ionophores are safe at prescribed concentrations in intended species.

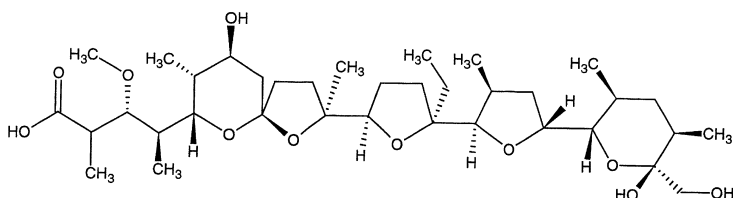


Figure 4-16 Chemical structure of monensin.

- The following management situations increase the possibility of toxicosis:
 - overdose (mixing errors, consumption of premix)
 - misuse in nontarget species (horses, adult turkeys, dogs)
- Concurrent administration of the following drugs can potentiate ionophore toxicosis:
 - erythromycin
 - sulfonamides
 - tiamulin

Toxicity

- In milligrams per kilogram of body weight:

	Horse	Cattle	Sheep	Chickens
Lasalocid	21.5	50–150	75–350	71.5
Monensin	2–3	20–80	12	200
Salinomycin	0.6	Not available	Not available	44.3

Clinical Signs

- Anorexia and depression are common clinical signs in animals intoxicated by ionophores.

HORSES

- Profuse sweating
- Colic
- Incoordination
- Hyperventilation

- Tachycardia and electrocardiographic alterations
- Prostration
- Death

CATTLE

- Diarrhea
- Labored breathing
- Ataxia
- Prostration
- Death

POULTRY

- Diarrhea
- Weakness, weak chirping
- Ataxia, resting on keel with wings and leg directed outward
- Decreased egg production

DOGS

- Lasalocid intoxication
 - clinical presentation similar to that of botulism
- Ataxia
- Mild muscular weakness of the hind limbs, quadriplegia
- Respiratory muscle paralysis

Clinical Pathology

- Elevated enzyme concentrations of muscle origin: aspartate aminotransferase, creatine kinase
- Possible elevations in serum (blood) urea nitrogen and bilirubin
- Possible decreases in serum calcium and potassium concentrations to life-threatening concentrations in horses

Gross and Histopathologic Lesions

- Pale skeletal and cardiac muscle
- Dilated ventricles with petechiae, ecchymosis, or yellowish-white streaks of necrosis in the myocardium

- Focal degeneration of myocytes
- Vacuolation, swelling, and eosinophilic staining of cardiomyocytes
- Ultrastructural vacuolation is caused by
 - swelling of mitochondria with disrupted cristae
 - condensation of matrical granules
 - cristolysis
 - swollen sarcoplasmic reticula
 - disruption of myofibrillar architecture

Differential Diagnosis

- The following are causes of myopathy and neuropathy:
 - vitamin E and selenium deficiency
 - intoxication with a poisonous plant
 - coffee senna (*Cassia occidentalis*)
 - coyotillo (*Karwinskia humboldtiana*)
 - white snakeroot (*Eupatorium rugosum*)
 - botulism
 - sodium chloride toxicosis (water deprivation)
 - In horses:
 - colic
 - blister beetle ingestion (cantharidin toxicosis)
 - azoturia

Mechanism of Action

- Carboxylic ionophores mediate an electrically neutral exchange of cations for protons across cell membranes without using ion channels.
- Electrochemical gradients are discharged in mitochondrial membrane.
 - decreased production of adenosine triphosphate
 - increased use of adenosine triphosphate to maintain cation concentration
 - cell death

- Another mechanism of action of carboxylic ionophores is disruption of calcium regulation.
 - influx of calcium into cell
 - calcium-mediated cell death

Diagnosis

- Initially tentative due to lack of pathognomonic clinical signs and lesions
- Presumptive diagnosis: any feed-related problem characterized by
 - anorexia, recumbency, acute mortality, myopathy
- Clinical signs
- History of exposure to feed containing ionophore or premix
- Confirmation requires chemical analysis for the ionophores
- Samples: feed (0.5–1 kg), liver, gastrointestinal contents, feces
- Distribution of monensin-induced muscular lesions
 - horses: primarily cardiac muscle lesions
 - sheep, swine, and dogs: primarily skeletal muscle lesions
 - cattle, poultry, and rodents: skeletal and cardiac muscle lesions equally distributed

Treatment

- There is no specific antidote for ionophores.
- The first step should be to reduce absorption.
 - mineral oil catharsis (horses)
 - activated charcoal
 - saline cathartic
- Remove medicated feed source
- Provide symptomatic treatment (primarily to horses)
 - intravenous fluids
 - electrolytes
 - potassium replacement if serum concentrations fall to less than 2 mEq/L (monitor closely)
- Monitor cardiac function

- Strict stall rest
- Horses that survive the initial episode of toxicosis may be unable to reach their previous concentration of athletic performance because of residual myocardial scarring.

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Iron

General

- Dogs that have ingested iron tablets may present a diagnostic challenge.
- Initially these animals have gastrointestinal signs followed by a phase of apparent recovery, which deteriorates into multisystem failure.

Source

- Iron dextran
 - **examples:** Nonemic, Ferrextran 100, Rubrafer; Rubrafer S-100
 - injectable products for piglets
- Iron supplements for rations
- Iron supplements for humans

Species

- All species are susceptible.
- Most clinical cases occur in foals, piglets, dogs.

Clinical Signs

CENTRAL NERVOUS SYSTEM

- Depression
- Coma
- Seizures

GASTROINTESTINAL

- Vomiting
- Gastroenteritis (possibly bloody)
- Diarrhea
- Acute hepatic failure

CARDIOVASCULAR

- Weak pulse
- Shock
- Anaphylaxis (histamine mediated)
- Hemorrhage
- Dehydration
- Acidosis

Toxicity

- More pronounced in newborn animals
 - greater gastrointestinal uptake of iron by neonates, especially animals marginal in iron stores (piglets)
- Newborn foals: 16 mg/kg

Mechanism of Action

CORROSIVE EFFECTS

- Direct gastrointestinal contact alters the mucosa.
- Mucosal damage occurs.

- hemorrhagic necrosis and perforation
- hypovolemia due to fluid loss

LIPID PEROXIDATION

- Associated with hepatic mitochondrial and microsomal dysfunction in experimental iron overload
- Increases lysosomal fragility
- Results of lipid peroxidation
 - reduced intracellular concentration of adenosine triphosphate
 - altered cellular calcium homeostasis
 - DNA damage

Diagnosis

- History of exposure
- Clinical signs
- Abdominal radiographs
 - iron capsules are radiopaque
 - may provide an idea of dose ingested
- Chemical analysis for iron
 - total serum iron
 - tissue iron concentration in liver

Treatment**DECONTAMINATION**

- Emetic therapy
- Activated charcoal not effective in binding iron
- Whole-bowel irrigation
- Polyethylene glycol

CHELATION THERAPY

- Deferoxamine
 - Iron is bound and eliminated through the urinary system.
vin rose; orange or pinkish-red discoloration of urine

SYMPTOMATIC AND SUPPORTIVE THERAPY

- Control of hypovolemia and shock
- Fluid therapy
- Possible transfusion for hemorrhage

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Ivermectin

General

- The chemical structure of ivermectin is shown in Figure 4–17.
- Small birds such as parakeets, because of their body weight and the difficulty in delivering the appropriate dose, can easily be overdosed with ivermectin after therapy for scaly leg mites.
- Ivermectin has a broad spectrum of activity against many internal and external parasites.
- Dogs usually are intoxicated with ivermectin because of inappropriate, extra-labeled use of products meant for cattle, sheep, or horses.
- Well-intentioned yet uninformed owners may “worm” a dog with a large-animal formulation.
- Any species can be affected if the dose is large enough to cross the blood-brain barrier.
- Ivermectin is only moderately metabolized by the liver; most ivermectin is excreted in the feces.
- In cattle, sheep, and horses large amounts of ivermectin can remain in fecal pats and decrease the number of dung beetles.

Source

- Ivermectin is a macrolide antibiotic.

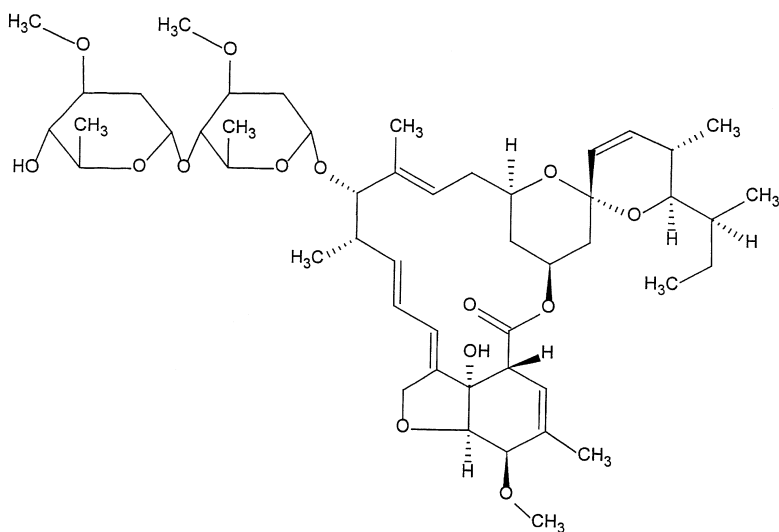


Figure 4-17 Chemical structure of ivermectin.

- Produced from a fungus first isolated from a soil sample in Japan
- *Streptomyces avermitilis*
- The avermectins are a class of chemicals that have a novel mode of action against nematode and arthropod parasites.
- Ivermectin is a mixture of the 22,23-dihydro derivative of avermectin B1
- Ivermectin was licensed for use in the United States in 1983.
- Formulations of ivermectin are as follows:
 - Ivomec (Merck): injectable, 10 mg/mL for swine and cattle
 - Equivalan (Merck): oral paste, 8.7 mg/mL for horses
 - Ivomec (Merck): oral drench, 0.8 mg/mL for sheep
 - Heartguard (Merck): oral tabs, 68, 136, and 272 µg for dogs

Species

- All species are susceptible.
- Dogs, especially collies, are at greatest risk.

Clinical Signs

- Convulsions or seizures are not commonly associated with ivermectin toxicosis.
- Ivermectin is a γ -aminobutyric acid (GABA) agonist that increases the effects of inhibitory neural pathways in the central nervous system and causes depression and stupor (see later).
- Common clinical signs:
 - mydriasis
 - depression
 - coma
 - tremors
 - ataxia
 - stupor
 - emesis
 - hypersalivation
 - death

Toxicity

- The doses of ivermectin reported to elicit clinical signs, most commonly ataxia and depression
 - Cattle: 4–8 mg/kg (20–40 times the therapeutic dose)
 - Horses: 2 mg/kg (10 times the therapeutic dose)
 - Pigs: 30 mg/kg (100 times the therapeutic dose)
 - Dogs
 - Collies: 0.1–0.2 mg/kg (15–30 times the therapeutic dose)
 - Beagles: 2.5–40 mg/kg (more than 200 times the therapeutic dose)
 - Cats
 - report of a kitten intoxicated by 0.3 mg/kg subcutaneously
 - adult cats possibly less sensitive
 - Chelonians (red-footed and leopard tortoises): 0.1–0.4 mg/kg
 - Leopard frogs:
 - 2.0 mg/kg IM can cause death
 - 20 mg/kg cutaneous had no effect in one study

Mechanism of Action

- Ivermectin is an agonist for the neurotransmitter GABA.
- GABA is a major inhibitory neurotransmitter.
- In mammals, GABA-containing neurons and receptors are present in the central nervous system.
- In arthropods and nematodes GABA is present primarily in the peripheral nervous system, specifically the neuromuscular junction.
 - reason for the safety margin of ivermectin in mammals
- Binding of ivermectin to neuronal membrane increases the release of GABA, which then binds to the GABA receptor–chloride channel complex of postsynaptic neuronal membranes and causes an influx of chloride ions.
- Ivermectin increases the conductance of chloride through the GABA-mediated chloride channel.
- Influx of chloride ions hyperpolarizes the neuronal membranes, making them less excitatory and decreasing nerve transmission.
- Hyperpolarization of neuronal membranes at the neuromuscular junction mediates a flaccid paralysis in arthropods and nematodes.

Diagnosis

- Clinical signs
- History of exposure to ivermectin-containing products
- Chemical analysis for ivermectin (usually not needed)
- Methods used: high-pressure liquid chromatography and enzyme-linked immunosorbent assay
 - Samples: liver, fat, gastrointestinal contents, feces

Treatment

- There is no safe specific antidote to ivermectin toxicosis.
- After oral exposure, the focus should be on gastrointestinal decontamination:
 - activated charcoal
 - saline or sorbitol cathartic
- Symptomatic and supportive care can help most intoxicated animals.

- prolonged treatment (days to weeks)
- intravenous fluids
- pads for the animal to lie on
- turning affected animals to prevent pressure sores
- control of bradycardia
- *The use of picrotoxin as a specific antidote is dangerous and cannot be recommended.*
- Picrotoxin is a potent convulsant and GABA antagonist and has a narrow margin of safety.
- Physostigmine
 - uncharged, reversible inhibitor of acetylcholinesterase that can penetrate the blood-brain barrier
 - shown to have some effect in the treatment of dogs with ivermectin poisoning by inducing a transient increase in acetylcholine in affected neurons
 - comatose animal may have increased mental alertness
 - may be beneficial to the veterinarian by helping to confirm the diagnosis of ivermectin toxicosis, possibly controlling the more severe cases, and giving owners hope that a comatose dog will survive.

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GABAergic drugs in cultured chick spinal neurons. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol.* 1989;93:97–104.

Lantana Camara

General

- Ornamental plant introduced into the United States
- Escaped cultivation in southern states
- Recently introduced animals are naive to this plant and may consume it readily.

Source

- Lantana (*Lantana camara*) and several other *Lantana* species, which grow in warmer climates
- Popular ornamental in gardens, landscapes
- A shrub that grows 2–4 feet (60–120 cm) tall
 - small, colorful flowers
 - small berry-like fruit that contains high concentration of toxins

Species

- Ruminants primarily

Clinical Signs

- Anorexia
- Ruminal stasis
- Depression
- Icterus
- Dehydration
- Photosensitivity
- Bloody diarrhea
- Necropsy and histopathologic findings
 - icterus
 - distended gallbladder
 - cholestasis

Toxicity

- Consumption of 1%–2% of body weight can induce toxicosis.

Mechanism of Action

- The toxic principles are triterpene acids (polycyclic triterpenoids).
 - lantadene A
most important of the lantadenes
 - lantadene B
less important because of lower toxicity
- The mechanism of intoxication is not well understood.
 - The lantadenes act on the hepatocytes and on the bile canaliculi to produce necrosis of both cell types
direct cytotoxicity
influence intermediate metabolic pathways
 - and cause
hepatic necrosis
cholestasis
- The direct cytotoxic effects may be the cause of gastroenteritis.

Diagnosis

- Clinical signs
- History of consumption of the plant
- Necropsy findings

Treatment

GASTRIC DECONTAMINATION

- Administer activated charcoal therapy.
- Provide fluids to increase movement in the gastrointestinal tract to correct ruminal stasis.
 - Plant and toxin can be absorbed over a long time.

SUPPORTIVE AND SYMPTOMATIC

- Provide fluid therapy to reverse dehydration and diarrhea.
- Administer oral fluid replacement therapy.

- Replace ruminal microflora.
- Manage photosensitivity if it occurs.
- Provide shade.

HEROIC MEASURES

- Perform rumenotomy to remove plant material.
- Consider the value of the animal.

PREVENTION

- Treat pastures that contain lantana with herbicides.

References

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Larkspur (*Delphinium* spp., Poisonweed)

General

- An important cause of sudden death in cattle of the western states.
- Tall species of larkspur poses a greater risk of intoxication.
- Cattle become accustomed to eating new growth of low species of larkspur in the spring.
- After moving to mountain pastures, animals eat the new growth of the more toxic tall larkspur.

Source

- A perennial plant that grows throughout the United States.
- Blue, purple, or white flowers with a prominent spur.

- Classified as tall (>3 feet [90 cm]) or low (<3 feet [90 cm]) species of larkspur.
- Tall larkspur—mountain ranges
- Low larkspur—lower-altitude pastures
 - Low larkspur
Delphinium andersonii
Delphinium nelsonii
 - Tall larkspur
Delphinium barbeyi
Delphinium troliifolium
Delphinium glaucum

Species

- Cattle predominantly
- Horses and sheep rarely affected

Clinical Signs

- Loss of motor function within a few hours of ingestion
- Sudden death
- Increased irritability
- Tremors and weakness
- Incoordination with swaying
- Stiffness
- Bloat
- Vomiting, regurgitation
- Constipation
- Collapse
- Convulsion
- Death due to respiratory paralysis or bloat
- Collapse with head downhill

Toxicity

- Cattle consuming 0.5% of body weight have been intoxicated.
- Single oral doses of tall larkspur (1.5 to 3 g/kg body weight) cause clinical signs of muscular tremors and collapse.

Mechanism of Action

- The toxic principles are diterpenoid alkaloids.
- Lycoctonine-type diterpenoid alkaloids are purported to be the toxic agents.
 - specific alkaloids most likely to cause intoxication
 - methyllycaconitine
 - 14-deacetylnudicauline
 - nudicauline
 - high concentrations of alkaloids in early growth
 - concentration of alkaloid not decreased with drying
- Methyllycaconitine
 - neuromuscular blocking agent
 - curare-like effects
 - acts on postsynaptic, nicotinic cholinergic receptors

Diagnosis

- Exposure to and consumption of the plant
- Clinical signs
- Necropsy
 - bloat, venous congestion
 - fragments of plant in rumen

Treatment

- Often only find in dead animals
- Move mildly affected cattle to a new pasture.
- Perform gastrointestinal decontamination with activated charcoal and cathartic agent.
- Administer antidote.
 - physostigmine: 0.04–0.08 mg/kg body weight IV, intraperitoneally, or subcutaneously
 - reversed clinical signs in recumbent animals
 - multiple doses may be necessary
 - neostigmine: 0.01–0.02 mg/kg IM
- Provide symptomatic and supportive therapy.

- Relieve bloat.
- Administer antibiotics for possible aspiration pneumonia.

Prognosis

- Guarded after clinical signs appear

Prevention

- Allow cattle to graze on larkspur only before or after flowering.
- Attempt aversion (of larkspur) behavioral therapy.
- Graze sheep before grazing cattle.
- Control larkspur with herbicides.

References

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Lead Poisoning (Plumbism)

General

- One of the oldest known metal intoxications
- Diminished risk of exposure due to banning of lead-based paints and lead additives to fuel

Source

- Lead-based paint, grease, oilfield waste, crank case oil, lead storage batteries (car batteries), lead gunshot, lead fishing weights, window putty, linoleum, forage contaminated with lead from smelter operations, forage grown on lead-contaminated soil

Species

- Cattle, dogs, horses, and waterfowl more commonly affected
- Cats, goats, sheep, and chickens less commonly affected
- Pigs reportedly insensitive to lead intoxication

Clinical Signs

- Anorexia and depression in all species

CATTLE

- Central nervous system
 - more common
 - blindness
 - circling
 - head pressing
 - slow, rhythmic twitching of ears, bobbing of head
- Gastrointestinal tract
 - decreased ruminal motility
 - bruxism
 - excessive salivation

DOGS

- Gastrointestinal tract
 - usually noticed first
 - more common
 - occur in older dogs
 - anorexia
 - vomiting
 - colic
 - diarrhea or constipation
- Central nervous system
 - posterior
 - convulsions
 - ataxia
 - blindness
 - mydriasis

HORSES

- Peripheral nervous system
 - predominant
 - roaring (recurrent laryngeal nerve paralysis)
 - regurgitation of water when drinking
 - pharyngeal paralysis
- Gastrointestinal tract
 - colic
 - diarrhea
 - weight loss

WATERFOWL

- Nonspecific, uncommon
- Possible decreased population of birds

Toxicity

- Younger animals are more greatly affected than older animals.

Mechanism of Action

- Lead is ingested and readily absorbed in the small intestine by the calcium transport system.
- Lead interferes with a variety of enzymes, especially sulfhydryl-containing enzymes.
- Lead can replace zinc as an enzyme cofactor in some metabolic pathways.
- In bone marrow, lead can inhibit several steps related to hemoglobin and erythrocyte synthesis.

Diagnosis

- Clinical signs

LEAD IN BLOOD

- concentrations >0.6 ppm or >0.35 ppm with appropriate clinical signs
- 90% of lead in whole blood is bound to erythrocytes.

- Blood should be collected in EDTA or heparin tubes.
- Elevated blood lead concentrations indicate exposure and not the dose ingested or the duration or severity of intoxication.

TISSUE LEAD

- Renal lead concentrations >10 ppm
- The liver and feces can be analyzed for lead.
- Basophilic stippling of erythrocytes
 - useful in horses, dogs, and cats
 - nonspecific
 - does occur in cattle but generally <0.1% of erythrocytes are affected
- Eosinophilic, acid-fast intranuclear inclusion bodies in the renal tubular cells and hepatocytes
- Serum or urinary aminolevulinic acid dehydrase: not commonly measured

Treatment**REMOVAL OF SOURCE OF LEAD**

- Administer cathartic agent to enhance elimination of lead particles from the gastrointestinal tract.
- Perform enterotomy or rumenotomy if necessary.
- Remove herbivores from contaminated pastures if possible.

CHELATION

- Cattle and horses
- Treatment in cattle may not be practical due to residual lead in the rumen.
 - calcium disodium edetate (CaEDTA) 70–100 mg/kg divided into 2–3 doses for 3 days, reevaluate
 - zinc supplementation to reduce adverse effects of CaEDTA therapy
 - thiamine 2–4 mg/kg to reduce central nervous system signs
- Dogs
 - CaEDTA: 100 mg/kg divided into 4 doses a day for 2–5 days, reevaluate
 - D-penicillamine

SEIZURE CONTROL

- Barbiturates
- Diazepam

References

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Locoweed (*Astragalus* spp. and *Oxytropis* spp.)

General

- The common names are locoweed and milk vetch.
- Locoweed grows throughout North America.
- Most species that produce locoism grow in the western United States.
- Locoweed generally has low palatability but is eaten by hungry animals.
- Many animals become habituated to locoweed and may not eat any other source of feed.

Source

- Consumption of locoweed (*Astragalus* spp. and *Oxytropis* spp.) for several weeks

Species

- Cattle, horses, and sheep

Clinical Signs

NEUROLOGIC SIGNS

- Weight loss
- Depression
- Dull eyes
- Excessive agitation when stimulated
- Gait abnormalities
- Inability to eat or drink
- Habituation
- General loss of sensory and motor nerve function
- More common than nonneurologic signs

NONNEUROLOGIC SIGNS

- Abortions
- Birth defects

Toxicity

- Locoism occurs after an animal ingests 30% of body weight in locoweed over 6 weeks or longer.

Mechanism of Action

SWAINSONINE

- The toxic principle is swainsonine, an indolizidine alkaloid (Figure 4-18).
- Reversible inhibitor of
 - lysosomal α -mannosidase
 - α -D-mannosidase
- Also inhibits the Golgi mannosidase II
- Is an alkaloid and a weak base
- Because of its charge, tends to accumulate in acidic intracellular areas (lysosomes)
- Lysosomal storage disease
 - increased swainsonine concentration in the tissues
 - more inhibition of α -mannosidase, especially in the lysosomes

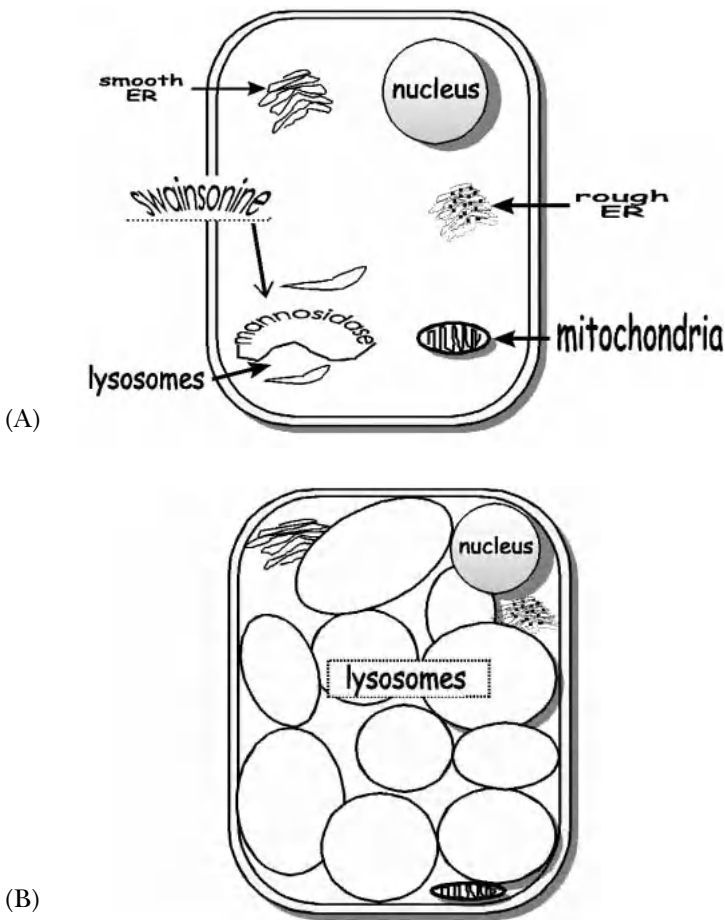


Figure 4-18 Mechanism of action of swainsonine on cellular function. (A) Normal cell after introduction of swainsonine. (B) Results of long-term intake of swainsonine-containing plants. Swainsonine inhibits the actions of different mannosidases within the cell. In this illustration, the lysosomal form of mannosidase is inhibited. This results in swelling of lysosomes (vacuolation) as they become increasingly filled with mannose, push the organelles to the periphery, and inhibit cellular function.

- accumulation of oligosaccharides and glycoproteins in the lysosomes because they cannot be processed by α -mannosidase
- Cytoplasmic vacuolation occurs in the renal tubules within a few weeks of consumption of locoweed.

- Central nervous system, lymphoid tissue, endocrine tissue, and liver all show vacuoles.

MISEROTOXIN "CRACKERHEEL"

- Caused by 3-nitropropanol and 3-nitropropionic acid
- From several species of *Astragalus*
- Peripheral neurotoxin

SELENIUM INTOXICATION

- Several species of locoweed can accumulate selenium.
- Chronic disease
- Odor of selenium-accumulating plants may prevent some animals from consuming locoweed.
- See *Selenium*.

Disease Syndromes Associated with *Astragalus* or *Oxytropis* spp.

Syndrome	Toxic Principle	Clinical Signs	Comments
Locoism	Swainsonine	Central nervous system (see earlier)	Most commonly associated syndrome
Abortions	Swainsonine	Abortions	Vacuolation of cells of the placenta
Teratogenesis	Possibly swainsonine	Crooked calf disease	May be related to decreased fetal activity and movement in utero
Brisket disease, high-mountain disease	Possibly swainsonine	Cardiomyopathy, congestive right ventricular failure	<i>Oxytropis sericea</i> and <i>Astragalus</i> spp. generally only in high-altitude pastures of western United States
Crackerheel	Miserotoxin 3-nitropropanol	Methemoglobinemia Knuckling on fetlocks Goose stepping	<i>Astragalus miser</i> (timber milk vetch) and others
Alkali disease	Selenium accumulation	Alopecia Deformed hooves Lameness Bob-tail appearance	See <i>Selenium</i>

Diagnosis

- Characteristic clinical signs
- Examination of pastures for plants or remnants of the plants
- Histopathologic examination of many tissues, especially brain, kidneys, and placenta
 - Vacuolation
 - Neurovisceral cytoplasmic vacuolation
 - Axonal dystrophy

Treatment

- Remove animals from the source of the poisonous plants, if possible.
- Offer high-quality forage (alfalfa hay) or grain supplement.
- Many animals refuse high-quality feed and selectively consume locoweed in the pasture.
- Most animals with mild clinical signs have gradual improvement within 1 to 2 weeks; however, animals with severe clinical signs may never recover.
- Animals recovering from locoism should not be offered for slaughter for 25 days to reduce the possibility of tissue residue of swainsonine.

References

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Stegelmeier BL, Ralphs MH, Gardner DR, et al. Serum alpha-mannosidase activity and the clinicopathologic alterations of locoweed (*Astragalus mollissimus*) intoxication in range cattle. *J Vet Diagn Invest.* 1994;6:473–479.

Marijuana (*Cannabis Sativa*)

General

- Other names include hemp, Mary Jane, grass, pot, weed, and hashish.
- Dogs can be poisoned by consuming baked goods containing tetrahydrocannabinol (THC) or hashish oil.
- Dogs can find the owner's supply and consume the drug.
- Cattle consume fresh plants during cultivation.
- Marijuana is generally considered unpalatable; however, when limited forage is available, the plant may be consumed.

Source

- Tall annual herb of the hemp family
- Hemp fiber previously grown for rope
- Grows throughout the United States
- Entire plant contains the toxic principle
- Concentration of toxin varies with season, location, sex of the plant, and variety.

Species

- Dogs, cats, cattle

Clinical Signs

SMALL ANIMALS

- Ataxia
- Vomiting
- Mydriasis

- Nystagmus
- Depression
- Hypothermia
- Bradycardia

LARGE ANIMALS

- Nervousness and irritability initially
- Central nervous system depression later

Mechanism of Action

- The toxic principles are resins with THC and related compounds responsible for toxic effects (Figure 4–19).
- THC and Δ THC (Δ 9-*trans*-tetrahydrocannabinol) are described as the most potent.
- THC and related compounds are potent antiemetic agents.
 - may be difficult to induce emesis in a poisoned patient

Diagnosis

- Clinical signs
- History of exposure
 - may be difficult to obtain this information from an owner

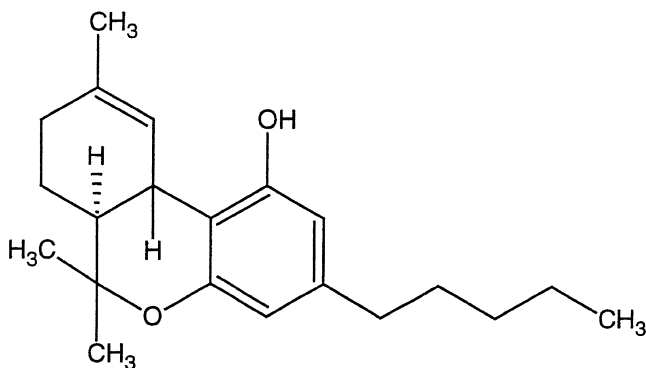


Figure 4–19 Chemical structure of tetrahydrocannabinol.

Treatment

GASTROINTESTINAL DECONTAMINATION

- Administer activated charcoal and cathartic.
- Emetic therapy may be attempted.

SUPPORTIVE TREATMENT

- Administer oxygen to assist respiration or relieve respiratory depression.
- Treat central nervous system depression.

Reference

Godbold JC Jr, Hawkins BJ, Woodward MG. Acute oral marijuana poisoning in the dog. *J Am Vet Med Assoc.* 1979;175:1101–1102.

Metaldehyde

Source

- Metaldehyde is a molluscicide that is generally formulated in corn-based pellets that animals mistake for kibble.
- Slug and snail bait are the most common sources of exposure for animals.
- Trade names of metaldehyde-containing baits include
 - Halizan
 - Meta-Fuel
 - Metason
 - Slug Death
 - Slugit Pellets

Species

- Dogs and cats primarily; cattle have been intoxicated

Clinical Signs

- Relate to nervous system derangement and can progress rapidly
- Incoordination
- Vomiting

- Diarrhea and colic in horses
- Nystagmus
- Tachypnea, tachycardia
- Cyanosis
- Muscle tremors leading to continuous convulsions

Toxicity

- LD50 for dogs: 100–1000 mg/kg
- LD50 for cats: approximately 200 mg/kg

Mechanism of Action

- Metaldehyde is a polymer of acetaldehyde.
- Mechanism of action is not fully understood.
- After ingestion, the toxin is metabolized to liberate acetaldehyde.
- Metabolites may have direct effects on neurotransmitters.
 - decrease in γ -aminobutyric acid (GABA)
 - decrease in norepinephrine
 - decrease in 5-hydroxytryptamine (serotonin)
- Direct mucosal irritant

Diagnosis

- History of exposure
- Presence of clinical signs
- Chemical analysis of stomach contents or vomitus for acetaldehyde

Treatment

- Control seizures with diazepam, phenobarbital, or phenytoin.
- Administer activated charcoal and cathartic therapy if ingestion is recent.
- *Do not induce emesis*; doing so can induce seizures.
- Provide symptomatic and supportive therapy.
 - Administer fluids.
 - Maintain acid-base balance.

References

- Booze TF, Oehme FW. Metaldehyde toxicity: a review. *Vet Hum Toxicol.* 1985;27:11–19.
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Methylxanthines

- See *Chocolate Poisoning (Theobromine)*.

Moldy Sweet Clover (*Melilotus* spp.)

- See *Anticoagulant Rodenticides*.

Molybdenum (Teart Scours, Peat Scours)

General

- Toxicosis manifests as copper deficiency.
- A complex interaction occurs between molybdenum, copper, and sulfur.
- See *Copper*.

Source

- Soil
 - higher concentrations in soil on the east and west coasts
 - higher concentrations in acidic, wet soil (peat bogs)
- Forage
 - Plants can accumulate molybdenum.
 - Concentrations are lowest in the winter and highest in summer and fall.
 - Legumes can be a contributor.
- Fertilizers

Species

- Cattle (young more susceptible than old) most commonly, sheep

Clinical Signs

- Diarrhea (teart scours)
 - fluid feces
 - gas bubbles in the feces
- Depigmentation of haircoat
 - periocular distribution
 - more noticeable on black animals
- Lameness
- Decreased growth rate
- Clinical pathology
 - decreased packed cell volume
 - microcytic, hypochromic anemia

Toxicity

- Interaction with other minerals
 - Elevated sulfur concentration in diet decreases copper and molybdenum uptake.
 - Molybdenum toxicosis can be potentiated by high sulfur content or low copper content.
- In ruminants (cattle) >10 ppm in the diet induces toxicosis.
- Accidental ration concentration of 1.9% induced acute toxicosis.
- A copper to molybdenum ratio less than 2:1 precipitates toxicosis.

Mechanism of Action

- Molybdenum toxicosis induces copper deficiency.
 - Copper is bound by molybdenum to form a soluble complex.
 - The complex is excreted in urine.
 - Body stores of copper decrease.
 - Activity of copper-sensitive enzymes (e.g., superoxide dismutase) decreases.

- Molybdenum may have direct effects on the liver and kidney through yet to be described mechanisms.

Diagnosis

- Clinical signs
- History of exposure to sources of molybdenum
- Chemical analysis
 - molybdenum concentration in liver >5 ppm
 - copper concentration in liver <10 ppm

Treatment and Prevention

- Remove animal from source of molybdenum (pasture or feed-stuff).
- Administer copper replacement therapy.
 - trace mineral mix free choice
 - copper glycinate injection
short duration of action
 - copper in the form of sulfate or oxide
provide 1 g copper per head per day

References

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Mycotoxins

- See *Aflatoxin (Aflatoxicosis)*, *Fescue (Festuca Arundinacea, Tall Fescue)*, *Fumonisin Intoxication*, *Slaframine (Slobber Factor, Black Patch Disease)*, *Trichothecenes*.

General

- Mycotoxins are the products of fungal growth and reproduction on grains and other feedstuffs (cottonseed, peanuts, or forages).
- Of the many mycotoxins, disease is caused primarily by a few common chemical entities (aflatoxin, zearalenone, trichothecenes).
- The relative importance and economic effect of mycotoxins can vary by year and geographic region.

Source

AFLATOXINS (B₁, B₂, G₁, G₂, M₁, M₂)

- *Aspergillus flavus*, *Aspergillus parasiticus*
- Affect corn, peanuts, and a variety of other cereal grains
- See *Aflatoxin (Aflatoxicosis)*.

TRICHOTHECENES

- Deoxynivalenol (DON), T-2, diacetoxyscripenol (DAS)
- *Fusarium* spp.
- Affect corn, wheat
 - often found as co-contaminants
 - stable to heat of processing
- See *Trichothecenes*.

ERGOT

- *Claviceps purpurea*, *Claviceps paspalli*, *Claviceps fusiformis*
- Toxins can produce several syndromes.
- See *Fescue (Festuca Arundinacea, Tall Fescue)*.

OCHRATOXIN AND CITRININ

- *Aspergillus ochraceus*, *Penicillium viridicatum*, *Penicillium citrinum*
- Mycotoxins can occur together in contaminated feedstuff.
- Cereal grains
- Primarily affect the kidney
- The chemical structure of ochratoxin is shown in Figure 4–20.

FUMONISIN

- *Fusarium moniliforme*, *Fusarium proliferatum*
- Affects corn
- Horses and swine primarily affected
- See *Fumonisin*.

SLAFRAMINE

- *Rhizoctonia leguminicola*
- Primarily on legume forage
- See *Slaframine* (*Slobber Factor*, *Black Patch Disease*).

ZEARELENONE

- *Fusarium graminearum*, *Fusarium roseum*
- Associated with corn, wheat, milo
- Affects swine primarily, reproductive
- The chemical structure of zearalenone is shown in Figure 4–21.

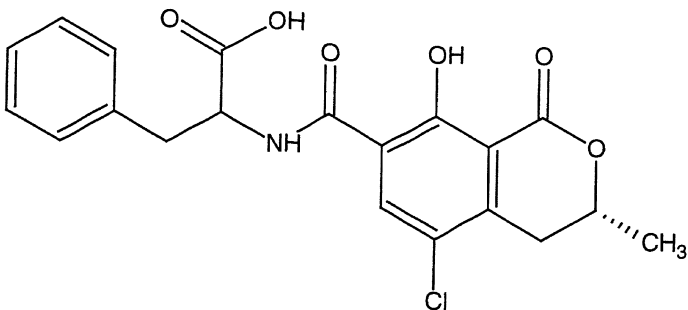


Figure 4–20 Chemical structure of ochratoxin.

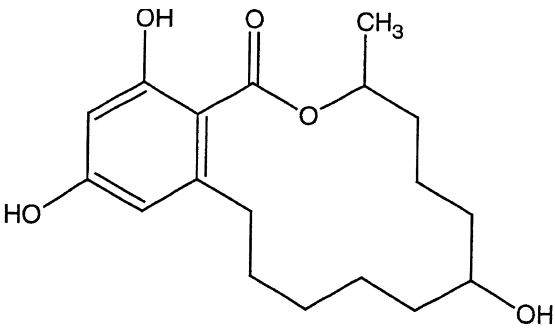


Figure 4–21 Chemical structure of zearalenone.

Effect of Mycotoxins by Body System

Organ System	Mycotoxin	Lesions or Effect
Hepatic	Aflatoxin	Bile duct hyperplasia, centrilobular hepatic necrosis, icterus, ascites
Renal	Aflatoxin Ochratoxin, citrinin	Tubular necrosis, polyuria, polydipsia, increased blood urea nitrogen and creatinine concentrations
Central nervous system	Ergot alkaloids Fumonisin Penitrem	Tremorgenic, dopaminergic action Horses—ELEM Tremorgenic
Gastrointestinal	Aflatoxin Slaframine Trichothecenes	Anorexia Cattle, horses; salivation All species feed refusal; necrosis of oral mucosa vomiting in swine
Reproductive	Zearalenone	Swine; swelling of the vulva, mammary gland enlargement, nymphomania, prolonged anestrus
Hematopoietic	Aflatoxin Dicumarol Ochratoxin Trichothecenes	Anemia, leukopenia, decreased platelet count, increased bleeding
Immune	Aflatoxin Ochratoxin Trichothecenes	Decreased B-cell and T-cell function, leukopenia, lymphoid atrophy

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Nitrate Intoxication

General

- A common intoxication of ruminants that can cause sudden death.
- Nitrate (NO_3) is absorbed by the roots of plants and converted to nitrite (NO_2).
- NO_2 is then incorporated into plant amino acids and proteins.
- NO_3 to NO_2 by the plant nitrate reductase system (NRS)
- The following genetic and environmental factors influence plant NRS:
 - *Sorghum* species have lower NRS capacity in response to stress.
 - Drought and reduced sunlight decrease activity.
- Nitrate is continuously absorbed by the plant even when the NRS is inhibited.

Source

- Many plants, especially from the genus *Sorghum*
 - Sudan grass
 - Sorghum
 - Johnson grass (*Sorghum vulgaris*)

- Corn (*Zea mays*)
- *Kochia* spp. (kochia, fireweed)
- Beets (*Beta* spp.)
- Rape
- Nitrogen fertilizers, drainage from fertilized fields, water sources.

Species

- Cattle, sheep, and goats are most commonly poisoned by nitrate.
- Neonatal animals are at greater risk.
- All species are susceptible to nitrite intoxication.

Mechanism of Action

- NO₃ is reduced by ruminal bacteria to NO₂.
- NO₂ is absorbed from the rumen into the bloodstream.
- NO₂ oxidizes the iron in hemoglobin from ferrous (Fe²⁺) to ferric (Fe³⁺) state.
- This form of hemoglobin is called methemoglobin (MetHb).
- MetHb is not capable of transporting oxygen to tissues.

Toxicity

Generalized Interpretation of Forage Nitrate Test

Nitrate (ppm dry matter)	Interpretation
0–3000	Generally safe for all cattle
3000–5000	Generally safe for nonpregnant beef cattle and older beef cattle A risk for dairy cattle
5000–10,000	Poses a risk for all cattle Do not feed to dairy cattle
>10,000	Potentially toxic for all cattle

Clinical Signs

- Rapid clinical course: signs to death generally less than 3 hours
- Sudden death with no signs

- Tachypnea, restlessness, dyspnea, ataxia, cyanosis, tachycardia, or terminal convulsions

Diagnosis

- History of feed-related intoxication or death
- Clinical signs
- Chocolate-brown-colored blood
- Chemical analysis of suspect feed and water
- Chemical analysis
 - serum
 - urine
 - ruminal contents
 - aqueous humor (eyeball)

Treatment

- Goal is to reduce methemoglobin to normal hemoglobin.
- Administer methylene blue 4–30 mg/kg IV of 1% solution.
 - rapidly reduced by NADPH MetHb reductase in erythrocytes
 - reduced methylene blue reverts MetHb back to Hb
- Remove the source (feed or water).

Prevention and Owner Education

- Test hay and feedstuffs before purchasing and feeding.
- Dilute high-nitrate feed with low-nitrate feedstuffs.
- Do not feed hungry animals high-nitrate feedstuffs (increased intake).
- Slowly adapt animals to nitrate-containing feed.
- Feed corn (concentrate) before nitrate to reduce risk of intoxication.
- Cut hay higher (less stalk).
- Attempt to reduce nitrate concentration by means of ensiling.
- Use propionibacterium products, which may increase ruminal metabolism of nitrate and decrease the risk of intoxication.
- When methemoglobin is $\leq 20\%$ animals will have mild clinical signs.

- At methemoglobin of 30–40%, clinical signs (increased respiratory rate, dyspnea, cyanosis) are obvious.
- Methemoglobin concentrations greater than 80% result in death.

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Nonprotein Nitrogen (NPN, Urea Intoxication, Ammonia Intoxication)

General

- The chemical structures of urea and biuret are shown in Figures 4–22 and 4–23.
- The use of nonprotein nitrogen (NPN) takes advantage of the microbial population of the rumen to provide an economical source of protein.
- Use of NPN requires careful management by the producer.
- Animals must have a readily available source of fermentable carbohydrate in addition to the NPN.
- Animals must adapt to NPN for 2 weeks to prevent intoxication.
- After a fasting period (during a snowstorm), animals must be slowly reacclimated to urea-containing rations.

Species

- Ruminants, primarily cattle and sheep

Source

- Primarily feed-grade urea, biuret, and ammonium salt used as feed additives in ruminant rations.
- Urea is found in range cubes, feed blocks, and lick tanks mixed with molasses as a supplement.

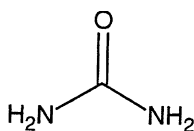


Figure 4-22 Chemical structure of urea.

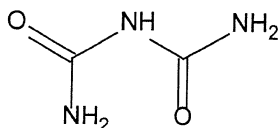


Figure 4-23 Chemical structure of biuret.

- Nitrogen fertilizers also are a source.

Toxicity

- Nonadapted cattle: 0.45 g/kg of urea
- Adapted cattle: 1.0–1.5 g/kg of urea

Mechanism of Action

- See Figure 4-24.
- Ammonia (NH₃) is produced in the rumen after microbial degradation of urea.
- In the environment of the rumen (pH 5.0–6.5), ammonia is converted to ammonium ion (NH₄⁺).
 - charged species: NH₄⁺ remains in the rumen
- Conversion of NH₃ to NH₄⁺ requires a hydrogen ion, which is provided by the ruminal environment.
- As the concentration of NH₄⁺ increases in the rumen, the pH of the rumen also increases.
 - becomes more alkaline owing to loss of hydrogen ions
 - process can occur very rapidly
- When the pH of the rumen reaches 8.0–9.0, NH₄⁺ reverts to NH₃.
 - NH₃ can be absorbed through the wall of the rumen into the bloodstream.

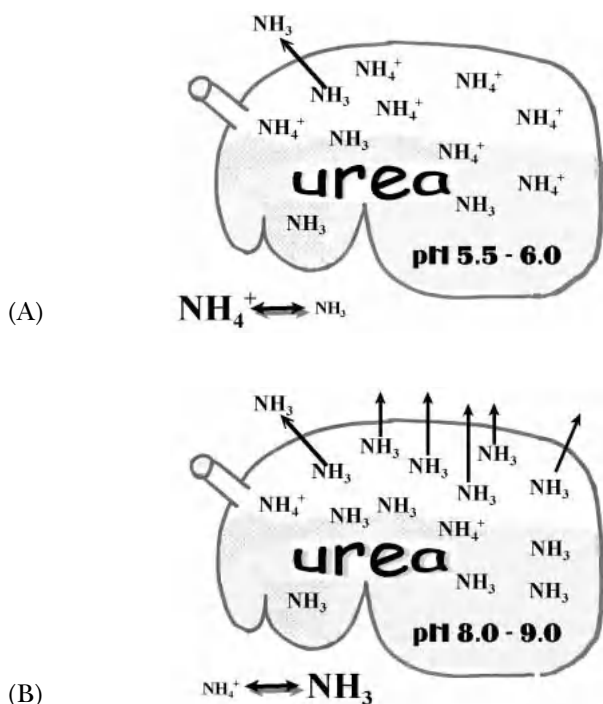


Figure 4-24 The pathophysiologic mechanism of urea (nonprotein nitrogen) intoxication. (A) After ingestion, urea is metabolized by bacterial urease to ammonia (NH_3). At a pH of 5.5–6.0 sufficient hydrogen ions are present to force the equilibrium toward ammonium ion (NH_4^+). This ionized species is only slightly absorbed by the wall of the rumen. As more urea is introduced into the rumen, fewer hydrogen ions are available, and the pH increases. (B) Effect of higher pH conditions. With fewer hydrogen ions available, ammonium reverts back to ammonia. The uncharged ammonia species easily crosses the wall of the rumen and is absorbed into the systemic circulation. The amount of ammonia quickly outstrips the capability of the liver to detoxify, and ammonia toxicosis ensues.

- A large volume of NH_3 outstrips the capability of the liver to detoxify.
- Results in ammonia intoxication.
- Ammonia can inhibit enzymes of the tricarboxylic acid cycle and decrease cellular energy.

Clinical Signs

- Rapid onset of clinical signs (30 minutes to 3 hours)
- Restlessness, belligerence, aggression
- Muscle tremors
- Salivation
- Bruxism
- Bloat
- Convulsions
- Death

Diagnosis

- Clinical signs with a history of exposure to an NPN feedstuff
- Odor of ammonia from the rumen (stomach tube or at necropsy)
- Ruminal alkalosis and metabolic acidosis
- Chemical analysis of ammonia concentration
 - ruminal pH within 2 hours of death >8.0
- Ruminal ammonia
 - Collect and freeze rumen content immediately.
 - >80 mg%
 - Ruminal ammonia is not a stand-alone diagnostic indicator.
 - Autolysis or slow freezing may falsely elevate NH_3 concentration.
- Blood ammonia
 - frozen EDTA or heparinized blood
 - >2 mg%
- Collect sample of feed for analysis.

Treatment

- No specific antidote
- Acetic acid 5% (vinegar)
 - Cattle: 2–6 L
 - Sheep, goats: 0.5–1 Lgiven through a gastric tube and followed by large volumes of cold water

Rationale is that acetic acid lowers ruminal pH.

This condition favors formation of NH_4 (ammonium ions).

- Rationale for cold water is that it reduces ruminal temperature.
 - decreasing the catalytic ability of urease
 - reducing rate of NH_3 formation from urea

CASE PRESENTATION

A producer decides to give his cows on a grass pasture a molasses protein supplement that contains urea. He gives the supplement to the animals in a lick tank. The cattle ignore the lick tank except to use it as a back scratcher. After a week, the producer is disappointed to see that little of the supplement has been consumed. The producer theorizes that if the cattle can taste the molasses, they will begin to consume the supplement. The producer removes the lid to the lick tank and goes home for the evening. The following morning six cows are dead, and four cows are recumbent.

ANALYSIS OF CASE

The animals were not acclimated to urea before the intake restriction (lick ball) was suddenly removed. The animals had unlimited access to molasses with urea, and ammonia (NPN) toxicosis developed rapidly.

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Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

General

- As a class, the NSAIDs are prevalent in most households in the United States; thus they pose considerable exposure potential.

- Animals may become poisoned by accidental ingestion (more common in dogs) or inappropriate administration by owners.
- Long-term use of NSAIDs in the management of orthopedic disease predisposes some animals to toxicosis.

Source

- Aspirin and the salicylates are carboxylic acid NSAIDs present in numerous over-the-counter sources that range from aspirin and arthritis cremes (methyl salicylate) to bismuth subsalicylate (e.g., Pepto-Bismol).
- Propionic acids are a class that includes ibuprofen (e.g., Advil, Nuprin), ketoprofen (Orudis), carprofen (Rimadyl), and naproxen.
- Enolic acids include oxyphenbutazone, phenylbutazone, piroxicam.
- Acetic acids include etodolac (EtoGesic), sulindac, indomethacin.

Species

- Dogs, cats, horses (foals) primarily
- Older and younger animals at greater risk of toxicosis

Clinical Signs

GASTROINTESTINAL

- Vomiting
- Anorexia
- Colic
- Hematemesis
- Melena
- Jaundice
- Hepatic encephalopathy

CENTRAL NERVOUS SYSTEM

- Depression
- Possibly seizures

OTHER SIGNS

- Hyperthermia
- Coagulopathy
- Methemoglobinemia in cats

RENAL

- Dehydration
- Oliguria

CLINICAL PATHOLOGY

- Metabolic acidosis: elevated anion gap suggests salicylate intoxication
- Decreased serum albumin concentration
 - noted with phenylbutazone intoxication due to protein-losing enteropathy
 - NSAID-induced gastric or intestinal ulcers and those that cause nephrotoxicity
- Hyperkalemia, increased blood urea nitrogen and creatinine concentrations with nephrotoxicity
- Elevated serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase concentrations and hyperbilirubinemia associated with hepatotoxic syndrome

LESIONS

- Erosions of the gastrointestinal mucosa
- Renal papillary necrosis, especially in horses

Toxicity

- Cats more susceptible because of relatively low capacity of hepatic glucuronyl transferase system
- Dehydration
 - therapeutic dose of phenylbutazone may be a toxic dose
 - predisposes animals to nephropathy
- A great deal of individual variability in doses that may elicit toxicosis
 - A dog can have gastritis after ingesting one 325-mg tablet of aspirin.
 - Repeated dosing increases the likelihood of toxicosis.

- Most over-the-counter products used by humans are developed for a 70-kg man, not a 4-kg dog.
- Aspirin
 - cat: >25 mg/kg
 - dog: 15 mg/kg every 8 hours
- Ibuprofen
 - dog: 50–100 mg/kg
- Indomethacin
 - dog: gastric ulcers may develop at doses of 2 mg/kg or greater
- Naproxen
 - dog: 220-mg dose may cause acute gastric ulceration
- Phenylbutazone
 - horses: 8.8 mg/kg per day for 4 days may induce toxicosis

Mechanism of Action

INHIBITION OF THE CYCLOOXYGENASE ENZYME SYSTEM

- Mediates production of cyclic endoperoxides from arachidonic acid to yield prostaglandins
- Two isoforms of the cyclooxygenase (COX) enzyme encoded by different genes
 - COX-1
 - COX-2
- Most antiinflammatory, analgesic, and antipyretic actions are caused by inhibition of COX-2.
- Most adverse effects are caused by inhibition of COX-1.
- COX-1 is the constitutive isoform, is present in almost all tissues, is produced continuously, and is involved in tissue homeostasis.
- COX-2 is the inducible isoform, is found in macrophages, fibroblasts, chondrocytes, epithelial, and endothelial cells, is highly regulated, and is produced in large amounts in response to infection or the presence of cytokines.

GASTROINTESTINAL TOXICOSIS

- Inhibition of COX isozymes
 - inhibition of prostaglandin E and prostaglandin I

- decreased cytoprotective properties of gastric mucus
- increased hydrogen ion release from the gastric gland through H^+, K^+ -adenosine triphosphatase system
- Direct drug effects
 - acidic nature of some NSAIDs decreases mucosal barrier
 - uncoupling of oxidative phosphorylation decreases mucous barrier function
 - potential of ion trapping of acidic NSAIDs results in a higher local concentration

NEPHROTOXICITY

- Inhibition of prostaglandin synthesis and renal blood flow
- Blocks production of prostaglandin I, prostaglandin E, and prostaglandin D
 - increased vascular resistance
 - constriction of renal capillary beds
 - redistribution of blood away from the medulla
- Vasoconstriction and medullary ischemia that cause renal papillary necrosis

HYPERTHERMIA

- More commonly associated with aspirin
- Uncoupling of oxidative phosphorylation (see Chapter 3)

HEPATOTOXICITY

- More commonly associated with carprofen (Rimadyl)
- Mechanism not well understood
- Thought to be an idiosyncratic susceptibility

Diagnosis

- History of exposure
- Clinical signs
- Clinical pathology
 - blood in stool
 - increased anion gap (aspirin)

- Serum drug concentration
 - available for salicylates and ibuprofen in many hospitals
 - not a useful tool in the treatment of a poisoned veterinary patient

Treatment

- No specific antidote

DECONTAMINATION

- Emesis for recent ingestion for species capable of vomiting
- Activated charcoal, kaolin, and sorbitol cathartic (Toxiban) to adsorb any drug remaining in the gastrointestinal tract
- Gastric lavage or whole-bowel irrigation for large overdoses if necessary
 - formation of bezoars (concretions) in the gastrointestinal tract

INCREASED ELIMINATION

- Aspirin: urinary alkalization with sodium bicarbonate
- Repeated dosing of activated charcoal
 - Many NSAIDs have enterohepatic recycling.

SUPPORTIVE AND SYMPTOMATIC THERAPY

- Fluid treatment of dehydrated patients
- Transfusion therapy if animal is anemic
- Gastrointestinal mucosal protection
 - may prevent further damage to the gastric mucosa
 - sucralfate
 - cimetidine
 - omeprazole
 - misoprostol
 - prostaglandin replacement
 - literature shows mixed results
- Acid-base status
 - Use of bicarbonate should be closely monitored for possible development of pulmonary edema.

- Hyperthermia
 - primarily due to salicylate intoxication
 - cooling blankets needed
- Control of seizures
 - diazepam

Prognosis

- Most gastrointestinal lesions are reversible.
- Perforation of the intestine has a more guarded prognosis because of the possible presence of peritonitis.
- Most renal effects are reversible after discontinuation of the drug.
- Renal papillary necrosis is a permanent change that may not adversely affect renal function in horses.

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Noxious Gases (Ammonia, Carbon Monoxide, Cyanide, Hydrogen Sulfide)

General

Noxious Gases in Veterinary Medicine

Agent	Source	Species	Clinical Signs
Ammonia	Breakdown of nitrogenous waste products Poor ventilation	Swine Poultry	Ocular discharge Ocular irritation Irritation of upper respiratory tract
Carbon monoxide	Incomplete combustion of fossil fuels Poor ventilation	Swine Dogs Cats	Weakness Unconsciousness Fatigue Abnormal reflexes Late-term abortions Cherry-red blood
Cyanide	Combustion of plastics House fires	Small animals	Unconsciousness Apnea Cherry-red blood
Hydrogen sulfide	Anaerobic metabolism of organic materials Sewage lagoons Petroleum production	Cattle Horses Swine	Sudden death Olfactory paralysis at concentrations slightly higher than threshold

Mechanism of Action

CARBON MONOXIDE

- Causes formation of carboxyhemoglobin
- Carbon monoxide has an affinity for heme 240 times that of oxygen.
- Shifts oxygen dissociation curve to the left

- Binding of one heme group to carbon monoxide increases the bond strength of the other oxygen molecules and inhibits oxy-hemoglobin dissociation.
- Binds other heme groups, including cytochromes and myoglobin.

CYANIDE AND HYDROGEN SULFIDE

- Act at the level of the electron transport chain
 - bind tightly to the iron in cytochrome chain
- Prevent oxidative phosphorylation

Diagnosis

- History of exposure
- Ammonia: odor, moist litter, must be evaluated at the animal's level
- Hydrogen sulfide: rotten-egg odor, near a lagoon or decaying organic matter
- Cyanide: bright cherry-red blood, perhaps a bitter almond smell, which cannot be detected by many persons
- Carbon monoxide: cherry-red blood

Treatment

- Often not an option—animals are found dead (hydrogen sulfide, cyanide)
- Identify and correct the source.
- Consider human safety first.
- Immediately remove animals from the contaminated environment.
- Administer first aid.
 - Control the airway.
 - Support breathing with ventilation.
 - Administer 100% oxygen.
 - Place an intravenous catheter and monitor cardiac function.
- Cyanide
 - Administer sodium thiosulfate (with or without sodium nitrite).
- Ammonia poisoning carries the best prognosis, but the animals are predisposed to respiratory infection.

Oak (*Quercus* spp.)

General

- There are more than 60 species of oak trees in the United States, and all species of oak should be considered toxic.
- Oak poisoning has a bimodal seasonal distribution—the number of occurrences increases in the spring and fall.
- In the spring the buds and leaves of shin oak (*Quercus havardii*) and Gambel oak (*Quercus gambell*) cause intoxication in the southwestern United States.
- In the fall, the acorns of all species can be a source of poisoning.
- Deer can survive the winter eating acorns.
- Deer and other browsers have a higher concentration of proline in the saliva.
 - The proline-containing glycoproteins in the saliva may bind the tannins in acorns and prevent absorption in the gastrointestinal tract.

Source

- Newly formed buds, leaves, and acorns from all oak (*Quercus*) species can cause intoxication.
- *Quercus gambelli* (Gambel oak, mountain oak) and *Quercus havardi* (Havard oak, shin oak, shinnery oak) are more commonly described.

Species

- Cattle primarily, especially calves
- Sheep and goats less commonly

Clinical Signs

- After 1–2 weeks of consumption, animals begin to show clinical signs
- Anorexia
- Depression
- Ruminal atony
- Wasting

- Polydipsia, polyuria
- Emaciation
- Ventral edema
- Constipation
- Recumbency
- Death
- Clinical pathologic signs indicative of renal failure
 - increased blood urea nitrogen concentration
 - increased creatinine concentration
 - decreased serum concentrations of sodium and chloride
- Necropsy and histopathologic findings
 - gross lesions in the gastrointestinal tract
 - ulcers
 - hemorrhage
 - perirenal edema
 - pale and sometimes swollen kidneys
 - coagulative necrosis of the proximal renal tubules

Toxicity

- Toxic principle is unknown but thought to be tannins (gallotannins) and their metabolites.
 - Acorns contain 3%–9% tannin.
 - Tannins are hydrolyzed in rumen to produce a number of phenolic compounds.

Mechanism of Action

- Hypothesized to be the action of absorbed phenolic substances or metabolites.
- The phenols bind to proteins and of particular interest are the renal tubular endothelial cells.

Diagnosis

- Season of the year
- Exposure to oak trees and clinical signs of renal failure

- Azotemia or dehydration with low specific gravity of urine is indicative of renal failure in cattle.

Treatment

- No specific antidote
- Remove from pasture.
- Provide symptomatic therapy.
 - Correct dehydration with IV fluids or oral replacement therapy.
 - Offer high-quality legume hay.
 - Administer propylene glycol by mouth to animals with severe anorexia.
 - In early spring and fall, limit exposure to pastures with a large number of oak trees.
 - Supplement with corn-based feed that has 10% calcium hydroxide (slaked lime).
Feed at a rate of 2 lb (0.9 kg) per head per day for calves.
4 lb (1.8 kg) per head per day for mature cattle.

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ORGANOCHLORINES (CHLORINATED HYDROCARBON INSECTICIDES)

General

- Because many representatives of this class of compounds are no longer approved for use in the United States, intoxication with these compounds is becoming less common.

- The primary reason for the diminished use in the United States is related to the environmental persistence of these compounds.
- They do not degrade rapidly in the environment.
- The organochlorines are highly lipid soluble and bioaccumulate in the food chain—one of the reasons the bald eagle was placed on the endangered species list.
- Animals can be exposed to discontinued organochlorines in old stores of insecticides in barns or sheds.

Source

DICHLORODIPHENYLETHANES

- Dichlorodiphenyltrichloroethane (DDT)
- Dicofol
 - Miticide for plants
- Methoxychlor
 - Flea and tick powder, fly dust, fruit tree sprays, insecticide for flowers, sprays for forage

ARYL HYDROCARBONS

- Lindane (Figure 4–25)
 - Mange and tick treatment, grain treatment, insecticide for trees and gardens
- Mirex
- Chlordecone (Kepone)
- Paradichlorobenzene (Figure 4–26)
 - Moth balls and moth repellent products

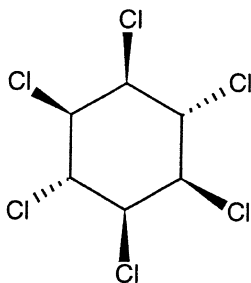


Figure 4–25 Chemical structure of lindane.

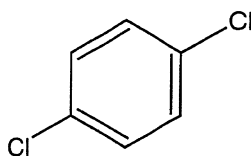


Figure 4-26 Chemical structure of paradichlorobenzene.

CYCLODienes

- Aldrin (Figure 4-27)
- Chlordane
- Dieldrin (Figure 4-28)
- Endosulfan
 - Insecticide for gardens and forages
- Endrin
- Heptachlor (Figure 4-29)
- Toxaphene

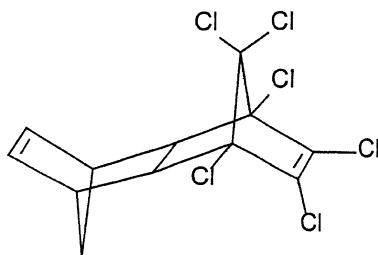


Figure 4-27 Chemical structure of aldrin.

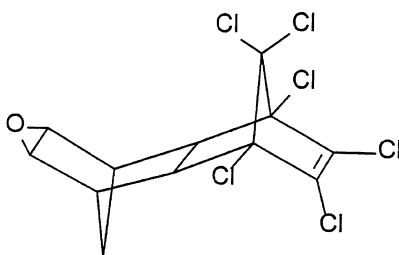


Figure 4-28 Chemical structure of dieldrin.

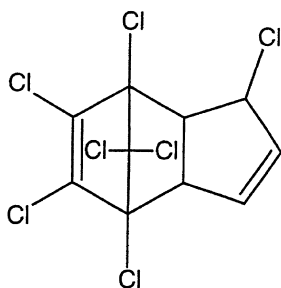


Figure 4–29 Chemical structure of heptachlor.

Species

- All species are susceptible.

Clinical Signs

- Neurologic syndromes
- Agitation, frenzied behavior
- Abnormal gait
- Hypersalivation
- Muscle fasciculation
- Blepharospasm
- Central nervous system depression
- Prolonged seizures
- Hyperthermia
- Decreased reproductive efficiency (long-term exposure)

Toxicity

- Cats are more susceptible than other species.
- The cyclodienes are the most toxic but are not currently approved.

Mechanism of Action

CYCLODIEINES

- Inhibition of γ -aminobutyric acid (GABA)–mediated chloride receptor

- GABA antagonist
- decreased repolarization of neuronal membrane
- See Chapter 3.
- Inhibition of adenosine triphosphatase in neuronal and cardiac membranes
- Increased calcium concentration in presynaptic terminal
- Increased calcium-mediated neurotransmitter release

DDT

- Diminished repolarization
- inhibition of adenosine triphosphate (ATPase) in neuronal cells
- actions on potassium channels
diminished potassium flux across neuronal membrane
- actions on sodium channels
diminished inactivation of sodium channels
increased sodium flux across neuronal membranes
- inhibition of calmodulin
decreased calcium-mediated neurotransmitter release in neurons
- Decreased threshold for stimulation of nerves

REPRODUCTIVE EFFECTS

- Lindane-treated rams
 - decreased concentration of luteinizing hormone
 - decreased concentrations of estrogen and testosterone
- Decreased in vitro ATPase activity in cells of oviduct or endometrium
- Disruption of estrus synchronization in ewes

Diagnosis

- History of exposure
- Presence of clinical signs
 - not pathognomonic
 - several other toxic exposures and infectious diseases cause tremors, seizures, and depression

- Chemical analysis for organochlorine insecticide
 - feed sources
 - blood
 - liver
 - brain
 - fat
 - milk
 - hair
 - kidney
 - stomach content

Treatment

DECONTAMINATION

- Dermal
 - Wash animals with mild detergent.
 - Prevent human exposure during washing.
- Oral
 - Administer activated charcoal and cathartic agent.
 - Repeat dosing of activated charcoal if necessary.
- Mineral oil may be more effective than saline cathartics or sorbitol.

SUPPORTIVE CARE

- Control seizures.
 - diazepam
 - phenobarbital
 - pentobarbital
- Move to an environment that prevents trauma during seizures.
- Facilitate elimination.
 - Food animals that survive an acute episode may contain insecticide residue in edible tissues.
 - Increased mobilization of fat increases elimination of insecticide.
 - Residues may exist for days or months.

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- Tiemann U, Kuchenmeister U. Influence of organochlorine pesticides on ATPase activities of microsomal fractions of bovine oviductal and endometrial cells. *Toxicol Lett.* 1999;104:75–81.
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Organophosphorus and Carbamate Intoxication

General

- Organophosphorus and carbamate compounds are commonly used in agriculture as an insecticide on forage, grain crops, or stored grain.
- They also are available for household use to control pests in the yard, garden, and home or directly on animals.
- The volume of organophosphorus and carbamate insecticides sold in the United States indicates there is continued risk associated with these compounds.

Source

- Liquid sprays (concentrates)
- Powders
- Dips
- Flea collars
- Fly bait (granular)

ORGANOPHOSPHORUS AGENTS

- Chlorpyrifos (Dursban) (Figure 4–30)
- Coumaphos (Co-Ral) (Figure 4–31)
- Diazinon (Diazinon) (Figure 4–32)
- Fenthion (Baytex, Tiguvon)
- Malathion (Cythion) (Figure 4–33)
- Methyl parathion (Penncap M)
- Temephos (Abate)

CARBAMATE AGENTS

- Aldicarb (Temik) (Figure 4–34)
- Carbaryl (Sevin)
- Carbofuran (Furadan)
- Methiocarb (Mesurol)
- Methomyl (Golden Marlin) (Figure 4–35)
- Propoxur (Baygon)

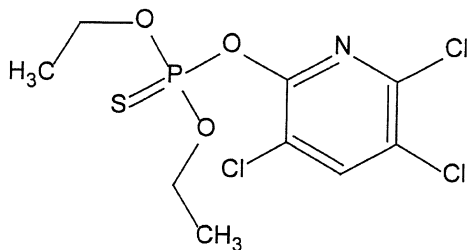


Figure 4–30 Chemical structure of chlorpyrifos.

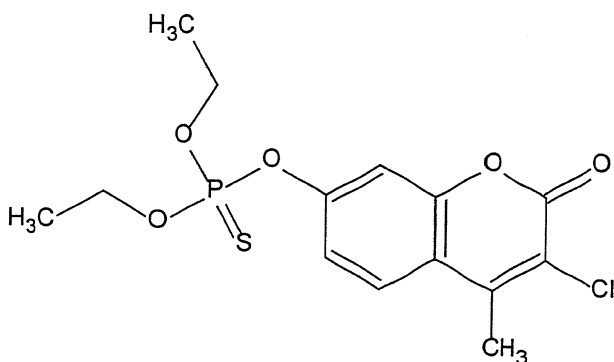


Figure 4-31 Chemical structure of coumaphos.

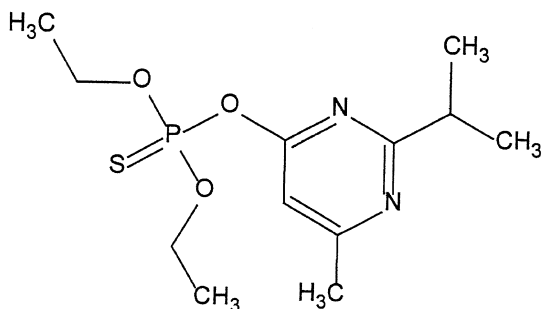


Figure 4-32 Chemical structure of diazinon.

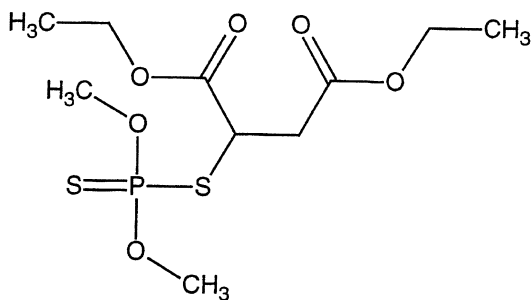


Figure 4-33 Chemical structure of malathion.

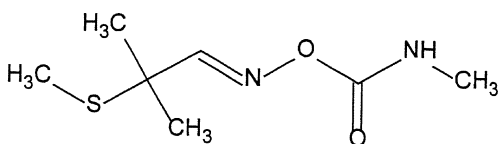


Figure 4–34 Chemical structure of aldicarb.

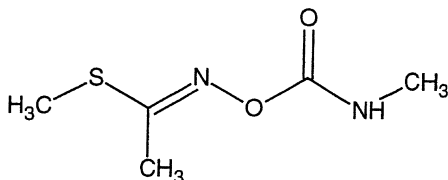


Figure 4–35 Chemical structure of methomyl.

Species

- All species are susceptible.

Clinical Signs

- Cholinergic signs predominate.

MUSCARINIC SIGNS

- Salivation
- Lacrimation
- Miosis
- Urination
- Dyspnea (bronchial secretions and bronchoconstriction)
- Defecation
- Colic

NICOTINIC SIGNS

- Muscle fasciculations
- Tremors
- Tachycardia

CENTRAL NERVOUS SYSTEM SIGNS

- Depression or stimulation
- Convulsions

Toxicity

- Toxic dose varies according to species and agent.
- Metabolism of agent may affect the probability of intoxication.
- Ester hydrolysis detoxifies organophosphorus compounds and decreases the risk of intoxication.

microsomal activation

organophosphorus agents with a sulfur moiety

sulfur replaced with oxygen after activation

resulting compound that is more potent than parent

example: parathion (Figure 4–36) is metabolized to paraoxon, and paraoxon presents a greater toxicologic risk

- Species differences
 - cats more susceptible than dogs
- Chlorpyrifos (Dursban) susceptibility
 - bulls more sensitive than steers

Mechanism of Action**ORGANOPHOSPHORUS AGENTS**

- Agent binds to the serine hydroxyl group of the esteratic site of the acetylcholinesterase enzyme.

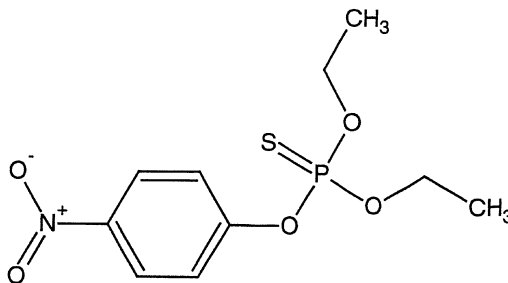


Figure 4–36 Chemical structure of parathion.

- Agent is partially hydrolyzed, resulting in a “leaving” group.
- The result is a stronger bond between the compound and the enzyme.
- With many organophosphorus agents, this bond produces an irreversibly bound enzyme (phosphorylated enzyme).
- Acetylcholine is not hydrolyzed in the synaptic cleft.
- Stimulation of the postsynaptic acetylcholine receptors is increased.
- Function of the synapse is normal when a new acetylcholinesterase enzyme is synthesized because spontaneous regeneration is slow.

CARBAMATES

- Binding and inhibitory actions are similar to those of organophosphorus agents.
- After hydrolysis of compound, acetylcholinesterase undergoes carbamoylation.
- Carbamates are poor substrates for acetylcholinesterase.
- Spontaneous reactivation of enzyme is rapid.

Diagnosis

- Pathognomonic clinical signs
- Chemical analysis of insecticide in gastric contents or tissues
 - only indicates exposure
- Cholinesterase inhibition
 - Cholinesterase activity is measured in the following samples:
 - whole blood (heparin or EDTA tubes)
 - blood, blood clots, brain, eyes chilled after necropsy
 - inhibition of activity by at least 50% indicative of intoxication
 - erythrocyte cholinesterase
 - “true cholinesterase” same as neural isoform
 - plasma cholinesterase
 - “pseudocholinesterase” produced in liver
- Methods of detection
 - Ellman
 - Michel
 - pH stat

Treatment

DECONTAMINATION

- Gastrointestinal
 - Administer activated charcoal and cathartic agent to prevent further absorption from the intestine.
- Dermal
 - Wash with mild detergent and warm water.
 - Wear protective clothing while washing animals.

SPECIFIC ANTIDOTES

- Atropine to control muscarinic parasympathetic signs (salivation and others)
- Oxime therapy (pralidoxime) to regenerate inhibited acetylcholinesterase
 - greater efficacy in the first 24 hours
 - not indicated for carbamate intoxication

SYMPTOMATIC

- Intubation and artificial respiration for animals with severe dyspnea
- Diphenhydramine to block the nicotinic effects

References

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Petroleum Products (Oil Intoxication, Hydrocarbon Intoxication)

General

- The primary mechanism of intoxication by petroleum products is aspiration pneumonia.

- The propensity for a specific hydrocarbon to induce toxicosis is related to the physicochemical properties of the hydrocarbon.
- The more important properties include viscosity, volatility, and surface tension.
- Common terms to describe the relative sulfur content of oil are “sweet” and “sour” for low and high sulfur, respectively.
- The sulfur content is not directly related to toxic potential.
- Cattle often are intoxicated around oil wells because of natural curiosity, indiscriminate eating habits, and contamination of pastures or water sources.

Source

- The sources of petroleum hydrocarbons range from crude oil to highly refined volatile petroleum distillates.
- Crude oil is a complex mixture of different hydrocarbon components.

PETROLEUM INTOXICATION

- Diesel fuel
- Engine cleaners
- Gasoline
- Kerosene
- Lamp oil
- Lighter fluid
- Lubricating and motor oils
- Mineral spirits
- Paint
- Paint thinner
- Propellants
- Vehicles for insecticides

CHLORINATED HYDROCARBONS

- Carbon tetrachloride
- Chloroform
- Methylene chloride
- Trichloroethylene

AROMATIC HYDROCARBONS

- Benzene
- Styrene
- Toluene
- Xylene

Species

- Dogs, cats, and cattle primarily

Clinical Signs

RESPIRATORY

- Aspiration pneumonia
- Dyspnea
- Coughing
- Increased respiratory rate
- Hypoxemia
- Death
- Lesions
 - tracheitis, bronchitis
 - bronchopneumonia
 - lipoid pneumonia

GASTROINTESTINAL

- Anorexia
- Bloat
- Weight loss
- Decreased ruminal motility
 - constipation

NEUROLOGIC

- Depression
- Posterior weakness
 - ataxia

OTHER SIGNS

- Arrhythmia
- Nephrotoxicity
- Renal tubular nephrosis

Toxicity

- Depends on the source of hydrocarbon
- Exposure may involve dermal or oral routes
 - effect of weathering on toxicity of crude oil in cattle

Weathered oil is crude oil that has been exposed to the environment with elimination of many of the volatile components.

fresh crude threshold dose: 2.5 to 5.0 mL/kg

weathered crude threshold dose: 8.0 mL/kg

Mechanism of Action

- The risk of aspiration pneumonia is indirectly proportional to viscosity and directly related to volatility.
 - probable aspiration: low viscosity (ether, mineral seal oil)
 - unlikely aspiration: high viscosity (tar, oil, grease)

MECHANISM OF ASPIRATION

- Aspiration occurs during ingestion or vomiting.
- Bronchospasm
- Deeper penetration into the lung by lower viscosity hydrocarbons
- Greater irritation by higher volatility compounds
- Decrease in surfactant caused by hydrocarbons, leading to alveolar collapse
- Direct chemical irritation of pulmonary tissues
- Capillary damage that causes chemical pneumonitis

LIPID PEROXIDATION

- Especially with chlorinated hydrocarbons
- Highly polar compounds concentrated in central nervous system and fat
 - production of reactive intermediates

GASTROINTESTINAL

- Disruption of ruminal function caused by
 - petroleum hydrocarbons
 - salt water
- Possible alterations in
 - ruminal flora and enzymatic processes
 - ruminal and gastrointestinal epithelium

Diagnosis

- History of exposure
- Clinical signs
 - oil staining around the mouth or nostril
 - oil in the feces, possibly several days after ingestion of oil
- Odor of hydrocarbons
- Diagnostic toxicology
- Because cases in cattle may involve litigation, contact a veterinary diagnostic laboratory before obtaining samples.
- Histopathology
 - formalin fixed tissues
 - liver, kidney, brain, lung, ruminal epithelium, gastrointestinal mucosa
- Refrigerated or frozen tissues obtained at necropsy
 - 500 g liver, kidney, rumen, and intestinal content
 - 200 g lung
 - half of brain
 - one eyeball
- Antemortem samples
 - 200–500 g ruminal content, fecal material
 - 10–20 mL anticoagulated whole blood, serum
- Suspect materials
 - 500 mL water, sludge pit sample
 - 200 mL spilled oil

Treatment

- No specific antidote

DERMAL DECONTAMINATION

- Wash with mild detergent.
- Observe for hypothermia.

GASTROINTESTINAL DECONTAMINATION

- Do not perform emesis and gavage.
 - may reexpose the respiratory system to the hydrocarbons
 - exception is hydrocarbons that are vehicles for more toxic agents (insecticides)
- Administer activated charcoal and cathartic agent.
 - may assist in removal of turpentine and kerosene

SUPPORTIVE AND SYMPTOMATIC

- Treatment of cattle for pneumonia usually is not successful.
 - Administer broad-spectrum antibiotics.
 - Do not market animals until complete resolution of clinical syndrome
- Remove cattle from area of contamination.
- Provide high-quality forage (alfalfa) and clean water.
- Provide oxygen therapy and cage rest for small animals with dyspnea.
- Monitor respiratory and cardiac function.

Prevention

- Construct good fences to prevent cattle from gaining access to wells or tank batteries.
- Monitor equipment and wells on property for signs that maintenance is needed.

Risks Associated with Petroleum Production (Primarily for Cattle)

PHYSICAL

- Trauma
 - well pumps

- stumbling into pits
- Electrocution
 - electric pumps, tank pumps
- Drowning
 - falling into sludge pits

METALS

- Lead
 - pipe joint compound (pipe dope)
 - See *Lead Poisoning (Plumbism)*.
- Arsenic
 - corrosion inhibitors
 - See *Arsenic (Inorganic and Organic)*.
- Chromate
 - corrosion inhibitors

SODIUM

- saltwater pumped out of well, separated from crude oil, and consumed by cattle
- See *Sodium Ion Toxicosis, Water Deprivation*.

SULFUR

- hydrogen sulfide production
- See *Noxious Gases (Ammonia, Carbon Monoxide, Cyanide, Hydrogen Sulfide)*.

CORROSIVES

- acids (hydrochloric, hydrofluoric, acetic, and formic) used to fracture oil-bearing geologic formations
- fracking
- See *Corrosives*.

PETROLEUM

- Crude oil
 - diesel fuel
- Grease
 - condensation petroleum “drips”

References

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Phenolics and Coal Tars (Pitch Poisoning, Clay Pigeon Poisoning)

General

- The use of phenol as a disinfectant is less common than in the past.
- Phenolics are a common ingredient in household cleaners and disinfectants.
- Coal tar shampoos can cause poisoning in small animals.
- Swine have been poisoned after consuming clay pigeons used for trap shooting.

Source

- Phenol (carbolic acid)
 - topical antiseptics (e.g., Campho-phenique)
 - antiseptics—no longer commonly used
- Other phenolics
 - coal tar shampoo
 - creosote
 - creosol
 - phenylphenol (active ingredient in Lysol)
 - dinitrophenol (see Chapter 3)
- Clay pigeons for trap shooting

Species

- All species are susceptible.
- Cats are particularly sensitive.
- Swine have been intoxicated after grazing on fields used for trap shooting.

Clinical Signs

- Acute gastrointestinal signs followed in some instances by fulminant hepatic failure or renal damage
- Hypersalivation
- Vomiting
- Ataxia and weakness
- Diarrhea
- Gastroenteritis
- Abdominal pain
- Muscle fasciculations
- Shock
- Methemoglobinemia
- Depression or unconsciousness
- Sternal recumbency

Toxicity

- Phenol is rapidly absorbed by the oral and dermal routes.

Mechanism of Action

- Phenol and related compounds are directly cytopathic.
 - denatures protein
 - alters the permeability of cell membranes
 - causes coagulative necrosis
- Phenolics can induce oxidative stress in a variety of cells.

Diagnosis

- History of exposure to phenol or phenolics
- Clinical signs

- Oral exposure
 - visual examination of the oral and pharyngeal mucosa
 - ulceration or chemical burns
- Dermal and ocular exposure
 - examination of skin for chemical burns
 - ophthalmic examination of cornea
- Chemical analysis
 - vomitus
 - urine
 - feces
 - blood
- Cyanosis or methemoglobin

Treatment

DERMAL OR OCULAR EXPOSURE

- Treat as a corrosive exposure.
- Wash
- Administer standard burn and wound therapy.

ORAL EXPOSURE

- *Do not induce emesis*—phenolics are corrosive.

DECONTAMINATION

- Administer activated charcoal and cathartic agent.
- Some authors suggest olive oil is more effective.
 - small animals
 - 10 mL/kg olive oil

SUPPORTIVE AND SYMPTOMATIC THERAPY

- *N*-Acetylcysteine
 - may prevent renal and hepatic damage
 - loading therapy: 140 mg/kg IV
 - maintenance therapy: 50 mg/kg every 4 hours for 15 doses
- Methemoglobinemia

- methylene blue: 8 mg/kg IV
- ascorbic acid: 50 mg/kg
- fluid therapy

References

- Abdullahi SU, Adeyanju JB. Phenol toxicity in a dog. *Vet Hum Toxicol.* 1983;25:407.
- Coppock RW, Mostrom MS, Lillie LE. Toxicology of detergents, bleaches, antiseptics and disinfectants. In: Kirk RW, Bonagura JD, eds. *Current Veterinary Therapy, 10: Small Animal Practice*. Philadelphia: WB Saunders; 1989:162–171.
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Pigweed (*Amaranthus Retroflexus* and Other *Amaranthus* spp.)

General

- Problem when animals are hungry and newly introduced to a young, dense stand of the plant
- Variable morbidity, high mortality

Source

- Members of the genus *Amaranthus* throughout the United States in waste areas, ditches, fields, barnyards
- Prominently spiked inflorescence

Species

- Pigs, calves, cattle, and possibly sheep

Clinical Signs

PERIRENAL EDEMA SYNDROME

- Occurs in pigs
- Death within 2 days of ingestion
- Incoordination

- Weakness
- Trembling and knuckling of hind limbs
- Sternal recumbency
- Paralysis
- Alert, good appetite
- Coma
- Ventral edema
- Distended abdomen
- Nephritis if the animal survives

CLINICAL PATHOLOGY

- Increased serum potassium, blood urea nitrogen, creatinine concentrations
- Hypocalcemia, hypomagnesemia, hyperkalemia
- Elevated creatinine phosphokinase concentration

GROSS AND HISTOPATHOLOGIC SIGNS

- Perirenal edema
- Pale kidneys
- Coagulative necrosis of proximal and distal convoluted tubules
- Shrunken glomeruli
- Casts in the collecting tubules

Toxicity

- Animals must consume large quantities for 5–10 days.
- Hay retains toxic properties.

Mechanism of Action

- Several possible toxic principles are present in pigweed.
- The toxic principle that causes perirenal edema and nephrosis is not known.
- Phenolics have been suggested.

OXALATE

- Pigweed contains oxalate.
- Oxalate-induced renal tubular damage can occur.
- As much as 30% of dry weight of plant may be oxalates.
- The concentration is higher in the leaves than in the stem.

NITRATE

- Pigweed can accumulate nitrates.
- 0.04%–30% of dry weight

Diagnosis

- History of exposure and consumption
- Clinical signs
 - posterior weakness, ataxia
 - sternal recumbency
 - normal temperature
- Gross pathologic signs

Treatment

- Therapy is of little value.
- Remove the animal from pasture.
- Slowly introduce pigs to pasture.
- Administer fluid therapy.
- Provide symptomatic therapy.

References

- Casteel SW, Johnson GC, Miller MA, et al. *Amaranthus retroflexus* (red-root pigweed) poisoning in cattle. *J Am Vet Med Assoc.* 1994; 204:1068–1070.
- Kerr LA, Kelch WJ. Pigweed (*Amaranthus retroflexus*) toxicosis in cattle. *Vet Hum Toxicol.* 1998;40:216–218.

Poison Hemlock (*Conium Maculatum*)

General

- Other common names are European hemlock and spotted hemlock.
- Although in the same family as the water hemlock, these plants are not synonymous.
- Intoxication with this plant is less common than intoxication with many others.

Source

- Fresh or dried stems, leaves, or seeds of the poison hemlock

Species

- Cattle, pigs

Clinical Signs

CENTRAL NERVOUS SYSTEM SYNDROME

- Stimulation followed by depression
- Nervousness
- Tremors
- Incoordination
- Hypersalivation
- Frequent urination
- Depression
- Progressive paresis
- Bradycardia
- Respiratory depression
- Coma
- Death due to respiratory paralysis

TERATOGENIC SYNDROME

- Carpal flexure
- Dam must be exposed early in gestation (days 50–75)

- Dam may not express any clinical signs
- Crooked calf syndrome
- Arthrogryposis (calves)
- Cleft palate (piglets)

Toxicity

- Cows: coniine 3.3 mg/kg body weight—clinical signs
- Mares: coniine 15.5 mg/kg body weight—clinical signs
- Ewes: coniine 44.0 mg/kg body weight—clinical signs
- Swine: fresh plant 9 g/kg body weight—lethal effects

Mechanism of Action

- The toxic principles are piperidine alkaloids.
 - coniine (Figure 4–37)
 - *N*-methyl coniine
 - γ -coniceine
 - conhydrine
 - pseudoconhydrine
- The piperidine alkaloids acts on the nicotinic receptors.
 - action of toxic principle or nicotinic receptors is similar to nicotine
 - initial stimulation followed by inhibition
 - central nervous system and neuromuscular junction blocking effects predominant
- Teratogenic effects (arthrogryposis) may be caused by reduced activity of the fetus.

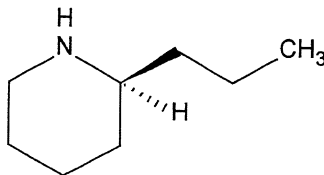


Figure 4–37 Chemical structure of coniine.

- This may be a common mechanism of action for alkaloids that induce crooked calf syndrome.

Diagnosis

- History of exposure to and consumption of the plant
- Clinical signs
- A mousy odor to the urine, expired breath, or ruminal contents

Differential Diagnosis

Teratogenic Plants

Common Name	Scientific Name	Animal Affected
Locoweed	<i>Astragalus</i> spp. <i>Oxytropis</i> spp.	Cattle, sheep
Lupine	<i>Lupinus</i> spp.	Cattle
Pea, peavine	<i>Lathyrus</i> spp.	Pigs, horses, cattle, sheep
Poison hemlock	<i>Conium maculata</i>	Cattle, pigs, sheep, goats
Skunk cabbage, veratrum	<i>Veratrum californicum</i>	Sheep
Sudan grass	<i>Sorghum</i> spp.	Horses
Tobacco, tree tobacco	<i>Nicotiana</i> spp.	Pigs, cattle, sheep

Treatment

- No specific antidote
- Symptomatic
- Prevention of intoxication
 - Fence off areas with the plants.
 - Apply herbicides to areas with the plants.

References

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Pyrethroids and Pyrethrins

General

- As a class of insecticides, these agents carry low risk of mammalian intoxication.
- Pyrethrum is a naturally occurring combination of insecticidal compounds derived from the flowers of *Chrysanthemum* spp. of plants.
- Pyrethrins are individual representatives of this group of compounds extracted from botanical sources.
- Pyrethroids are synthetically produced chemicals similar to natural pyrethrins.
- Pyrethroids have a broader insecticidal spectrum of activity and greater environmental stability.
- Most commercially available pyrethroids also contain synergists (piperonyl butoxide or MGK 264) that inhibit metabolism of the insecticide and may potentiate intoxication.

Source

- Insecticides (dips, shampoos)
- Type I compounds
 - allethrin
 - permethrin
 - pyrethrin (Figure 4–38)
 - tetramethrin
- Type II compounds
 - cypermethrin
 - deltamethrin
 - fenpropanthrin
 - fenvelerate (Figure 4–39)

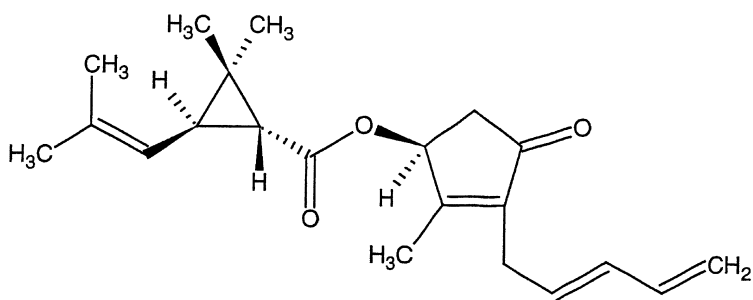


Figure 4–38 Chemical structure of pyrethrin.

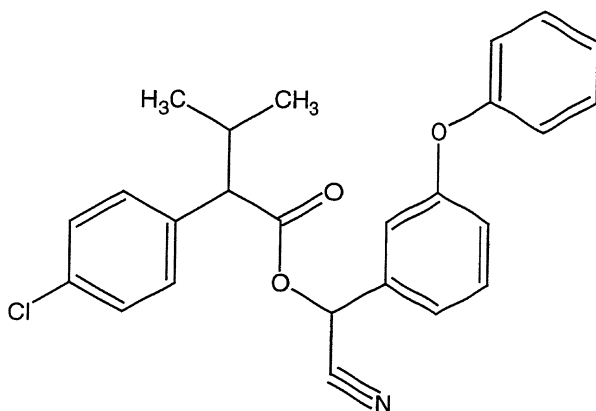


Figure 4–39 Chemical structure of fenvalerate.

Species

- Cats and dogs more commonly
- Fish more sensitive than mammals

Clinical Signs

- Hypersalivation
- Tremors
- Hyperexcitability or depression

- Seizures
- Vomiting
- Diarrhea

Mechanism of Action

- Pyrethroids act on several intracellular, neuronal sites.
- A common feature of the proposed mechanisms is an increase in the amount of neurotransmitter released from presynaptic nerve terminals.
- The action on neuronal sodium channels is persistent depolarization.
 - prolonged sodium influx through the channel
 - delay in closure of the “inactivation” gate of the sodium channel
- Antagonism of the γ -aminobutyric acid (GABA)–mediated chloride channel, especially type II pyrethroids
 - antagonism of the GABA receptor complex
 - reduction of chloride influx through the channel
- Inhibition of synaptic Ca^{2+} , Mg^{2+} -adenosine triphosphatase
 - increased intracellular calcium
- Inhibition of neuronal calmodulin
 - increased intracellular calcium

Diagnosis

- Clinical signs
- History of exposure
- No specific diagnostic test for pyrethroids
- Whole-blood analysis for acetylcholinesterase activity to differentiate from carbamate and organophosphorus intoxication
 - Animals with pyrethroid intoxication should have normal acetylcholinesterase activity.
- Some laboratories can perform chemical analysis for presence of pyrethroids.
 - fat, skin, liver, and brain samples obtained at necropsy
 - only indicates exposure, not a definitive diagnosis

Treatment

SEIZURE CONTROL

- Administer diazepam 0.2–2.0 mg/kg IV.

DERMAL DECONTAMINATION

- Use a mild detergent with warm water.
- Wear gloves and protective clothing while washing the animal.

GASTROINTESTINAL DECONTAMINATION

- Induce emesis, if indicated, within 1–2 hours of ingestion.
- Administer activated charcoal and cathartic agent within 3–4 hours of ingestion.

SYMPTOMATIC THERAPY

- Administer fluids to correct dehydration after vomiting or diarrhea.
- Inject atropine to decrease salivation, especially in the treatment of cats.

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Pyrrolizidine Alkaloid Intoxication

General

- Also called *walking disease* or *river bottom disease*.
- As a chemical entity, pyrrolizidine alkaloids have a common mechanism of action with a similar clinical presentation.
- Many plants from the Boraginaceae, Compositae, and Leguminosae families contain these alkaloids.
- These plants are not palatable and are not readily consumed by animals unless they are very hungry or no other forage is available.
- Another means of intoxication is incorporation of these plants into hay, harvesting of the plant with grains, or grinding them into complete feeds.
- Animals readily consume the hay or complete feed.

Source

- Members of the genera *Senecio*, *Crotalaria*, *Echium*, *Heliotropium*, and others
- Broom groundsel (*Senecio spartioides*)
- Common groundsel (*Senecio vulgaris*)
- *Crotalaria* (*Crotalaria retusa*)
- *Echium* (*Echium vulgare*)
- *Echium*, Patterson's curse (*Echium lycopsis*)
- Heliotrope (*Heliotropium* spp.)
- Hound's tongue (*Cynoglossum officinale*)
- Rattle pod, showy crotalaria (*Crotalaria spectabilis*)
- Riddell's groundsel (*Senecio riddellii*)
- Tansy ragwort (*Senecio jacobaea*)
- Woolly groundsel (*Senecio douglasii* var. *longilobus*)

Species

- Horses and cattle primarily
- Horses more sensitive than cattle
- Sheep less sensitive unless they have copper toxicosis.

Clinical Signs

ACUTE SYNDROME

- Acute hepatic failure
 - icterus
 - anorexia
 - depression (hepatoencephalopathy)
 - edema
 - ascites
- Gastrointestinal ulcers
- Rectal prolapse
- Extensive centrilobular hepatic necrosis and hemorrhage

CHRONIC SYNDROME

- No signs of hepatic disease in some instances
- Anorexia, emaciation
- Decreased milk production
- Weakness
- Recumbency
- Abdominal straining, rectal prolapse
- Photosensitization
- Markedly increased serum hepatic enzyme activity
- Liver firm and small
- Multifocal hepatic necrosis
- Megalocytes
- Portal fibrosis
- Proliferation of the bile ducts
- Photosensitization (see Chapter 2)

Toxicity

- Content of the alkaloids in plants can vary greatly.
 - *Senecio riddellii* can range from 0.2%–18% alkaloid.
 - plants more toxic immediately before flowering
- Consumption of 1%–5% of body weight over a period of several days can induce acute toxicity.

Mechanism of Action

- Examples of pyrrolizidine alkaloids
 - *Senecio* spp.
 - retrorsine
 - riddelliine
 - senecionine
 - seneciphylline
 - *Crotalaria* spp.
 - monocrotaline
- The parent compound (alkaloid) does not produce damage.
 - Metabolites induce liver injury.
- Species differences in metabolism
 - Sheep and goats are more tolerant of the pyrrolizidine alkaloids.
 - Suggested mechanisms explaining the differences are as follows:
 - differences in ruminal metabolism of the alkaloids
 - differences in hepatic metabolism of the alkaloids
 - differences in absorption or excretion
- Pyrrolizidine alkaloid metabolism occurs through the mixed-function oxidases of the liver.
 - Reactive metabolites (pyrroles) interact with sulfhydryl group of proteins, peptides, and enzymes within hepatic tissues.
 - Glutathione is depleted.
 - Pyrroles can form adducts with DNA and RNA or may interact and inactivate DNA or RNA polymerases.
 - decreased protein synthesis
 - decreased cell replication
 - production of enlarged cells (megalocytes) in the liver

Diagnosis

- Clinical signs
- Evidence of exposure to and consumption of the plant
- Histopathologic examination of liver
- Chemical analysis of tissue-bound metabolite (pyrroles)

- not commonly performed
- may be inconclusive in chronic syndrome

Treatment

- Treatment is of little value if an animal has clinical signs.
- Liver damage is extensive by this time.
- Regeneration is not likely.
- Surviving animals are “poor doers.”

PREVENTION

- Grazing sheep on pastures before grazing cattle
- Feeding sulfur-containing amino acids has not proved beneficial in livestock.

RESIDUES

- Alkaloids and metabolites may be passed in milk.
- Animals presented for slaughter with subclinical toxicosis have tissue residues, especially in the liver; their livers may be condemned because of gross abnormalities.

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White RD, Swick RA, Cheeke PR. Effects of dietary copper and molybdenum on tansy ragwort (*Senecio jacobaea*) toxicity in sheep. *Am J Vet Res.* 1984;45(1):159–161.

Red Maple (*Acer Rubrum*)

General

- Intoxication is more common in the late summer and fall because of consumption of wilted or dried leaves.
- Animals can be poisoned by branches downed in a storm.
- The tree grows primarily in the eastern United States; however, intoxication can occur throughout the United States.

Source

- Leaves, particularly wilted or dried, of the red maple tree.
- Other members of the genus *Acer* may contain the toxic principle.

Species

- Horses and other members of the equid family are most sensitive.

Clinical Signs

- Signs associated with methemoglobinemia and hemolytic anemia
- Icterus
- Cyanosis
- Depression
- Dehydration
- Hemoglobinuria
- Decreased packed cell volume
- Heinz bodies
- Methemoglobinemia
- Polypnea
- Tachycardia

Toxicity

- Experimental studies have reproduced the syndrome in animals fed 1.5–3.0 mg/kg body weight.

- Overnight freezing did not reduce the toxicity of the leaves.
- Toxicity was retained in dried leaves for 30 days.
- Freshly harvested leaves fed immediately did not cause toxicosis.

Mechanism of Action

- The toxic principle
 - is unknown.
 - is found in the leaves of the red maple tree.
 - causes oxidative stress with resulting methemoglobin, Heinz body formation, and anemia.

Diagnosis

- Clinical signs
- Spectrophotometric determination of blood for methemoglobin
- Complete blood cell count
 - evidence of hemolytic anemia
 - decreased packed cell volume
- Exposure to wilted or dried red maple leaves

Differential Diagnosis of Hemolytic Anemia in Horses

- Autoimmune hemolytic anemia
- Ehrlichiosis
- Equine infectious anemia
- Leptospirosis
- Disorders caused by other plants or chemicals
- Piroplasmosis
- Red maple poisoning

Treatment

- Remove leaves and tree limbs from the area where the horses are kept.
- Blood transfusion if packed cell volume decreases to less than 10%
- Administer fluid therapy.

- Prevent shock.
- Correct dehydration and electrolyte abnormalities.
- Maintain perfusion to the kidneys.
- Prevent hemoglobin-induced renal damage.
- Manage methemoglobinemia.
- Administer ascorbic acid.
- Do not administer methylene blue—may induce Heinz body formation in horses and is ineffective in reducing methemoglobin.

References

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Selenium

General

- Selenium intoxication may manifest as an acute or chronic syndrome.

- Plants that accumulate selenium generally have an objectionable odor and are not consumed by animals given a choice of forage.
- Wilted plants may not possess this refusal property.
- Animals poisoned may have a garlic-like odor.

Source

OBLIGATE SELENIUM INDICATOR PLANTS

- Need selenium for growth and can accumulate several hundred parts per million selenium
 - *Astragalus* spp. (locoweed)
 - *Oenopsis* spp. (goldenweed)
 - *Stanleya* spp. (prince's plume)
 - *Xylorrhiza* spp. (woody aster)

FACULTATIVE SELENIUM INDICATOR PLANTS

- Selenium not needed for growth; may accumulate 25–100 ppm selenium if present in soil
 - *Atriplex* spp. (saltbush)
 - *Machaeranthera* spp.
 - *Sideranthus* spp.

DIETARY SUPPLEMENTATION

- Prevention of white muscle disease (selenium deficiency)
- Errors in calculation

GRAIN

- Grains grown in areas with soil high in selenium
- Northern plains states

Species

- Swine, horses, cattle, sheep, waterfowl

Clinical Signs

ACUTE AND SUBACUTE INTOXICATION

- Ataxia, lack of coordination

- Anorexia
- Dyspnea
- Abdominal pain (grinding of teeth)
- Cyanosis
- Increased heart rate
- Gross lesions
 - pale myocardium
 - petechiae and ecchymosis of epicardium and endocardium
 - congestion of gastrointestinal organs
 - pulmonary edema

CHRONIC INTOXICATION

- Alterations of hair (coat)
 - loss of tail switch (bobtail)
 - thin mane
 - alopecia
 - roughened coat
- Laminitis and lameness
 - sloughing of hoof
 - breaks in hoof at coronary band
- Poor growth, decreased weight gain

Toxicity

- Dietary concentrations >5 ppm may induce toxicosis.
- Acute intoxication may follow doses of 1–5 mg/kg.

Mechanism of Action

- Elevated selenium concentration
 - Selenium can act as an oxidant that causes oxidative stress.
decreased glutathione peroxidase activity
increased lipid peroxidation
 - Selenium can interfere with the action of sulfhydryl groups.
- Displacement of sulfur or sulfur-containing amino acids

Diagnosis

- Clinical signs
- Exposure to selenium source
- Chemical analysis
 - concentration of selenium in blood and liver >2 ppm
 - concentration of selenium in hoof or hair >5 ppm

Treatment and Prevention

- Remove animals from source of selenium.
- Increase the quality and quantity of protein in diet.
- Increase sulfur in diet to prevent accumulation of selenium.
- Use corrective shoeing for horses.
 - long-term commitment
 - frequent hoof trimming and shoeing
 - nonsteroidal antiinflammatory agents needed
- Antioxidant therapy
 - Administration of vitamin E may be beneficial in acute cases.

References

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Senna (*Cassia* spp., Coffee Senna, Sickle Pod)

General

- Plants grow from Texas to South Dakota and eastward to the Atlantic coast.

- *Cassia* plants grow in disturbed areas, such as roads and overgrazed pastures.
- Cattle may consume the plant or hay containing the plant.
- The seeds may be harvested with grains.

Source

- *Cassia occidentalis* (coffee senna)
- *Cassia tora* (sickle pod)
- Other representatives of *Cassia*
- All parts of the plant are potentially toxic; the seeds pose the greatest risk of intoxication.

Species

- Most reports are of cattle and poultry, but all species are susceptible.

Clinical Signs

- Muscle weakness
- Incoordination
- Reluctance to move
- Sternal and lateral recumbency
- Diarrhea
- Dark urine (myoglobinuria)
- Gross and histopathologic lesions
 - white to whitish-yellow areas of skeletal muscle
 - necrosis of skeletal and cardiac muscle
 - centrilobular necrosis

Toxicity

- Consumption of 1% of the animal's body weight of the plant

Mechanism of Action

- The exact mechanism and toxic principle are not known.
- Most species of *Cassia* contain quinones that act as cathartics.
- Possible mechanisms are as follows:
 - increased lysosomal acid phosphatase activity in muscle

- mitochondrial myopathy
enlarged mitochondria
disrupted or excessively branched cristae

Diagnosis

- History of exposure to and consumption of the plants
- Clinical signs
- Gross and histopathologic lesions
- Elevated concentration of creatine kinase in the serum
- Some diagnostic laboratories can examine grains for *Cassia* seeds.

Treatment

- Remove the animal from the source of the plants or grain containing seeds.
- Provide symptomatic and supportive therapy.
- Recovery occurs in a few days; abnormal gait may remain for a few weeks.

References

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Slaframine (Slobber Factor, Black Patch Disease)

General

- Slaframine poisoning occurs in animals grazing in a pasture or fed contaminated hay.
- The fungal organism that produces slaframine also may produce swainsonine on some feeds (see *Locoweed* [*Astragalus* spp. and *Oxytropis* spp.]).

Source

- This syndrome is caused by fungal growth on clover, most commonly red clover (*Trifolium pratense*).
- The fungal organism that causes production of slaframine is *Rhizoctonia leguminicola*.

Species

- Horses, cattle, and sheep

Clinical Signs

- Pronounced hypersalivation
 - may occur within 30 minutes of consumption of infected feed
- Other clinical signs:
 - piloerection
 - respiratory distress
 - diarrhea
 - lacrimation
 - decreased feed intake

Mechanism of Action

- Parasympathomimetic agent
 - high affinity for muscarinic receptors of the gastrointestinal tract
 - some actions of the toxin prevented by muscarinic receptor antagonists

Diagnosis

- Clinical signs
- History of introduction to new feedstuff or pasture
- Chemical analysis of hay not performed
- Test feeding of the suspect hay

Treatment

- Remove source of contaminated feed.
- Ensure proper drying of forage during haying.
 - Toxin degrades over time in stored hay.

Prognosis

- Generally self-limiting and nonfatal
- Recovery in 1 to 3 days

References

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Soaps and Detergents

Soaps

- Low risk of serious intoxication
- Irritation of mucous membranes, gastrointestinal irritation, nausea and vomiting, diarrhea

- Treatment
 - ocular
Rinse with lukewarm water for 15 minutes.
 - ingestion
Dilute with clear liquids and water.
Observe for signs of aspiration.

Detergents

- Severe intoxication is uncommon.
- Detergents contain a mixture of surfactants and builders.

SURFACTANTS

- Surfactants break the surface tension of water and allow dispersion and emulsion of dirt.
- Anionic surfactants, which are mildly irritating, include
 - alkyl sodium sulfates or sulfonates
 - sodium lauryl sulfate
- Nonionic surfactants, which are mildly irritating, include:
 - alkyl ethoxylate
 - alkyl phenoxy polyethoxy ethanols
 - polyethylene glycol stearate
- Cationic surfactants, greatest risk of intoxication, include
 - benzalkonium chloride
 - alkyl dimethyl ammonium chloride
 - cetylpyridinium chloride

BUILDERS

- Increase the effectiveness of the surfactant
 - sodium carbonate
 - sodium metasilicate
 - sodium silicate
 - sodium tripolyphosphate

ADDITIVES

- Usually present in low concentration, not an important source of injury
- Bleach
- Bactericidal agents
- Whiteners
- Fragrance
- Enzymes

Mechanism of Toxicity

- Products that contain cationic surfactant
 - precipitate and denature proteins
 - irritating
 - corrosive

Treatment after Anionic and Nonionic Exposures

INGESTION

- Rarely serious
- Presentation
 - local irritation
 - possibly spontaneous emesis
 - possibly diarrhea
- Treatment
 - Dilute with milk or water (small amounts).
 - Provide fluid replacement if diarrhea occurs.

DERMAL

- Only minor irritation
- Flush with water.

OCULAR

- Seldom serious
- Presentation
 - irritation
 - lacrimation

- ocular pain
- Treatment
 - Flush the eyes for a minimum of 15 minutes.

Management of Cationic Exposure

- Severity depends on strength of the product.
- Ranges from 0.5% to 20% cationic surfactant
- Less than 1% in most household cleaners

INGESTION

- Greater absorption, systemic intoxication
- Presentation
 - can be difficult to diagnose because of the multitude of chemicals and the degree of absorption
 - nausea and vomiting
 - possibly diarrhea
 - burns
 - possible systemic effects
 - hemolysis
 - confusion
 - cyanosis
 - convulsions
 - shock, coma
- Treatment
 - Do not induce emesis.
 - Dilute with milk or water.

DERMAL

- Burns more severe with concentrated solutions
- Milder solutions or minimal exposure
 - dilution
- Severe exposure
 - Flush with water for a minimum of 15 minutes.
 - Manage burns.

OCULAR

- Causes immediate pain and irritation
- Flush eyes for 15–20 minutes.
- Perform ophthalmic examination.

References

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Sodium Ion Toxicosis, Water Deprivation

General

- Prevention is crucial.
- After the onset of the syndrome, as many as 50% of affected animals die.
- Animals can tolerate large dietary quantities of salt as long as sufficient fresh water is available to them.

Source

- Elevated sodium concentration in the diet
- Water deprivation due to unpalatable water supply, frozen water lines, lack of awareness of water source in an enclosure, mismanagement, overcrowding

Species

- Swine, poultry, and cattle

Clinical Signs

- Mammals: central nervous system signs more common
- Poultry: respiratory distress in addition to central nervous system signs

CENTRAL NERVOUS SYSTEM

- Convulsions
- Recumbency
- Depression
- Head pressing
- Paddling
- Blindness

GASTROINTESTINAL TRACT

- Constipation
- Ascites
- Diarrhea

Mechanism of Action

- Increased sodium in diet or restricted access to water
 - Sodium concentration in the serum increases.
 - Serum sodium concentration in the tissues, especially the brain, increases.
 - Elevated concentration of sodium in the serum inhibits glycolysis.
 - Sodium is trapped in tissues because sodium pumps do not have sufficient energy to return sodium to serum.
- Water supply is returned to animals
 - Animals are thirsty and consume large amounts of water.
 - Water is absorbed.
 - Water follows the sodium.
 - Cerebral edema occurs.

Diagnosis

- Clinical signs
- Clinical pathology
 - elevated sodium concentration
 - concentration in the serum and cerebrospinal fluid >180 mEq/L
 - concentration in the brain >1800 ppm
 - ocular fluid

- Gross pathologic lesions
 - nonspecific: gastritis, gastric ulcers
- Histologic findings
 - eosinophilic perivascular cuffing (meningoencephalitis)
 - only in swine
 - only if animals die within first 24 hours
 - after 24 hours, empty spaces are present
 - animals that survive a few days and die generally have cerebral edema and necrosis

Treatment

- Generally not rewarding
- Allow animals limited access to water.
 - Let them slowly return to normal consumption.
 - Provide frequent opportunities to ingest small quantities of water.

Control and Prevention

MAXIMUM SODIUM CONCENTRATION OF WATER OFFERED TO LIVESTOCK

- Poultry: 2500 ppm
- Pigs: 4000 ppm
- Horses: 7000 ppm
- Cattle: 8000 ppm
- Sheep: 10,000 ppm

References

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Soluble Oxalate-Containing Plants

General

- Plants that contain soluble oxalates are common in pastures.
- The percentage of oxalates increases during the growing season.
- Intoxication is more common when hungry, naive animals rapidly consume oxalate-containing plants.
- Limited exposure to water can increase the severity of the syndrome.

Source

- Relative oxalate concentration: leaves > seeds > stems

MAIN SOURCES

- Beets (*Beta vulgaris*)
- Curly dock, dock (*Rumex* spp.)
- Greasewood (*Sarcobatus vermiculatus*)
- Halogeton (*Halogeton glomeratus*)
- Lamb's quarter (*Chenopodium* spp.)
- Pigweed (*Amaranthus* spp.)
- Pokeweed (*Phytolacca* spp.)

OTHER SOURCES

- Rust remover
- Bleach
- Primarily small animals affected by these household sources.

Species

- Sheep more commonly affected
- Cattle susceptible

Clinical Signs

SIGNS REFERABLE TO HYPOCALCEMIA

- Similar to milk fever in cattle
- Tremors
- Depression

- Tetany
- Coma
- Convulsions

SIGNS REFERABLE TO GASTROENTERITIS

- Colic
- Dehydration
- Restlessness

SIGNS REFERABLE TO RENAL FAILURE

- Anorexia, depression, weight loss
- Polyuria or anuria

Toxicity

- The toxicity of oxalate-containing plants depends on the following factors:
 - prior exposure of animals to oxalate-containing plants
 - degree of hunger
 - availability of other feedstuffs
- Sheep can die after consumption of 0.1% of body weight (hungry animals) or 0.55% of body weight (animals not hungry).

Mechanism of Action

TOXIC PRINCIPLE

- Soluble oxalates
 - potassium acid oxalate
 - potassium oxalate
 - sodium oxalate
 - ammonium oxalate

DISPOSITION OF OXALATE IN THE RUMINANT GASTROINTESTINAL TRACT

- Degradation by the ruminal microflora
- Combination with calcium, which renders oxalate insoluble and not absorbed

- Absorption from the rumen into the bloodstream (toxic form)

DISPOSITION OF ABSORBED OXALATE IN THE SYSTEMIC CIRCULATION

- Combination with calcium, which can precipitate hypocalcemia
- Interference with carbohydrate metabolism
- Precipitation of calcium oxalate crystals in the blood vessels
 - vascular necrosis
- more common in the gastrointestinal tract, causing rumenitis, also noted in the lung

Diagnosis

- History of exposure
 - walk through the pasture
- Clinical signs
- Histopathologic findings
 - birefringent oxalate crystals in the renal tubules

Treatment

- Of minimal benefit
- Intravenous administration of calcium gluconate to correct hypocalcemia
- Supportive nursing care

Prevention

- Limit access to pastures containing the plants.
- Do not introduce hungry animals to a new pasture.
- Use herbicides on dense stands of oxalate-containing plants.

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Sorghum Cystitis (Equine Cystitis, Equine Ataxia, Sudan Grass Intoxication)

General

- Sorghum cystitis is a toxicologic syndrome most commonly associated with consumption of sudan grass by mares.
- Most cases are diagnosed during periods of rapid plant growth (late summer and fall).

Source

- Sudan grass pastures

Species

- Horses primarily, possibly cattle

Clinical Signs

- Urinary signs indicating cystitis
 - both sexes
 - urinary incontinence
 - urine scald
- Ataxia, primarily associated with hind limbs
- Weakness
- Teratogenesis, arthrogryposis
 - Critical period is day 20–50 of gestation.
 - Fetus may have
 - flexion of joints
 - ankylosis of joints

Mechanism of Action

- Toxic principle is β -cyanoalanine.

- cyanogenic glycoside
- mechanism different from acute cyanide intoxication

Diagnosis

- Clinical signs
- Urinalysis and urine culture
 - Positive results indicate infection.
- Histopathologic lesions
 - wallerian degeneration of white matter of spinal cord
 - cerebellar peduncles
 - cerebellum
 - ventromedial and dorsolateral funiculi of the spinal cord

Treatment

- Remove animals from suspect pastures.
- Administer antimicrobial therapy.
 - for cystitis
 - predisposition to subsequent bouts of cystitis

Prognosis

- Poorer prognosis after onset of incontinence.

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Spiders

General

- There are more 50,000 species of spiders in the United States.
- Only a small number of spiders cause serious medical problems.
- Spiders have eight legs and a pair of fangs, the chelicerae, that are part of the jaws.

Source

- There are two important types of spiders in the United States.

WIDOW SPIDERS (*LATRODECTUS* spp.)

- *Latrodectus mactans*
- Also known as the black widow spider, brown widow, red-legged spider, murderer
- Red, hour-glass mark on the ventral abdomen
- Male small and not offensive
- Often found in woodpiles

RECLUSE SPIDERS (*LOXOSCELES* spp.)

- *Loxosceles reclusa*
- Also known as brown recluse spider, fiddleback spider, violin spider
- Dark brown, violin-shaped marking on the dorsum of the cephalothorax
- Often found in closets and rarely worn clothing (snow boots)

Species

- Cats and dogs more commonly affected
- Cats more sensitive to envenomation by black widow spiders

Clinical Signs

NEUROTOXIC SYNDROME

- *Latrodectus* spp.
- Abdominal pain
- Abdominal rigidity without tenderness or pain

- Paresthesia
- Muscle fasciculations
- Spasms
- Possibly seizures
- Ataxia
- Flaccid paralysis

DERMATONECROSIS

- *Loxosceles* spp.
- Bite initially painless
- Fever
- Nausea and vomiting
- Bluish-gray macular halo (not always present)
- Vesicle bulla formation
- Rupture of the bulla
- Formation of necrotic ulcer
- May take 6 months to heal
- Necrosis more severe in areas of fat deposits

Mechanism of Action: Toxic Principles**LATRODECTUS: α -LATROTOXIN**

- A labile protein that is neurotoxic
- Binds to synaptic membrane receptors
- Nonspecific activation of cation channels
- Increased influx of calcium
- Increased release of neurotransmitters
 - norepinephrine and acetylcholine
 - ascending motor paralysis

LOXOSCELES

- Cytolytic venom that contains
 - spreading factors
 - enzymes: hyaluronidase, collagenase, esterase, protease, phospholipase, deoxyribonuclease, ribonuclease

- Sphingomyelinase D
 - cytotoxic
 - recruitment (chemotaxis) of leukocytes to the bite site
- Venom causes rapid coagulation and occlusion of the smaller vessels in the skin.
- Severe dermatonecrosis results.

Diagnosis

- History of exposure to one of the species of spiders
- Difficult to see the bite wound
- Clinical signs

Treatment

SUPPORTIVE AND SYMPTOMATIC

- Wound care
- Cardiovascular and respiratory support

SPECIFIC THERAPY FOR BITES BY *LACTRODECTUS* spp.

- Calcium gluconate (10% solution)
 - cats: 5–15 mL
 - dogs: 10–30 mL
- Antivenin therapy
 - not usually necessary
 - only one vial needed
- Pain management
 - morphine

SPECIFIC THERAPY FOR BITES BY *LOXOSCELES* spp.

- Wound management
 - antibiotic therapy
 - dressings
- Dapsone therapy
 - inhibits influx of leukocytes to the wound
 - may induce methemoglobinemia

- No antivenin available
- Glucocorticoids contraindicated
- Excision of wound contraindicated

References

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Strychnine

General

- The chemical structure of strychnine is shown in Figure 4–40.
- An alkaloid derived from the seed of *Strychnos nux-vomica*, a tree native to India
- A nonspecific pesticide that has been replaced in many cases

Source

- Bait used to control gophers, moles, rats, and coyotes
- Contains 0.5%–0.3% strychnine, is pelleted, and is dyed green or red

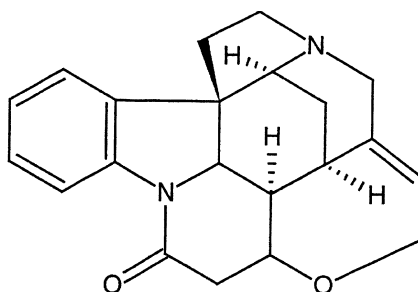


Figure 4–40 Chemical structure of strychnine.

Species

- All species are susceptible.
- Often used in malicious poisoning of dogs

Clinical Signs

- Usually present within 1 hour of ingestion
- Tetanic seizures (spontaneous or induced)
- Sawhorse stance
- Apnea during seizures
- Usually no loss of consciousness
- Death due to anoxia and exhaustion

Toxicity

- Dogs: 0.75 mg/kg
- Cats: 2.0 mg/kg
- Cattle: 0.5 mg/kg
- Horses: 0.5–1.0 mg/kg
- Swine: 0.5–1.0 mg/kg

Mechanism of Action

- Acts on the glycine receptors of the spinal cord and medulla
- Acts as a competitive and reversible glycine receptor antagonist

- Prevents glycine binding to the postsynaptic receptor on the soma of motor neurons; the result is uncontrolled stimulation of skeletal muscles
- Induces a pronounced extensor rigidity and the classic sawhorse stance

Diagnosis

- History of exposure
- Clinical signs
- Chemical analysis of the following frozen samples:
 - gastric contents
 - liver (necropsy)
 - possibly urine and kidney
- In cases of possible malicious poisoning, chemical analysis should be conducted regardless of clinical outcome.

Treatment

- Focus on controlling tetanic seizures and respiratory support.

SEIZURE CONTROL

- Administer pentobarbital to effect.
- Be prepared to intubate and ventilate the animal.

RESPIRATORY SUPPORT

- Provide artificial ventilation if necessary if animal is hypoxic.

DECONTAMINATION

- Perform before clinical signs appear.
- Intubate and begin gastric lavage.
- Do not induce emesis if the animal is having seizures.

INCREASE ELIMINATION

- Administer ammonium chloride to increase urinary elimination.
- Do not administer ammonium chloride to animals with acidosis due to tetanic seizures.

FLUID THERAPY

- Promote diuresis and increase urinary excretion of strychnine.

References

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Sulfur

General

- Elemental sulfur is an essential nutrient.
- It is necessary for optimal ruminal microbial growth and digestion.
- It is a component of methionine and other amino acids.
- High sulfur intake can decrease absorption of copper and selenium.

Source

- Elevated concentration of dietary sulfur
- Water high in sulfur (gyp water)
- Heavy fertilization of fields

Species

- Ruminants: cattle, sheep, and goats
- More common in feedlot cattle

Clinical Signs

- Anorexia
- Diarrhea
- Central nervous system signs

- depression
- head pressing
- excitation
- lack of coordination
- animals with cortical blindness
- Sudden death
- Histopathologic findings
 - polioencephalomalacia

Toxicity

- Recommended dietary sulfur concentration of 0.15% of the total dry matter
 - A dietary sulfur concentration of 0.1%–0.12% may be adequate.
 - Maximum tolerable sulfur concentration is 0.4%.
- As dietary concentrations increase, feed intake begins to decrease.
- Water concentration of sulfur may be unknown, and this is an important risk factor.
 - especially during periods of warm weather
 - greater risk of intoxication when sulfur content of water is greater than 500 ppm
 - some water sources may contain more than 5000 ppm sulfur

Mechanism of Action

- The exact mechanism of sulfur intoxication is debated.
- Ingested sulfur enters the rumen and is converted to hydrogen sulfide.
- Hydrogen sulfide is absorbed from the rumen and can interact with
 - cytochrome oxidase system
 - hemoglobin
- Polioencephalomalacia may not be caused by thiamine deficiency.
 - blood thiamine concentrations may be within normal limits because of
 - a possible direct effect of sulfur (hydrogen sulfide)

the possible presence of a sulfur metabolite
production of a thiamine antimetabolite

Diagnosis

- Odor of hydrogen sulfide
 - detected in the rumen at necropsy
 - of eructations of affected animals
- Brain fixed in buffered formalin for histopathologic examination
- Blood for thiamine determination
- Samples collected for sulfur analysis:
 - all feed sources
 - water
 - ruminal contents

Treatment

- Prevention is essential to avoid economic losses.
 - Remove all possible sources of sulfur (feed, water).
 - Understand the sulfur content of the total ration.
- Dilute high-sulfur feedstuffs with feed containing less sulfur.
- Administer thiamine.
 - reported to be unrewarding
 - area of active research
 - cattle doses of thiamine:
 - 10 mg/kg IV loading dose
 - 10 mg/kg IM every 12 hours for 2–3 days

References

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Trichothecenes

General

- A large group of mycotoxins with similar chemical structures
- Usually found together in contaminated feed
- Deoxynivalenol (DON) commonly present with zearalenone
- Can act in an additive manner with other trichothecenes or mycotoxins

Source

- DON, also called *vomitoxin* (Figure 4–41)
- Trichothecene T-2 toxin
- Diacetoxyscripenol (DAS)
- Trichothecenes are mycotoxins are produced from *Fusarium roseum* and *Fusarium sporotrichiodes*.

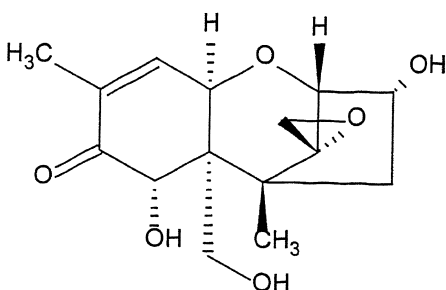


Figure 4-41 Chemical structure of deoxynivalenol.

Species

- Swine are more commonly affected, but all species are susceptible.

Clinical Signs

- Several possible clinical syndromes, some ill-defined
- Gastrointestinal signs
 - ulceration of oral mucosa
 - gastroenteritis
 - vomiting
 - feed refusal
- Decreased body weight gain
- Decreased milk production
- Increased susceptibility to infectious agents
- Decreased egg production in poultry

Toxicity

- Swine are the most sensitive species; cattle and poultry are less sensitive.
- Males are more sensitive than females.

Mechanism of Action

- Sesquiterpene lactones with an epoxide group
 - The epoxide is important in the pathophysiologic mechanism of intoxication.

- Epoxides can interact with and bind to opposing strands of DNA.
decreased DNA and RNA synthesis
DNA fragmentation
- Apoptosis is induced in a variety of cell types.
- Production of free radicals and lipid peroxidation
- Possible inhibition of protein synthesis
 - binding to the 60s ribosomal unit
 - binding to the ribosomal peptidyltransferase site
activation of JNK/p38 kinases
induction of rapid apoptosis
- synergistic inhibition of protein synthesis and induction of apoptosis
- Feed refusal and vomiting
 - Trichothecenes and related metabolites of *Fusarium* spp. growth have been shown to cause vomiting in swine.
 - Concentrations of tryptophan and serotonin are elevated in the brain.
- Oral lesions caused by direct cytotoxic effect of trichothecenes

Diagnosis

- Clinical signs and presence of lesions
 - may be difficult because many signs are not specific
- Chemical analysis of grain and feed
 - enzyme-linked immunosorbent assay
 - usually only accurate on grain
 - submission of 5 kg of feed or grain to a diagnostic laboratory is best
can examine several mycotoxins in one screening
interpretation from a toxicologist beneficial
- DON possibly useful as a chemical indicator of conditions well suited to fungal growth and mycotoxin production

Treatment

- Remove suspect feed.
- Administer activated charcoal for acute intoxication.

- Provide supportive and symptomatic therapy.
- Provide high-quality feed.
- Observe closely for signs of infectious disease and treat the animal aggressively.

Prevention

- Screen grain before incorporating it into feedstuffs.
- Feed grain to less susceptible species.

References

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Tricyclic Antidepressants

General

- Tricyclic antidepressants are being replaced to a great extent with newer drugs that have fewer adverse and potentially toxic effects.
- Many pet owners still take these drugs.
- The five examples are on the 1999 “Top 200” drug list, an annual ranking of the most frequently filled prescription drugs in the United States (see Mosby at http://www1.mosby.com/genrxfree/Top_200_1999/Top_200_alpha.html).

Source

- Amitriptyline (Elavil, Endep)
- Desipramine (Norpramin)
- Doxepin (Sinequan, Zonalon)
- Imipramine (Tofranil)
- Nortriptyline (Aventyl, Pamelor)

Species

- Small animals, especially cats

Clinical Signs

- Anticholinergic effects
 - sedation
 - mydriasis
 - decreased gastrointestinal motility
- Cardiovascular effects
 - tachycardia
 - myocardial depression

- conduction blockade: widened QRS complexes
- Central nervous system effects
 - depression
 - coma
 - possibly seizures
- Vomiting
- Death

Toxicity

- Animals that ingest a lethal dose >15 mg/kg body weight may die within 1 hour.

Mechanism of Action

- The antidepressant mechanism of the tricyclic antidepressants is not completely understood.
- Effects of these drugs include the following:
 - decreased reuptake of norepinephrine and serotonin
 - peripheral α -adrenergic receptor blockade
 - inhibition of sodium channels of the myocardium

Diagnosis

- History of exposure to tricyclic antidepressants
- Clinical signs

Treatment

GASTROINTESTINAL DECONTAMINATION

- Do not induce emesis because this procedure can decrease the seizure threshold.
- Administer activated charcoal and sorbitol cathartic therapy.
- Consider whole-bowel irrigation.
- Repeat administration of activated charcoal if necessary because of the action of tricyclic antidepressants on depressed gastrointestinal motility.

ANTIDOTAL THERAPY

- Sodium bicarbonate
 - 2–3 mEq/kg IV, repeat as needed
 - can rapidly reverse the prolonged QRS complexes

SUPPORTIVE AND SYMPTOMATIC THERAPY

- Control seizures with diazepam.
- Monitor the electrocardiogram.

Reference

Johnson LR. Tricyclic antidepressant toxicosis. *Vet Clin North Am Small Anim Pract.* 1990;20:393–403.

Venomous Reptiles**General**

- Venomous organisms produce a poison (venom) *and* have a specialized delivery system, such as fangs.
 - **example:** venomous reptiles
- Poisonous organisms do not have a delivery system.
 - **example:** poisonous plants
- There are only a few species of venomous snakes and lizards in the United States.
- It is crucial to “treat the patient, not the snake.”
- Classification of venoms from different snakes as neurotoxic, hemotoxic, or cardiotoxic is oversimplification and can lead to missed diagnosis and insufficient care of the patient.
 - Venoms are complex mixtures of polypeptides and enzymes.
 - A “neurotoxic” venom can cause cardiovascular and local hematologic effects.

Source**LIZARDS**

- Gila monster (*Heloderma suspectum*)

- found in southwestern United States
- not a common source of animal envenomation
- Mexican beaded lizard (*Heloderma horridum*)

ELAPID SNAKES: CORAL SNAKES

- *Micurus* spp., *Micruroides* spp.
- Brightly colored rings
- Coral snakes: “black on yellow, kill a fellow”
- Nonvenomous snakes: “red on black, friend of jack”

COLUBRID SNAKES

- Several species
 - Sonoran lyre snake (*Trimorphodon lambda*)
 - vine snake (*Oxybelis aeneus*)
 - king snakes (*Lampropeltis* spp.)
- Fixed fang in rear of mouth
- Must “chew” on victims
- Not a significant cause of envenomation

CROTALID SNAKES (PIT VIPERS)

- Copperheads (*Agkistrodon contortrix*)
 - found in eastern United States
- Water moccasins (*Agkistrodon piscivorus*)
 - also known as the cottonmouth
 - semiaquatic, found primarily in the southeastern United States
- Small rattlesnakes
 - Pygmy rattlesnakes (*Sistrurus miliaris*)
 - Massasauga (*Sistrurus catenatus*)
- Rattlesnakes (*Crotalus* spp.)
 - found throughout the United States

Species

- All species susceptible
- Dogs, cats, and horses commonly envenomated species
 - usually bitten on the nose and front legs

Clinical Signs

- Tissue damage
- Hypotension and shock
- Local edema
 - possibly progressing to regional swelling
 - dyspnea if bite is on face or nose
- Bleeding
 - from bite site
 - ecchymosis
 - discoloration of the affected area
- Hemoglobinuria or myoglobinuria
- Pain
- Respiratory failure
 - more common with coral snake bites

Toxicity

- Varies greatly with snake
- As many as 40% of strikes are dry bites—no envenomation

Mechanism of Action

- Enzymes in the venom break down tissues.
 - spread of venom
 - production of edema at bite site
 - spread to surrounding tissues

VENOM METALLOPROTEINASES

- Important mediators in tissue damage
- Release tumor necrosis factor
- Produce local inflammation

MYOTOXIN-A

- Increases intracellular concentration of calcium, and the high calcium concentration causes myonecrosis.
 - increased sodium influx through sodium channels

- increased intracellular concentration of sodium induces release of calcium from the sarcoplasmic reticulum through the ryanodine receptor
- inhibition of Ca^{2+} -adenosine triphosphatase reuptake at the sarcoplasmic reticulum

COAGULOPATHY

- Venoms increase or decrease coagulation through acting upon
 - fibrinogen or fibrinolytic enzymes
 - plasminogen activators
 - prothrombin activators
 - phospholipase inhibitors
 - factor X, V, IX, or C activators
 - induce or inhibit platelet aggregation

HYPOTENSION

- Caused by hypovolemia and third-space fluid loss

NEUROTOXIC SIGNS (WEAKNESS AND PARALYSIS)

- Envenomation by coral snakes and Mojave rattlesnakes
- Action on neuronal synapses
 - Venom constituents bind almost irreversibly to acetylcholine-releasing sites.
 - neuromuscular blockade
 - treatment usually unsuccessful
- Calcium channel blockade prevents neurotransmitter release.

Diagnosis

DETERMINING WHETHER ENVENOMATION HAS OCCURRED

- Mark the affected extremity in three places:
 - at the bite
 - proximally and distally to the bite
- Measure the diameter of each of the marks every 15–30 minutes to assess the progression of swelling.

CLINICAL PATHOLOGY

- Complete blood cell count
- Platelet count
- Prothrombin time, partial thromboplastin time
- Fibrin degradation products
- Creatine kinase
- Urine dipstick for myoglobin

Treatment**EMERGENCY THERAPY**

- Management of airway, breathing, circulation (ABCs)
 - If a bite wound is on nose or if there is pronounced swelling of the larynx, tracheotomy may be needed.
- Fluid therapy
 - crystalloids
 - two intravenous lines may be needed
- Oxygen therapy
- Analgesia

SPECIFIC THERAPY

- Fluid therapy
 - Maintain adequate volume of fluids to prevent cardiovascular collapse.
 - Administer lactated Ringer solution, normal saline solution, or crystalloid.
- Diphenhydramine
 - sedation
 - pretreatment for anaphylaxis against antivenin

ANTIVENIN THERAPY

- Polyvalent crotalidae antivenin
 - rattlesnakes
 - derived from horse serum (possible anaphylaxis)
 - intradermal test before treatment

- several vials possible
- control of clinical signs and progression
- expensive
- *Micrurus fulvis* antivenin
 - eastern or Texas coral snake
 - not effective for bites of Sonoran or western coral snake
 - not as readily available as crotalidae antivenin
 - horse-derived product—hypersensitivity possible
 - intradermal test before treatment

SYMPTOMATIC AND SUPPORTIVE THERAPY

- Severe bleeding
 - Prepare for transfusion.
- Respiratory dysfunction
 - Provide oxygen.
 - Provide mechanical ventilation if necessary.
 - Monitor oxygenation.
 - Perform pulse oximetry.
 - Measure arterial blood gases.
- Bite wound
 - Clean and lightly wrap.

PATIENT MONITORING

- Monitor hemodynamic values.
- Monitor coagulation status.
- Monitor respiratory function.

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Water Hemlock (*Cicuta Maculata*, *Cicuta Douglasii*)

General

- Also called snakeweed, beaver poison, death-of-man, children's bane, spotted cowbane, poison parsley.
- Cattle are more commonly poisoned in the spring, when there is limited new forage.
- Animals may trample the ground around streams or waterholes, expose the roots of this plant, and eat them.

Source

- Plants from the genus *Cicuta* grow in wet area near streams, ponds, or rivers.
- The plants grow in sparse stands.
- The plant is a member of the carrot family; it is a tall perennial that often has purple streaks on the stalk and roots.
- The root has hollow chambers that hold an oily, yellow liquid that turns reddish-brown when exposed to air.
- Human intoxication has occurred because the plant looks like wild parsley.

Species

- Cattle, sheep, horses

Clinical Signs

- Signs within 30 minutes of ingestion of a lethal dose
- Mild muscular twitching
- Tremors
- Excessive salivation
- Grinding of teeth
- Convulsions
- Death due to asphyxiation

Toxicity

- Consumption of only a few roots (rootstocks) can cause clinical signs in cattle.
- Sheep have been experimentally poisoned by means of oral administration of 1.2–2.7 g fresh tuber per kilogram body weight.
- Toxicity is not reduced by maturation or drying of the plant.

Mechanism of Action

- The toxic principles, cicutoxin and cicutol, are resinoid alcohols.
- Cicutoxin and cicutol act on the central nervous system and are potent convulsants.
- Cicutoxin may act through the γ -aminobutyric acid (GABA) receptor as a GABA antagonist.

Diagnosis

- Clinical signs
- Finding consumed plants
- Finding rootstock in the esophagus of a dead animal
- Animals may be found dead.

Treatment

- No specific antidote
- Decontamination
 - activated charcoal and cathartic
- Symptomatic therapy
 - Control seizures with pentobarbital.
 - Animals that survive the first 2 hours have a better prognosis.
- Prevention
 - Use herbicides to control plants in wet areas.
 - Limit grazing near water.
 - Offer supplemental feedstuffs (hay) in the early spring.

References

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- Smith RA, Lewis D. *Cicuta* toxicosis in cattle: case history and simplified analytical method. *Vet Hum Toxicol*. 1987;29:240–241.

White Snakeroot (*Eupatorium Rugosum*)

General

- The chemical structure of tremetone, the toxic principle of white snakeroot, is shown in Figure 4–42.
- Also called richweed, white sanicle, fall poison, thoroughwort, white-top, poolwort, and bonewort

Source

- Grows in moist, shaded areas, such as banks of streams
- Identification difficult because of existence of many nontoxic species of *Eupatorium*

Species

- Cattle, horses, sheep, and goats
- Humans by means of consuming milk from a cow that has consumed *Eupatorium*—milk sickness.

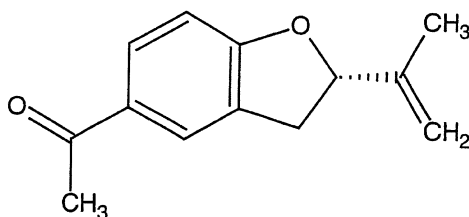


Figure 4–42 Chemical structure of tremetone.

Clinical Signs

- Syndrome called *trembles* or *shakes*
- Weight loss
- Listlessness and reluctance to move
- Weakness
- Muscular tremors
- Tremors more prominent during forced movement
- Stiffness
- Collapse and coma

CATTLE

- Death in approximately 2 weeks
- Tremetol excreted in milk, which protects lactating animals
- Human health hazard

SHEEP

- Death in a few days

HORSES

- Death in 1 or 2 days
- In addition to the aforementioned signs:
- Swallowing difficulties
- Hypersalivation
- Congestive heart failure (jugular pulse, tachycardia)
- Elevated creatine kinase and liver enzyme concentrations
- Pale, white streaks in the myocardium

Toxicity

- Animals must consume 5%–10% of body weight to develop toxicosis
- Cumulative effect
- Toxicity retained during drying and in hay

Mechanism of Action

- The toxic principle is tremetol, which
 - inhibits the Krebs cycle

- causes acidosis, hyperglycemia, and ketonemia

Diagnosis

- Clinical signs
- Observation of animals consuming the plant

Treatment

- Remove animals from the plant sources (pasture or hay).
- Offer high-quality hay.
- Perform gastrointestinal decontamination with activated charcoal and a cathartic agent.

References

- Beier RC, Norman JO. The toxic factor in white snakeroot: identity, analysis, and prevention. *Vet Hum Toxicol.* 1990;32:81–88.
- Nicholson SS. Tremorgenic syndromes in livestock. *Vet Clin North Am Food Anim Pract.* 1989;5(2):291–300.
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Yellow Star Thistle (*Centaurea Solstitialis*)

General

- Russian napweed (*Centaurea repens*) causes a similar syndrome.
- A chronic syndrome of horses that occurs after they have eaten a relatively large amount of the plant over a period of months.
- The plants are native to the western United States and are well adapted to the climate.
- Eliminating the plant often is not possible.

Source

- Both *Centaurea solstitialis* and *Centaurea repens* have been implicated in the disease.
- They are annual weeds with yellow flowers.

Species

- Horses

Clinical Signs

- Excessive muscular tone of the facial and lip muscles—lips contracted to expose teeth
- Mouth held open with tongue protruding
- Dunking head into water to assist in swallowing
- Chewing movements without the ability to chew and swallow
- As horse chews, food falls out of the mouth
- Yawning
- Death due to starvation

Toxicity

- Consumption of several hundred pounds of the weed precedes the onset of clinical signs.
- The toxicity of the plant is retained in the dried material, so hay contaminated with this plant is a source of intoxication.

Mechanism of Action

- Unknown toxic principle
- Recent research has identified possible neurotoxic compounds.
 - Solstitialin A 13-acetate and cynaropicrin were isolated from the upper portions of the plant.
 - In vitro these substances had toxic effects on cultures of rat substantia nigra.
 - It was not determined whether these effects were specific to these cells.
- In another study aspartic and glutamic acids (excitotoxins) were identified in yellow star thistle.

Diagnosis

- Clinical signs
- History of exposure and consumption of the plant

- Nigropallidoencephalomalacia at histopathologic examination
 - ischemic necrosis of substantia nigra
 - malacia (softening) of the area
 - accumulation of gitter cells (neuronal phagocytic cells)

Treatment

- Poor prognosis after clinical signs develop
- Treatment is not rewarding; the animal's brain is permanently damaged.

References

- Cheng CH, Costall B, Hamburger M, Hostettmann K, Naylor RJ, Wang Y, et al. Toxic effects of solstitialin A 13-acetate and cynaropicrin from *Centaurea solstitialis* L. (Asteraceae) in cell cultures of foetal rat brain. *Neuropharmacology*. 1992;31:271–277.
- Roy DN, Peyton DH, Spencer PS. Isolation and identification of two potent neurotoxins, aspartic acid and glutamic acid, from yellow star thistle (*Centaurea solstitialis*). *Nat Toxins*. 1995;3:174–180.

Zinc

General

- Repeated exposure or consumption of a source of zinc
- Consumption of zinc-containing foreign body that liberates zinc from the acid environment of the stomach

Source

- Galvanized metal, especially nuts from cages
- Pennies minted after 1983
- Diaper rash ointment
- Zinc oxide sunscreen
- Board game pieces
- Galvanized metal bird cages
- Feed mixing error

Species

- Dogs primarily, but all species are susceptible

Clinical Signs

ACUTE

- Ingestion of a large amount of zinc oxide
- Vomiting
- Diarrhea
- Anorexia

CHRONIC

- Ingestion of zinc-containing foreign body, such as a penny
- Icterus
- Intravascular hemolytic anemia
- Decreased packed cell volume
- Hemoglobinemia
- Hematuria
- Increased number of nucleated erythrocytes
- Increased basophilic stippling

Toxicity

DOGS

- 1 g/kg body weight 40% zinc oxide ointment
- 700 mg/kg body weight galvanized nuts

PSITTACINES

- 2 mg/week causes dullness, weight loss, and intermittent excretion of greenish droppings

Mechanism of Action

- Acute ingestion of zinc causes direct irritation of the gastrointestinal tract.
- The mechanism of chronic intoxication (hemolytic anemia) is not well understood.

- It probably involves oxidative damage to hemoglobin and erythrocyte cell membrane proteins.
- This increases the fragility of the erythrocyte and causes hemolysis.

Diagnosis

- History of exposure to and ingestion of zinc
- Clinical signs
- Increased concentration of zinc in the serum
 - >2.0 ppm suggests intoxication
 - concentration of zinc in the serum during intoxication is markedly elevated
- Blood sample for zinc analysis
 - Obtain blood in tube with royal blue top.
 - Do not allow blood to touch rubber stoppers, seals, or grommets that contain zinc.
- Abdominal radiographs for detection of metallic foreign bodies
- Complete blood cell count—indicates intravascular hemolysis
- Analysis for zinc
 - liver and kidney

Treatment

- Gastrointestinal decontamination
 - emetic therapy to remove zinc
 - activated charcoal and cathartic agent
- Surgical removal of foreign body
- Chelation therapy
 - calcium disodium edetate
 - D-penicillamine
- Fluid therapy or transfusion to maintain blood volume

References

- Breitschwerdt EB, Armstrong PJ, Robinette CL, et al. Three cases of acute zinc toxicosis in dogs. *Vet Hum Toxicol.* 1986;28:109–117.

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- Luttgen PJ, Whitney MS, Wolf AM, et al. Heinz body hemolytic anemia associated with high plasma zinc concentration in a dog. *J Am Vet Med Assoc.* 1990;197:1347–1350.
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- Robinette CL. Toxicology of selected pesticides, drugs, and chemicals: zinc. *Vet Clin North Am Small Anim Pract.* 1990;20:539–544.

5

Therapeutic Approach to the Poisoned Veterinary Patient

Treat the Patient, Not the Poison

- Telephone triage (initial contact)
- Keep the patient alive.
 - emergency stabilization
 - supportive therapy
- Obtain a history.
- Decontamination
- Reduce absorption.
- Make a working diagnosis.
 - base initial therapy on diagnosis
- Consider specific antidotal therapy.
- Increase elimination.
- Confirm the toxin with chemical analysis.
 - not necessary in all cases
 - legal aspects
- Client education

- prevent future exposures
- determine the source of toxin

Telephone Triage

Small Animal

- Be calm, clear, and concise.
- Obtain a cursory history.
- Ascertain clinical signs, if present.
- Ask owner to identify the following:
 - probable toxin
 - route of exposure
 - amount ingested
- Instruct the owner to transport the animal to the clinic immediately if it is unconscious or has severe clinical signs.
- Determine whether the owner should induce emesis.
 - Do not delay emergency medical treatment.
 - generally not necessary unless animal is a long distance from the clinic
- Instruct the owner to collect vomitus or diarrhea in clean containers.

Large Animal

- Be calm, clear, and concise.
- Obtain a cursory history.
 - number of animals involved
 - recent management change
 - pasture
 - feed
 - water source
 - clinical signs
- Ask the owner to identify the possible toxin.
- Instruct the owner to collect feed and water samples.
 - minimum of 1 pound (0.45 kg) complete ration

- samples from hay or silage sources
- approximately 1 gallon (3.8 L) water from each source in clean jars
- Farm visit may be necessary if multiple animals are affected.

Emergency Therapy: Keep the Patient Alive

Emergency Stabilization

- Correct life-threatening conditions.
- Use the ABCs of emergency medicine.
- After attending to the ABCs, move to D, decontamination.

ABCs of Emergency Triage

AIRWAY

- Is the airway patent?
- Does the animal have a gag reflex?
- Is intubation necessary?

BREATHING

- Is the animal breathing spontaneously?
- What color are the mucous membranes?

CIRCULATION

- Pulse rate
- Blood pressure
- Insert venous catheter
- Electrocardiogram (depending upon clinical presentation)
- Treat arrhythmias

Supportive Care

FLUID THERAPY

- Intravenous access may be necessary for administration of antidote.
- Protracted vomiting or diarrhea may dehydrate a poisoned patient.
- Normal saline solution or lactated Ringer solution is a good choice for initial fluid therapy.

- Often fluid volume is more important than fluid composition.
- Diuresis may be needed for increased elimination or to prevent renal failure.

SEIZURE CONTROL

- Not a common presentation in large animals.
- Diazepam is a good first-choice therapeutic agent.
 - small animal: 0.5 mg/kg IV, 1.0 mg/kg rectally
 - cattle: 0.5–1.5 mg/kg IV
 - horses (adult): 25–50 mg IV
- Phenobarbital
 - small animals: 5–20 mg/kg IV to effect
- Pentobarbital
 - small animals: 5–15 mg/kg IV to effect
 - cattle: 1–2 g IV

MAINTENANCE OF BODY TEMPERATURE

- Hypothermic patient
 - warmed fluids
 - warm water recirculating pads
 - blankets
 - close monitoring of circulatory status during rewarming
- Hyperthermic patient
 - Initiate evaporative cooling.
 - Dampen the fur.
 - Place fans close to the patient.
 - Immerse patient in a bathtub if necessary.
 - Spray large animals with water from a hose and place them in a shaded enclosure.
 - Control seizures, if present.
 - Reduce heat generated by muscular activity.
 - Control shivering.
 - Do not use chlorpromazine (may lower seizure threshold).
 - Diazepam may reduce shivering.

Decontamination

- Decontamination is the process of removing a toxin from an animal.
- The primary goal of decontamination is to prevent additional toxin exposure.
- Most veterinary intoxications occur through the dermal or oral route.

Ocular Decontamination

- If the animal had an ocular exposure to a toxin or irritant, ocular decontamination may be warranted.
- Flush the affected eye with copious volumes of sterile saline solution or water.
- Flush for 10–15 minutes.
- Do not attempt to use fluids (acid or alkaline) to neutralize the toxin.
- Evaluate the cornea and adnexa after complete irrigation.
- Ocular exposure to alkaline substances may require immediate ophthalmic care.

Dermal Decontamination

- Animals often are exposed to poisons (pesticides) by the dermal route and may need decontamination to reduce further exposure.
- The hair or fur can serve as a reservoir for continued absorption of a toxin.
- It is critical that the persons performing dermal decontamination be protected from exposure to the toxin during the procedure.
 - Wear rubber gloves and a raincoat.
 - Wash the animal with a mild shampoo (not insecticidal) or dish soap.
 - Rinse completely.
 - Repeat the procedure until all traces of odor are removed from the animal.
- A mildly alkaline dip (sodium bicarbonate) may promote hydrolysis of some insecticides.

- Observe animal for any signs of hypothermia or seizure activity.
- Use high-pressure spraying of groups of animals if herd exposure has occurred.

Gastrointestinal Decontamination

- Usually comprises the following steps:
 - emesis or emetic therapy
 - possibly gastric lavage
 - whole bowel irrigation
 - activated charcoal therapy
 - cathartic therapy
 - enterotomy or rumenotomy in special cases
- An area of debate among toxicologists who treat humans
- Common in veterinary medicine
- The primary area of discussion in the human medical field is whether the complication rate after emesis and gastric lavage is justified in the absence of controlled clinical studies.
- In veterinary medicine, the patient population does not attempt suicide.
 - Intoxications are real, not an attempt to gain attention.
- Many intoxicated veterinary patients benefit from gastrointestinal decontamination.
- The use of activated charcoal is generally safe and accepted by both veterinary and human toxicologists.

Methods of Gastrointestinal Decontamination for Veterinary Patients

Agent or Method	Primary Use	Limitation or Contraindication
Activated charcoal	Absorbent material with enormous surface area Can bind most drugs and toxins	Some toxins not adsorbed (see "Activated Charcoal" section later in chapter)
Apomorphine	Emetic agent for dogs, pigs	May cause prolonged vomiting Conjunctival administration causes redness and inflammation

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Agent or Method	Primary Use	Limitation or Contraindication
Enterotomy	Removal of metallic foreign bodies or concretions from the intestine	Must weigh the surgical and anesthetic risk with potential benefit in a poisoned patient
Gastric lavage	Removal of concretions (bezoars) Sustained-release products For massive overdoses	Risk of esophageal or gastric perforation and rupture Do not use with intoxications that weaken the gastric wall
Rumenotomy	Removal of toxins or foreign bodies from the rumen	Anesthetic risk of the surgical procedure and the value of the animal must be weighed
Syrup of ipecac	Emetic agent for dogs	Not effective for cats Not a reliable emetic agent for dogs Use may delay administration of activated charcoal
Whole-bowel irrigation	Removal of sustained-release pharmaceuticals For toxins not adsorbed by activated charcoal	Primarily for small animals Not to be used if obstruction is present May cause prolonged diarrhea
Xylazine	Emetic agent for cats	May cause hypotension and bradycardia

Emetic Therapy

General

- Emesis is more effective early in intoxication.
 - Can be extremely beneficial if induced within minutes of ingestion of toxin.
 - May be induced by the owner at home.
 - Outer limit of effectiveness is 3–4 hours after ingestion.
 - varies with toxin ingested and physiologic condition of the animal
- Emetic therapy is useful after ingestion of toxins that are not adsorbed by charcoal.
 - **example:** ethylene glycol, iron

- Emetic therapy should not delay administration of activated charcoal or antidotal therapy.

Emetic Agents Not Recommended for Veterinary Patients

COPPER SULFATE

- Ineffective emesis
- Risk of copper intoxication

TABLE SALT

- Ineffective emesis
- Risk of hypernatremia

DRY MUSTARD

- Ineffective emesis

DIRECT DIGITAL PHARYNGEAL STIMULATION

- Ineffective emesis
- Danger to the owner, veterinarian, or technician

Locally Acting Emetic Agents

HYDROGEN PEROXIDE (3%)

- Indications
 - induction of emesis
 - removal of toxin
- General
 - Use only 3% hydrogen peroxide (not the hair-bleaching formulation, which is 30%).
 - Not reliable enough for use in the clinic—generally administered by the owner.
- Mechanism of action
 - Direct irritation and stimulation of the mucosa of the pharynx and esophagus
- Contraindications
 - same as general contraindications to emesis
- Therapeutic dose

- dogs and cats: 5–25 mL per 10 lb (4.5 kg) by mouth
- dose may be repeated in 5–10 minutes
- Adverse effects
 - ineffective or inconsistent emesis that can delay charcoal therapy

SYRUP OF IPECAC

- General
 - locally and centrally acting emetic agent
 - mixture of plant-derived alkaloids
 - emetine
 - cephaeline
 - supplied as a syrup in 15-mL or 30-mL bottles in all pharmacies
 - long-term use by humans, as by persons with bulimia, can cause cardiomyopathy and arrhythmia
- Mechanism of action
 - locally acting emetic action
 - direct irritation of the gastric mucosa
 - centrally acting emetic action
 - direct stimulation of the chemoreceptor trigger zone
 - emesis generally occurs within 30 minutes
- Indications
 - induction of emesis in dogs
 - use at home by owners
 - not commonly used in veterinary clinics
- Contraindications
 - same as general contraindications to emesis
 - cats may be more sensitive to the possible cardiotoxic effects
- Therapeutic dose
 - dogs: 1–2 mL/kg by mouth
 - some sources suggest not exceeding a 15-mL total dose
 - follow immediately with 5 mL/kg water
 - cats: 5–10 mL by mouth
 - may have to dilute (50:50) with water
 - may require use of gastric or nasogastric tube

- slower than apomorphine
- less reliable—may delay the onset of charcoal therapy
- Adverse effects
 - CNS depression

Centrally Acting Emetic Agents

APOMORPHINE

- General
 - The chemical structure of apomorphine is shown in Figure 5–1.
 - Apomorphine is a derivative of morphine.
 - has minimal analgesic properties
 - has marked emetic activity
 - no longer used in human medicine because it causes respiratory depression
 - unstable in light and air
 - becomes discolored
 - Greenish color indicates partial decomposition.
- Availability of apomorphine
 - often difficult to obtain
 - Consult local pharmacist for assistance.
 - Compounding pharmacist may be needed to produce a specific formulation.
- Mechanism of action

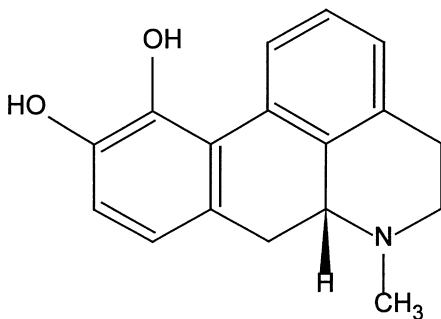


Figure 5–1 Chemical structure of apomorphine.

- stimulation of dopamine receptors in the chemoreceptor trigger zone
- stimulation, which causes emesis, followed by inhibition
- Indications
 - emetic agent for dogs
- Contraindications
 - same as general contraindications to emesis
 - controversial in treatment of cats
- Therapeutic dose
 - must be made fresh
 - grind up a tablet and dissolve in water
 - pass through filter to sterilize before intravenous administration
 - crush tablets and instill in conjunctival sac
 - 0.03 mg/kg IV
 - immediate (<1 min) onset of emesis
 - 0.04–0.08 mg/kg IM or subcutaneously
 - emesis within 5 minutes
 - 0.25 mg/kg into the conjunctival sac
 - a common route of administration of apomorphine
 - slightly less effective than intravenous or intramuscular administration
 - sac flushed with physiologic saline solution after emesis to remove apomorphine
 - is possible to modulate the duration of apomorphine-induced emesis
- Adverse effects
 - 0.1 mg/kg can cause protracted vomiting and depression
 - not for cats
 - unreliable given by mouth
 - may cause depression of the medulla and decrease respiratory function
 - antagonists of apomorphine used to limit the emetic action:
 - Naloxone hydrochloride (Narcan) 0.04 mg/kg IV, IM, or subcutaneously

Nalorphine hydrochloride (Nalline) 0.1 mg/kg IM IV, or subcutaneously

Levallorphan tartrate (Lorfan) 0.02–0.2 mg/kg IV, IM, or subcutaneously

SYRUP OF IPECAC

- See earlier.

XYLAZINE (ROMPUN)

- Especially for cats
- 0.5 mg/kg IV or 1.0 mg/kg IM or subcutaneously
- May aggravate respiratory depression and induce bradycardia

Contraindications to Emesis in Veterinary Medicine

- Ingestion of corrosives
- Ingestion of volatile hydrocarbons, petroleum distillates
- Unconscious patient, no gag reflex
- If the patient is a rodent, rabbit, horse, or ruminant
- Ingestion of convulsant agents
- Seizures or convulsions
- Coma

Gastric Lavage

General

- Invasive procedure that has inherently greater risk than emetic therapy
- Slightly more effective than administration of ipecac in management of recent ingestion of liquid toxin
- A prepackaged gastric lavage system (Easi-Lav; Ballard Medical Products) used in humans has the following features:
 - closed system
 - separate ports and valves for fluid inflow and outflow
 - easy introduction of activated charcoal
 - removal of the syringe not needed at every stroke

- this system could be used to lavage dogs and cats

Indications

- Massive overdose
- Ingestion of toxins that delay gastric emptying (tricyclic anti-depressants)

Treatment

- Administer anesthesia.
- Insert a cuffed endotracheal tube to protect the airway.
- Insert a large-bore gastric tube.
 - largest bore possible
 - multiple holes at distal end
 - measure and mark the tube from the tip of the nose to the xiphoid cartilage
- Lower the animal's head slightly.
- Remove as much stomach content as possible.
- Administer activated charcoal slurry to adsorb free toxin before lavage is instituted.
- Introduce tepid water or saline solution.
- Approximate the volume of water or charcoal slurry needed.
 - 5–10 mL/kg
- Remove water.
 - Use minimal pressure on the abdomen and stomach.
 - Stomach may be friable because of toxin exposure.
- Repeat cycle of instillation and removal of tepid water until the water is clear.
- Instill charcoal slurry (see “Activated Charcoal” section later in chapter).

Adverse Effects

- Perforation of esophagus or stomach
- Aspiration
- Movement of toxin from the stomach into the small intestine

Ruminal Lavage

- Similar to gastric lavage
- Performed on conscious animals—animal's head must be lower than the torso
- Insert a large-bore gastric tube through a mouth speculum.
- Insert a smaller tube inside the large tube.
- Administer water through the smaller tube.
- Remove the smaller tube and allow water to exit the rumen through the large tube.
- Continue in cycles until the water is clear.
- Administer activated charcoal and remove the tubes and the speculum.

Whole-Bowel Irrigation

General

- May be safer than gastric lavage
- Polyethylene glycol administered in balanced salt solution

Composition of Whole-Bowel Irrigation Products

- Same products used for intestinal evacuation before gastrointestinal examination or surgery
- Commonly used in human medicine
- Polyethylene glycol is nonabsorbable
 - acts as an osmotic agent
 - increases volume within the gastrointestinal tract
 - increases gastrointestinal tract motility
 - decreases residence time

GOLYTE POWDER

- Polyethylene glycol 60 g/L
- Sodium chloride 1.46 g/L
- Potassium chloride 0.745 g/L

- Sodium bicarbonate 1.68 g/L
- Sodium sulfate 5.68 g/L
- Flavor ingredients 0.805 g/L

GOLYTELY POWDER

- Polyethylene glycol 49.2 g/L
- Sodium bicarbonate 4.7 g/L
- Sodium chloride 1.22 g/L
- Potassium chloride 0.619 g/L

Indications

- Ingestion of sustained release formulations of pharmaceuticals
- Massive overdose
- Overdose of toxins that are poorly adsorbed by activated charcoal

Contraindications

- Caution should be used in treatment of debilitated patients.
- Intestinal obstruction
- Intestinal perforation
- Ileus
- Hemodynamic instability
- Compromised unprotected airway

Therapy

- Add water before use—product provided in powdered formulations
- Small animal dose
 - 25 mL/kg by mouth
 - repeat dose in 2–4 hours
- Introduce the product through a gastric or nasogastric tube.
- Continue therapy until the fecal material is clear.
- Activated charcoal can be administered before whole-bowel irrigation.

Adverse Effects

- Nausea and vomiting
- Fluid and sodium retention in rare instances

Gastrotomy and Rumenotomy

- Surgical procedure for removal of a foreign body that cannot be removed by other means
 - lead sinkers
 - zinc nuts and bolts
 - pennies
 - bezoars (concretions of pharmaceuticals)
- Stomach or rumen is surgically opened and the foreign body removed.
- Not commonly performed for decontamination—considered only after other methods have proved unsuccessful
- Endoscopy should be considered first in treatment of small animals.
- Poisoned patient may be a greater anesthetic risk.
- In the treatment of food animals, the economic value of the animal must be weighed against the cost of the surgical procedure.

Activated Charcoal

General

- Activated charcoal is a black, odorless, fine powder derived from vegetable matter, such as wood pulp, that is heated to 900°C, washed, and activated by steam or strong acids.
- One gram of activated charcoal contains approximately 1000 m² of surface area.
- To be defined as activated charcoal in the United States Pharmacopoeia, 1 g of charcoal must adsorb 100 mg of strychnine sulfate in 50 mL of water.
- It has been estimated that a 50-g dose of activated charcoal has a surface area approximately equal to that of ten football fields.

Mechanism of Action

- Activated charcoal adsorbs many drugs and chemicals and thus reduces the amount available for absorption (Figure 5–2).
- The mechanism of adsorption involves chemical binding of the drug to the walls of liquid-filled pores of each charcoal particle.
- The efficacy of adsorption by activated charcoal depends on the following factors:
 - delayed absorption of toxin
 - charcoal to drug ratio
 - pH
 - stomach contents
 - drug dose
 - time since ingestion
- A general guideline for the ratio of activated charcoal to toxin is 10:1.

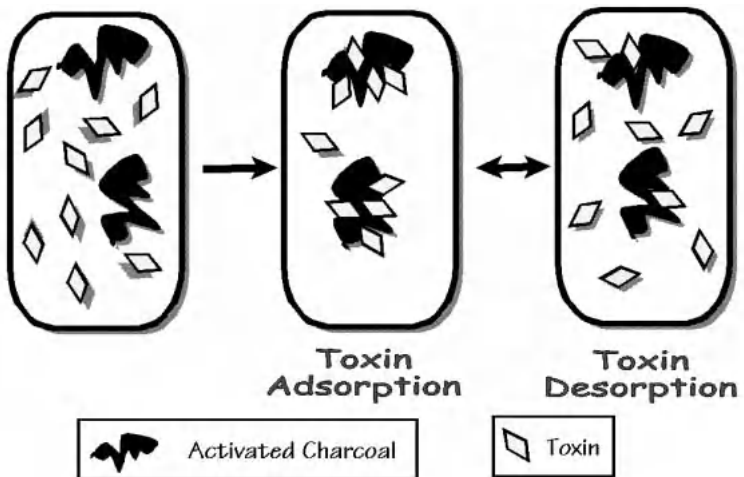


Figure 5–2 Mechanism of adsorption of ingested toxins by activated charcoal. After activated charcoal is introduced into the gastrointestinal lumen, toxins are adsorbed to the charcoal. If the charcoal-toxin complex stays too long in the gastrointestinal lumen, the toxin begins to desorb and is available for absorption into the systemic circulation.

- Adsorption of toxin to charcoal is a reversible binding process; toxins may desorb from charcoal if the residence time in the intestine is prolonged.
- Repeated dosing with activated charcoal may be beneficial for toxins that exhibit enterohepatic recycling (Figure 5–3).
 - digitoxin
 - digoxin
 - nortriptyline
 - phenobarbital
 - phenytoin
 - theophylline

Indications

- Adsorption and prevention of absorption of chemicals and toxins.
- In humans, activated charcoal has been shown to be more effective than gastric lavage and at least as effective as syrup of ipecac, if not superior, in preventing absorption of many drugs and chemicals.

Contraindications

- There are no specific contraindications to the use of activated charcoal to treat poisoned patients.

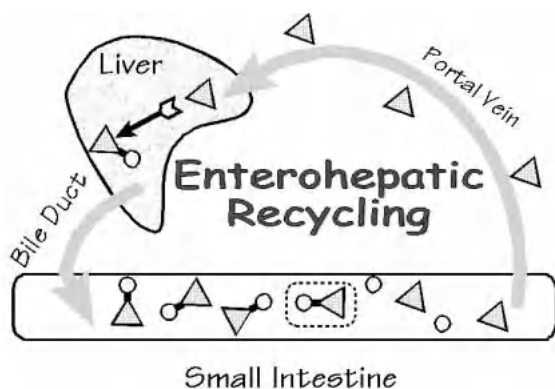


Figure 5–3 Process of enterohepatic recirculation of drugs and toxin. A toxin is conjugated in the liver and excreted into the bile. In the lumen of the gastrointestinal tract, the conjugate sugar is removed and the toxin is reabsorbed.

- The following toxins are poorly adsorbed by activated charcoal:
 - cyanide
 - ethanol
 - ethylene glycol
 - iron
 - methanol
 - strong alkalis
 - strong acids

Therapeutic Dose

- A guideline is to administer approximately ten times the amount of ingested drug.

DOGS AND CATS

- 1–4 g/kg dissolved in 50–200 mL water and given by mouth
- Administer an osmotic cathartic 30 minutes after the charcoal.
- Repeated dosing of activated charcoal may be beneficial in removing toxins that exhibit enterohepatic recycling.

RUMINANTS

- 1–3 g/kg in a slurry of 1 g charcoal in 3–5 mL water
- Administer a saline cathartic after the activated charcoal.
- This dose may be repeated in 8–12 hours.

HORSES

- Foals: 250 g (minimum dose)
- Adults: up to 750 g in a slurry of up to 4 L water depending on size of patient
- Administer with a gastric tube and leave in the gastrointestinal tract for 20–30 minutes.
- After this time give a laxative to enhance removal.

Treatment

- Powdered or liquid formulation is preferred over tablets.
- Tablets are approximately 25% less effective than powder or liquid.

330 Therapeutic Approach to the Poisoned Veterinary Patient

- If the product used is a dry powder, a slurry must be made with 3–50 mL water per gram of activated charcoal.
- The slurry must be mixed thoroughly and administered through an orogastric tube.
- If the activated charcoal is given through a nasogastric tube, more water may be needed to facilitate administration.
- The charcoal should be administered and the patient housed in an area that can be easily cleaned.

Adverse Effects

- Constipation, aspiration, and vomiting (rare)

Products

- The following products are approved for veterinary use:

TOXIBAN GRANULES

- 47.5% activated charcoal (MedChar)
- 10% kaolin
- 42.5% wetting and dispersing agents, including sorbitol
- rapidly dissolves in water

TOXIBAN SUSPENSION

- 10% activated charcoal (MedChar)
- 6.25% kaolin in an aqueous base

TOXIBAN SUSPENSION WITH SORBITOL

- 10% activated charcoal (MedChar)
- 10% sorbitol
- 6.25% kaolin in an aqueous base

Cathartics

General

- Cathartic agents commonly used in veterinary medicine include the following:

- saline solutions
 - magnesium citrate
 - magnesium sulfate (Epsom salt)
 - sodium sulfate (Glauber salt)
- saccharides (sorbitol)
- mineral oil
- Sorbitol, sodium sulfate, and mineral oil are the best cathartics because they have fewer adverse effects.
- The primary role of cathartics in gastrointestinal decontamination is to decrease gastrointestinal transit time, increase the movement of toxins, or charcoal-toxin complex, and decrease possible absorption of the toxin.
- The use of cathartics reduces time to first stool among poisoned patients (human and veterinary).

Indications

- Adjunct to activated charcoal therapy to reduce transit time of toxins in the gastrointestinal tract
- Stimulation of gastrointestinal motility and prevention of residence of toxin in the intestinal tract
- Possibly decrease the constipating effects of charcoal

Mechanism of Action: Osmotic Cathartics

- Unabsorbed, bulk source of solute
- Retention of fluid within the lumen of the gastrointestinal tract
- Activation of motility reflexes and enhancement of gastrointestinal bulk movement

Contraindications

- Ingestion of corrosive substance
- Severe diarrhea
- Adynamic or dynamic ileus
- Serious electrolyte imbalance
- Recent bowel surgery—cathartics should be used with caution when bowel sounds are absent

Therapeutic Dose and Treatment

DOGS

- Sodium sulfate 5–25 g
- Oil 5–30 mL

CATS

- Sodium sulfate 2–5 g
- Oil 2–6 mL

CATTLE

- Sodium sulfate 500–750 g in 6% solution through a gastric tube
- Oil 0.25–0.5 L

HORSES

- Sodium sulfate 250–375 g
- Oil 0.25–1 L
- Sodium sulfate is generally mixed with 5–10 volumes of water prior to administration.

Adverse Effects

- Hypermagnesemia likely after administration of magnesium-based cathartic agent
 - more likely if patient has renal insufficiency
 - greater amount of absorption than previously thought

Comments

SORBITOL

- Should be considered in treatment of a poisoned small animal
- In the treatment of humans, more effective than saline cathartics
- May increase the palatability of activated charcoal and maintains charcoal particles in suspension
- Component of several activated charcoal preparations (e.g., ToxiBan)

LARGE ANIMALS

- Saline cathartic such as sodium sulfate (Glauber salts) more commonly used

- Mineral oil commonly used to treat horses

Enemas

- Enemas have limited use in the treatment of a poisoned patient.
- The use of enemas with a cathartic offers little advantage over whole-bowel irrigation.
- Fleet enemas are contraindicated in cats and small dogs.
 - The main ingredients, sodium biphosphate and sodium phosphate, are a hypertonic solution.
 - As such they can cause serious morbidity and mortality, especially in cats.
 - Substantial absorption of magnesium, phosphorus, and sodium occurs.
- Castile soap in water is a safe alternative to Fleet enemas.

Elimination

- Additional techniques to rid the body of toxin
- Performed after emergency therapy, stabilization, and decontamination
- Not a routine part of therapy; consider possible benefits for each patient.

Manipulation of Urinary pH

REQUIREMENTS

- Toxin must be eliminated via the urine.
- There must be minimal active resorption of the toxin.
- Minimal protein binding of the toxin
- The pKa of the toxin must be in the range of normal urinary pH.

PRINCIPLES OF THE HENDERSON-HASSELBALCH EQUATION

- See Chapter 1.
- Acidification of the urine may increase urinary elimination of basic compounds.
- Alkalization of the urine may increase urinary elimination of acidic compounds.

INCREASING URINARY PH (SODIUM BICARBONATE)

- Acidic drugs are ionized in the tubular lumen.
- The ionized form is “trapped.”
- This species is unlikely to be passively reabsorbed.

EFFECTS OF ION TRAPPING IN THE URINARY SYSTEM

- Normal urinary pH
 - carnivores: 5.5–7.0 (acidic)
 - domestic herbivores: 7.2–8.2 (alkaline)
- May be possible to manipulate urine pH to increase elimination of compounds
- The rules of urinary trapping are as follows:
 - Most of the compound must be eliminated unchanged.
 - The compound must be primarily eliminated in the urine.
- Urinary alkalization with sodium bicarbonate
 - hastens elimination of acidic compounds
salicylate
sulfisoxazole
phenobarbital
- Urinary acidification with ammonium chloride
 - hastens elimination of alkaline compounds
amphetamine
strychnine

Peritoneal Dialysis

- Most effective in the treatment of a patient with anuria or a patient with a large overdose.
- Requirements for this method to be useful are as follows:
 - toxin must have low molecular weight
 - toxin should be in the plasma (central compartment)
highly tissue-bound toxins, such as dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyl (PCB) not likely in the plasma
- The peritoneum is a large surface area for the interchange of toxin.

- The primary principle is diffusion.
Inject warmed, sterile saline into the peritoneal cavity.
Let the fluid equilibrate (diffusion of toxin into saline).
Remove the fluid.
- The net result is increased removal of the toxin.
- Used mainly to treat small animals

Specific Antidotes

Acetylcysteine

GENERAL

- *N*-acetylcysteine (NAC; Mucomyst)
- The chemical structure of acetylcysteine is shown in Figure 5–4.
- Acetylcysteine is a source of sulfhydryl groups for metabolic reactions and a precursor to glutathione.
- Acetylcysteine therapy increases intracellular stores of glutathione, increases glutathione conjugation, and decreases the concentration of reactive metabolites.
- Some questions have been raised concerning concurrent use of activated charcoal and acetylcysteine in humans due to possible adsorption of *N*-acetylcysteine to the activated charcoal.
- The consensus is that use of activated charcoal does not necessitate an increased dose of *N*-acetylcysteine.

MECHANISM OF ACTION

- Acetylcysteine is a donor of sulfhydryl (SH) groups during biotransformation of toxicants (acetaminophen); it maintains cellular glutathione concentration and prevents organ damage caused by reactive metabolites.

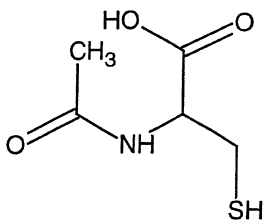


Figure 5–4 Chemical structure of acetylcysteine.

Antidotal Therapy in Veterinary Medicine

Antidote	Toxin
<i>N</i> -Acetylcysteine (Mucomyst)	Acetaminophen
Antivenin polyvalent (Crotalidae)	Envenomation by Crotalidae (rattlesnake family)
Atropine sulfate	Organophosphorus insecticides, cholinergic compounds, slaframine, pyrethrins, cardiac glycosides
Calcitonin	Cholecalciferol rodenticides, vitamin D overdose
Calcium disodium edetate (Versenate)	Lead
Calcium (calcium gluconate, calcium chloride)	Oxalate
Deferoxamine (Desferal)	Iron
Digoxin immune Fab (Digibind)	Digitalis overdose
Dimercaprol (BAL)	Arsenic, mercury
Ethanol	Ethylene glycol, methanol
Fomepizole (4-methyl-1H-pyrazole)	Ethylene glycol
Methylene blue	Nitrites, chlorates, methemoglobinemia
D-Penicillamine (Cuprimine)	Arsenic, copper, mercury
Physostigmine salicylate (Antilirium)	Atropine, belladonna alkaloids, ivermectin
Phytonadione, vitamin K ₁ (Aquamephyton, Mephyton)	Warfarin and other anticoagulant rodenticides, coumarin
Pralidoxime chloride (2-PAM; Protopam)	Organophosphorus insecticides
Protamine sulfate	Heparin overdose, bracken fern
Sodium bicarbonate	Tricyclic antidepressants
Succimer (Chemet)	Lead and arsenic

INDICATIONS

- Poisoning caused by
 - acetaminophen (cats and dogs)
 - reversal of methemoglobinemia (cats)
 - carbon tetrachloride
 - chloroform

CONTRAINDICATIONS

- Known hypersensitivity to acetylcysteine
- Generally no contraindications for use as an antidote

TREATMENT

- Dogs and cats
 - 140–150 mg/kg by mouth or IV as a loading dose
 - followed by 50–70 mg/kg every 4–6 hours
- No acetylcysteine products are approved for veterinary use.
- Human formulations approved for oral or intratracheal administration are supplied as 10% or 20% solution.
- Acetylcysteine has a strong sulfhydryl odor and taste (rotten eggs) and may require administration through an oral or nasogastric tube.

ADVERSE EFFECTS

- Emesis with oral administration
- Hypersensitivity (anaphylactic) reaction with intravenous administration

Antivenin Polyvalent (Crotalidae)**GENERAL**

- A mixture of immunoglobulins produced in horses against the venom of:
 - *Crotalus adamanteus* (eastern diamondback rattlesnake)
 - *Crotalus atrox* (western diamondback)
 - *Crotalus durissus terrificus* (cascabel, tropical rattlesnake)
 - *Bothrops atrox* (fer-de-lance)
- Not effective against coral snakes

INDICATIONS

- Envenomation by members of the Crotalidae family of snakes

MECHANISM OF ACTION

- Combination of immunoglobulins that bind venom, rendering the venom inactive

CONTRAINDICATIONS

- Hypersensitivity to horse serum or serum products (not an absolute contraindication—if patient needs antivenin, it must be given)

TREATMENT

- One vial (10mL) for most envenomations
- Contact a regional poison control center to obtain the antivenin.
- Administer intravenously.
 - Start with a slow drip.
 - Increase rate if animal tolerates the antivenin.
- Because this is a protein product, gently swirl the antivenin and diluent for reconstitution—vigorous shaking may destroy the immunoglobulins

ADVERSE EFFECTS

- Anaphylaxis is possible
 - Pretreat with diphenhydramine to reduce risk.
- Delayed hypersensitivity

Amyl Nitrite

- See *Sodium Nitrite*.

Atropine Sulfate

- The chemical structure of atropine sulfate is shown in Figure 5–5.

GENERAL

- Atropine is commonly used as a preanesthetic agent in dogs, cats, and swine.
- Low doses of atropine sulfate block the muscarinic cholinergic receptor; higher doses block the nicotinic cholinergic receptor.
- Atropinization of a poisoned patient varies among individuals.
- The dose ranges provided are a guide.
- Atropine is administered to control and reduce the symptoms of cholinergic activity (salivation, lacrimation, and dyspnea).

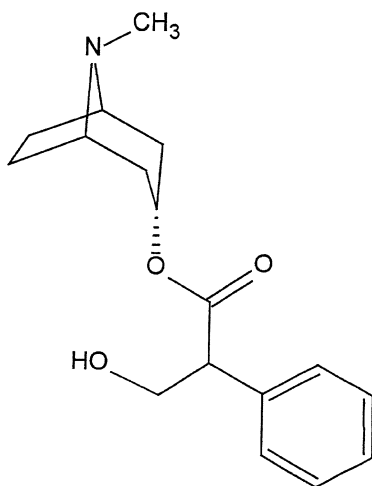


Figure 5-5 Chemical structure of atropine.

MECHANISM OF ACTION

- Atropine is a parasympatholytic agent that binds to and blocks the actions of acetylcholine at postsynaptic muscarinic receptors.
- This prevents prolonged action of acetylcholine within the synaptic cleft.
- Atropine has little, if any, effect at the neuromuscular junction of skeletal muscles.

INDICATIONS

- Poisoning caused by the following:
 - organophosphorus insecticides (all species)
 - carbamate insecticides (all species)
 - muscarinic mushrooms (more commonly dogs)

TREATMENT

- Dogs and cats
 - 0.2–2 mg/kg
- Ruminants
 - 0.2–0.5 mg/kg
 - may repeat dose every 3–4 hours for 1–2 days

- Horses
 - 1 mg/kg, may repeat the dosing every 1.5–2 hours as needed
 - Auscult the abdomen during administration to reduce the possibility of colic.
- In most instances, 25% of the dose is given intravenously and the rest intramuscularly or subcutaneously.
- Atropine is given to effect (reduction of salivation).

ADVERSE EFFECTS

- All species
 - tachycardia
 - hypertension
 - hyperthermia
 - xerostomia
 - dysphagia
 - reduced gastrointestinal motility
 - constipation
 - urinary retention
 - drowsiness
- Species-specific adverse reactions
 - cattle and sheep: ruminal stasis
 - horses: colic

Calcitonin (Salmon Calcitonin)

GENERAL

- Supplied as an injectable liquid
 - 200 IU/mL, 2-mL vials
- Effective in small quantities
 - 1 mg can decrease serum calcium concentration 1–2 mg%

MECHANISM OF ACTION

- Prevents calcium mobilization from bone
- Increases urinary excretion of calcium, sodium, and phosphorus

- Increases excretion of sodium and phosphorus
- Decreases tubular reabsorption of calcium, sodium, and phosphorus

INDICATIONS

- Cholecalciferol rodenticide intoxication
- Vitamin D intoxication

CONTRAINDICATIONS

- Hypersensitivity to calcitonin

TREATMENT

- Dogs
 - 4–6 IU/kg subcutaneously every 2–3 hours
 - Monitor serum calcium level for efficacy.
 - Continue therapy until serum calcium level stabilizes in the normal range.
- Used in conjunction with the following treatments:
 - saline diuresis
 - prednisone
 - furosemide

ADVERSE EFFECTS

- Nausea and vomiting are possible.

***Calcium Disodium Edetate (CaEDTA, Versenate, Edetate
Calcium Disodium, Calcium Edetate)***

GENERAL

- The chemical structure of CaEDTA is shown in Figure 5–6.
- CaEDTA is an effective chelating agent for several heavy metal intoxications; however, this agent is not widely available.
- Veterinary formulations of CaEDTA have been withdrawn.
- Veterinarians may have to use the product approved for humans or enlist the services of a compounding pharmacist to use this antidote.

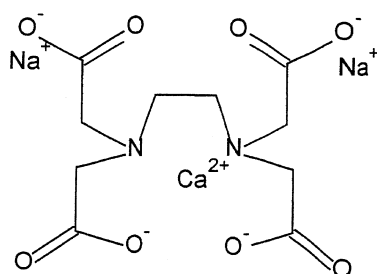


Figure 5-6 Chemical structure of calcium disodium edetate.

MECHANISM OF ACTION

- CaEDTA is a complex of edetate with calcium and sodium ions.
- The calcium ions can be replaced by lead and zinc to form a water-soluble heavy metal carrier eliminated in the urine.
- Other metals that can replace calcium in the CaEDTA complex but are not excreted in large amounts are cadmium, copper, iron, and manganese.

INDICATIONS

- Lead intoxication

CONTRAINDICATIONS

- Anuria
- Use of other nephrotoxic drugs

TREATMENT

- Dogs and cats
 - 100 mg/kg subcutaneously every 6 hours
- Horses
 - 75 mg/kg IV by means of slow infusion for 4–5 days
 - Stop for 2 days.
 - Repeat dosing regimen for another 4–5 days.
- Cattle
 - 67–73 mg/kg per day divided into two or three doses by means of IV slow infusion for 2–5 days

- Withhold dose for 2 days and repeat the treatment cycle if necessary.
- General treatment recommendation is to remove the animal from the source of lead or remove the lead objects from the animal before chelation therapy.
- The product used by humans usually is diluted in 5% dextrose in water or saline solution before intravenous administration.
- Intramuscular injection can cause pain that can be dampened by diluting the CaEDTA with procaine.

ADVERSE EFFECTS

- All species: renal tubular necrosis
- Dogs: depression and vomiting or diarrhea
- Oral administration of CaEDTA may increase intestinal absorption of lead.

Deferoxamine Mesylate (Desferal)

GENERAL

- The chemical structure of deferoxamine mesylate is shown in Figure 5–7.
- Poorly absorbed by the oral route, must be given intramuscularly or intravenously
- Deferoxamine and iron produce a characteristic reddish color of urine (vin rose).
- Supplied as a lyophilized powder in 500-mg or 2-g vials.

MECHANISM OF ACTION

- Deferoxamine chelates iron and aluminum.
- The chelator forms complexes with iron to form ferrioxamine.
 - This chelate is inert and cannot interact with cellular macromolecules.
 - The chelated iron complex is water soluble.
 - The complex is excreted in the urine.

INDICATIONS

- Iron toxicosis
- Aluminum intoxication

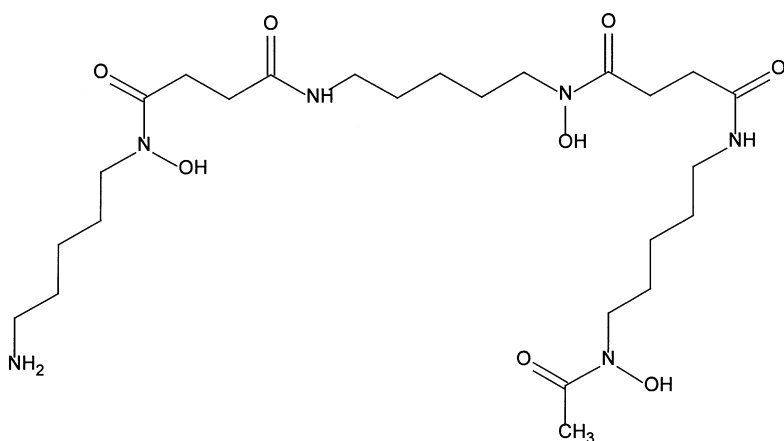


Figure 5-7 Chemical structure of deferoxamine mesylate.

CONTRAINDICATIONS

- Known hypersensitivity to deferoxamine

TREATMENT

- Dogs
 - 10 mg/kg IM or IV every 8 hours for 24 hours
 - Monitor urinary iron excretion and serum iron concentration.

ADVERSE EFFECTS

- Uncommon

Dimercaprol (British Anti-lewisite, BAL)

GENERAL

- The chemical structure of dimercaprol is shown in Figure 5-8.
- Dimercaprol is an oily preparation and must be administered by means of deep intramuscular injection.

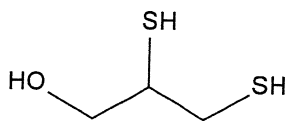


Figure 5-8 Chemical structure of dimercaprol (British anti-lewisite).

MECHANISM OF ACTION

- The sulfhydryl groups of dimercaprol are bound by arsenic or other metals that prevent binding to sulfhydryl-containing enzymes.

INDICATIONS

- Chelation of arsenic intoxication—more effective with inorganic arsenic
- Also used to chelate lead and mercury

CONTRAINDICATIONS

- Chelation of iron, selenium, or cadmium—the chelated complex is more toxic than the metal itself.

TREATMENT

- Dogs and cats
 - 2.5–5.0 mg/kg IM
 - every 4 hours for the first 48 hours
 - every 8 hours on the third day
 - every 12 hours for the next 10 days
 - Closely monitor renal and hepatic function.
 - Maintain renal function and urine flow during therapy.

ADVERSE EFFECTS

- Nephrotoxicity; use with caution when treating patients with decreased renal function.
- Urinary alkalization may prevent renal damage.

Ethanol (Grain Alcohol, Alcohol)**GENERAL**

- Ethanol is readily available and an economical antidote.
- Ethanol is much more effective if administered in the first 8–12 hours after antifreeze ingestion.
- A recently approved antidote, fomepizole (4-MP, Antizol-Vet), has greater affinity for the target and a more favorable pharmacokinetic profile with less central nervous system depression but is not used widely in veterinary medicine primarily because of the cost.

MECHANISM OF ACTION

- Ethanol inhibits cellular alcohol dehydrogenase and prevents production of toxic metabolites from agents metabolized through this pathway (see Chapter 4, *Ethylene Glycol*).

INDICATIONS

- Acute ethylene glycol (antifreeze) intoxication among dogs and cats
- Methanol intoxication from windshield washer fluid, antifreeze, or paint remover

CONTRAINDICATIONS

- No absolute contraindications as an antidote

TREATMENT

- Dogs and cats
 - 5.5 mL/kg of 20% ethanol solution IV every 4 hours for five treatments
 - followed by same dose every 6 hours (dogs) or 8 hours (cats) for four treatments
- Intravenous therapy is more reliable than oral administration because of the risk of gastric irritation and vomiting.
- This concentration of ethanol is hyperosmotic and must be diluted in fluid.
- Ethanol must be filtered before intravenous administration.
- Careful monitoring of fluid and electrolyte status is necessary during therapy because ethanol and ethylene glycol inhibit antidiuretic hormone and induce diuresis.

ADVERSE EFFECTS

- Respiratory and central nervous system depression

Fomepizole (4-MP, Antizol-Vet)

GENERAL

- FDA approved for treatment of dogs
- May be effective at higher doses in treatment of cats
- Supplied by Orphan Medical, Inc. of Minnetonka, MN

MECHANISM OF ACTION

- Inhibition of alcohol dehydrogenase prevents metabolism of ethylene glycol to glycolic and glyoxylic acids.
- The remaining nonmetabolized ethylene glycol and its metabolites are excreted in the urine.

INDICATIONS

- Ethylene glycol (antifreeze) poisoning among dogs

CONTRAINDICATIONS

- None when used as an antidote

TREATMENT

- Dogs
 - 20 mg/kg IV loading dose
 - 15 mg/kg IV at 12 and 24 hours
 - followed by 5 mg/kg IV at 36 hours
- Provided as a kit with one vial containing 1.5 g fomepizole (1.5 mL 1.0 g fomepizole per milliliter sterile aqueous solution) and a second vial containing 30 mL 0.9% sodium chloride injection as a diluent
- Fomepizole has slower elimination rate and fewer adverse effects than does ethanol.

ADVERSE EFFECTS

- Minimal central nervous system depression

Methylene Blue (Methylthionium Chloride)**GENERAL**

- The chemical structure of methylene blue is shown in Figure 5–9.
- Methemoglobinemia can be caused by a variety of agents that oxidize hemoglobin (see Chapter 2).

MECHANISM OF ACTION

- Methylene blue acts as an electron acceptor from the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) in erythrocytes.

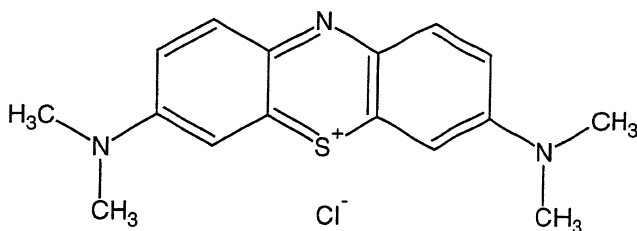


Figure 5-9 Chemical structure of methylene blue.

- activates the reductase enzyme system, which usually is dormant
- reduces methylene blue to leucomethylene blue
- leucomethylene blue can reduce methemoglobin to hemoglobin
- Leucomethylene blue becomes an electron donor for methemoglobin.
- This allows reduction of iron from the ferric [Fe^{3+}] to the ferrous [Fe^{2+}] state and regeneration of hemoglobin.

INDICATIONS

- Treatment of methemoglobinemia

CONTRAINDICATIONS

- Hypersensitivity to methylene blue
- Renal insufficiency

TREATMENT

- Cattle
 - 8.8 mg/kg by means of slow IV injection of 1% solution
 - Repeat dose in 30 minutes if no response occurs.
- Sheep and other species
 - 4.4 mg/kg by means of slow IV injection of 1% solution
- Methylene blue can stain fur and clothing.

ADVERSE EFFECTS

- Cats are highly sensitive to methylene blue—small doses can cause severe, even fatal, Heinz body anemia.

- Higher doses of methylene blue can cause methemoglobinemia through direct oxidization of hemoglobin.
- Methylene blue is not an effective agent in the treatment of methemoglobinemia in horses.

***D-Penicillamine (Cuprimine, D-Panamine,
Depen, Metalcaptase)***

GENERAL

- Administered orally
- Animals can be monitored at home
- Can be used as an adjunct after calcium disodium edetate therapy for lead intoxication

MECHANISM OF ACTION

- Chelation—binding of heavy metals
- The combination of the heavy metal and penicillamine produces water-soluble complexes.
- The complex is eliminated from the body through the urinary tract.

INDICATIONS

- Chelation of
 - lead
 - copper
 - mercury
 - iron
- Copper storage disease among dogs

CONTRAINDICATIONS

- Possibly if there is a known hypersensitivity to penicillin

TREATMENT

- Dogs
 - 110 mg/kg per day by mouth divided into three or four doses
 - Treat for 1–2 weeks.
 - Reduce the dose by one-half if side effects occur.

- Cats
 - 125 mg/kg by mouth every 12 hours
- Allow adequate access to fresh water during therapy.
- Monitor urinary function.
- Measure blood lead concentration to evaluate the efficacy of therapy.

ADVERSE EFFECTS

- Similar to those of penicillin
- Gastrointestinal: anorexia, nausea, and vomiting
- Hematologic: thrombocytopenia
- Renal: proteinuria, glomerulonephritis
- Dermatologic (rare): rash, pruritus

Physostigmine Salicylate (Antilirium)

GENERAL

- Not commonly used
- Can cross the blood-brain barrier and stimulate the central nervous system

MECHANISM OF ACTION

- Reversible inhibitor of acetylcholinesterase
- Increases concentration of acetylcholine in the synaptic cleft and increases stimulation by acetylcholine at muscarinic and nicotinic receptors

INDICATIONS

- Anticholinergic overdose (atropine, *Datura* spp.)
- Ivermectin overdose (for diagnostic purposes)
- Larkspur (*Delphinium* spp.) poisoning

CONTRAINDICATIONS

- Organophosphorus insecticide overdose
- Overdose of other compounds that inhibit acetylcholinesterase
- Concurrent use of nondepolarizing neuromuscular blocking agents

- Overdose of tricyclic antidepressant

TREATMENT

- Dogs
 - 1 mg every 12 hours to comatose animals
 - increase in responsiveness lasts 30–90 minutes
- Cattle
 - 0.04 to 0.08 mg/kg body weight IV, intraperitoneally, or subcutaneously

ADVERSE EFFECTS

- Vomiting, diarrhea, and hypersalivation

Phytonadione, Vitamin K, (Aquamephyton, Mephyton)

GENERAL

- The chemical structure of phytonadione is shown in Figure 5–10.
- Effective antidote in the treatment of bleeding patients
 - If bleeding is severe, the patient may need fresh frozen plasma.
- Supplied as
 - injectable formulation: 2 mg/mL, 10 mg/mL
 - oral formulation: 5-mg tablets
- Vitamin K₃ is ineffective.

MECHANISM OF ACTION

- Vitamin K is a source of carboxyl groups that aid in carboxylation of vitamin K–dependent coagulation factors.

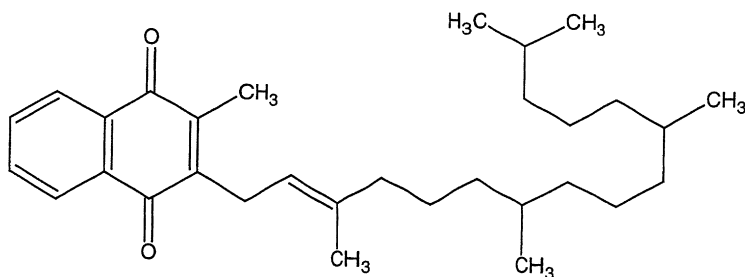


Figure 5–10 Chemical structure of phytonadione.

- This step is essential in producing active coagulation factors from inactive precursors.

INDICATIONS

- Anticoagulant rodenticide intoxication
- Moldy sweet clover (dicumarol) intoxication of cattle or horses

CONTRAINDICATIONS

- No absolute contraindications in management of intoxication

TREATMENT

- Dogs and cats
 - 2.5–5.0 mg/kg by mouth or subcutaneously
- Cattle, horses, swine, and sheep
 - 0.5–2.5 mg/kg IM
- Dosing guidelines
 - Administer orally for greater absorption, if the animal can tolerate it.
 - If animal is vomiting, use the subcutaneous route for 2–3 days, then switch to oral administration.
 - Divide the subcutaneous dose and inject into several sites.
 - Use the smallest gauge needle possible.
 - Do not give intramuscularly or intravenously due to risk of anaphylaxis.
- Duration of therapy
 - 3–4 weeks to ensure protection from the longer-acting anticoagulant rodenticides
- Monitoring of therapy
 - Repeat measurement of prothrombin time 2–5 days after cessation of therapy.
 - Improvement in clotting function should occur within 12 hours.
- Owner education
 - When sending an animal home with vitamin K₁ tablets or capsules, instruct owner to continue therapy until results of clotting tests are normal.
 - Restrict animal's activity during treatment to prevent trauma.

- Observe closely for clinical signs.

ADVERSE EFFECTS

- Hemorrhage from subcutaneous or intramuscular injection of vitamin K
- Anaphylaxis with intravenous administration
- Relapse of bleeding
 - generally caused by premature cessation of therapy

Pralidoxime Chloride (2-PAM, Pyridine-2-Aldoxime Methochloride, Protopam)

GENERAL

- The chemical structure of pralidoxime chloride is shown in Figure 5-11.
- Most effective if administered within 24–36 hours after exposure to organophosphorus insecticide
- Not generally effective in carbamate intoxication
- Reverses muscular paralysis associated with organophosphorus intoxication and has greater effect on nicotinic blockade without marked reversal of muscarinic signs
- Crosses the blood-brain barrier slowly, if at all
- Used with atropine

MECHANISM OF ACTION

- Reactivates acetylcholinesterase that has been inactivated by organophosphorus insecticide

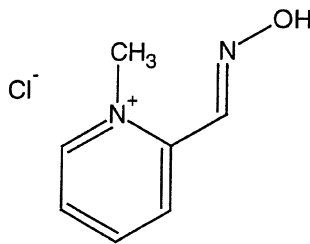


Figure 5-11 Chemical structure of pralidoxime chloride.

- Acts as a nucleophile and draws organophosphorus insecticide from the phosphorylated acetylcholinesterase enzyme
- This opens the active site of the enzyme and allows continued catalysis of acetylcholine.

INDICATIONS

- Intoxication with organophosphorus insecticide

TREATMENT

- Administered after atropine therapy
- Dogs and cats
 - 25 mg/kg slow IV
 - In severe intoxication a second dose can be given in 1 hour if muscular weakness has not improved.
- Information from the manufacturer states that the intraperitoneal or intramuscular route of administration is possible in the treatment of small dogs and cats.
- Horses
 - 2 g slow IV
 - In severe cases of intoxication a second dose can be given 1 hour after the first if muscular weakness has not been relieved.
- Cattle
 - 20–50 mg/kg IV in 20% solution
- Protopam is the only product approved for veterinary use.
 - Sterile pralidoxime chloride is packaged as a kit with one vial containing 1 g sterile pralidoxime chloride powder and a second vial containing 20 mL sterile water.

ADVERSE EFFECTS

- Uncommon

Protamine Sulfate**GENERAL**

- Derived from the sperm or testes of salmon
- Not a common antidote

MECHANISM OF ACTION

- Protamine exhibits ionic attraction for heparin.
- Protamine binds to heparin and forms an inactive complex.
- The kinetics of the protamine-heparin complex are not well understood.

INDICATIONS

- Heparin overdose among small animals
- Poisoning by bracken fern among cattle (suggested in conjunction with whole-blood transfusion)

CONTRAINDICATIONS

- Known hypersensitivity to the product
- Not common

TREATMENT

- Dogs and cats
 - 1 mg protamine per milligram heparin by means of slow IV injection
 - Dose can be decreased by 50% if there is a delay between poisoning and initiation of protamine therapy.
- Cattle
 - 10 mL 1% protamine sulfate by means of slow IV injection
 - usually in conjunction with whole-blood therapy

ADVERSE EFFECTS

- Because protamine sulfate is a protein from a foreign source, anaphylactic reactions can occur.

Sodium Bicarbonate**MECHANISM OF ACTION**

- In acidosis, sodium bicarbonate combines with organic acids to increase pH.
- In tricyclic antidepressant intoxication, sodium bicarbonate antagonizes the sodium channel blockade effects of the antidepressant and allows a return to normal QRS complexes.

INDICATIONS

- Correction of acidosis
- Adjunctive therapy for ethylene glycol intoxication
- Management of tricyclic antidepressant overdose
- Alkalization of urine to increase elimination of acidic drugs and to prevent hemoglobin and myoglobin from damaging the renal tubules

CONTRAINDICATIONS

- Use with caution in the treatment of
 - patients with hypocalcemia because it may induce tetany
 - patients with hypochloremia such as those with excessive vomiting

TREATMENT

- Dogs and cats
 - Antidote to ethylene glycol, tricyclic antidepressant
 - Alkalinize the urine
0.5–1 g/kg body weight
 - Tailor dose to the patient.
 - Monitor the efficacy of therapy by measuring urinary pH.
- Monitor serum bicarbonate level, arterial pH, urinary pH.
- Goal for urine alkalization is to maintain urinary pH between 7.0 and 7.5.

ADVERSE EFFECTS

- Metabolic alkalosis
- Alteration of concentrations of potassium and calcium in the serum

Sodium Nitrite

GENERAL

- Traditionally was a component of the treatment of cyanide (with sodium thiosulfate)
- Still available (3% solution) as a component of the cyanide antidote kit used to treat humans

- Amyl nitrate works by the same mechanism but is inhaled rather than injected.
- At this time it is not commonly used in veterinary medicine.

MECHANISM OF ACTION

- Acts by inducing methemoglobinemia (convert iron in hemoglobin to ferric state)
- The cyanide binds to the methemoglobin rather than the cytochrome oxidase of the mitochondria.
- Sodium thiosulfate can serve as a sulfur donor for the rhodanese enzyme.

CONTRAINDICATIONS

- Induces methemoglobinemia.
- Do not use in conjunction with other agents that can induce methemoglobinemia.

TREATMENT

- Cattle/sheep
 - 10–20 mg/kg IV

COMMENTS

- Not needed in the treatment of cyanide intoxication
- Sodium thiosulfate alone is effective at producing thiocyanate.
- The additional risk of inducing methemoglobinemia in a patient with cyanide poisoning does not result in more favorable outcomes.

Succimer (2,3-Dimercaptosuccinic Acid, DMSA, Chemet)

GENERAL

- Water-soluble analogue of dimercaprol (BAL)
- Can be given orally
- Generally less nephrotoxic than dimercaprol
- Succimer is used to treat human patients with high blood lead concentrations.

MECHANISM OF ACTION

- Dithiol chelator that is relatively selective
 - does not bind iron
 - can administer iron with succimer to patients with anemia and lead intoxication
- Binding of lead to form a water-soluble complex that is excreted in the urine

INDICATIONS

- Lead intoxication
- Arsenic intoxication
- Mercury intoxication

CONTRAINDICATIONS

- Hypersensitivity to the drug

TREATMENT

- Dogs
 - 10 mg/kg by mouth every 8 hours for 10 days
- Monitor renal function and urinary output.
- Maintain urine flow to decrease adverse effects.
- Monitor clinical signs for chelation efficacy.

ADVERSE EFFECTS

- Nausea and vomiting

Thiamine (Vitamin B₁)

GENERAL

- The chemical structure of thiamine is shown in Figure 5–12.
- Water-soluble vitamin rapidly absorbed after administration
- Administered parenterally

MECHANISM OF ACTION

- Combines with adenosine triphosphate in most vital organs to produce thiamine diphosphate.

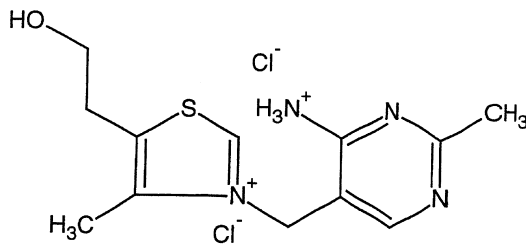


Figure 5-12 Chemical structure of thiamine.

- Thiamine diphosphate acts as a coenzyme in carbohydrate metabolism
 - transketolation reactions
 - hexose-monophosphate shunt
- A decrease in thiamine level causes
 - decreased conversion of pyruvate to acetyl coenzyme A
 - prevention of entrance of pyruvate into the tricarboxylic acid cycle
 - increase in pyruvate concentration
 - conversion of pyruvate to lactic acid
 - risk of lactic acidosis
 - decreased production of the reduced form of nicotinamide adenine dinucleotide (NADH)

INDICATIONS

- Bracken fern intoxication
- Polioencephalomalacia among cattle
- Possibly in sulfur-induced polioencephalomalacia
- Adjunct therapy for lead intoxication
- Adjunct therapy for ethylene glycol intoxication to detoxify glyoxylate

CONTRAINDICATIONS

- Hypersensitivity to thiamine

TREATMENT

- Cattle
 - polioencephalomalacia dosing
10 mg/kg IV loading dose
followed by 10 mg/kg IM every 12 hours for 2–3 days
 - lead intoxication dosing
2 mg/kg IM
continued for several days
- Dogs
 - 10–100 mg/d by mouth

ADVERSE EFFECTS

- Not common

Thiosulfate (Sodium Thiosulfate)

GENERAL

- Sulfur donor in the management of cyanide intoxication
- Often used in conjunction with sodium nitrite

MECHANISM OF ACTION

- The proposed mechanism of action is shown in Figure 5–13.
- Exact mechanism of action not completely understood
- As a sulfur donor, thiosulfate acts as a cofactor for the enzyme rhodanese (thiosulfate sulfurtransferase)
 - mediates the addition of a sulfur molecule to cyanide
 - resulting compound is called *thiocyanate*
 - thiocyanate is eliminated in the urine

INDICATIONS

- Cyanide intoxication (prussic acid intoxication)
- Proposed for arsenic and other heavy metal intoxications

CONTRAINDICATIONS

- No absolute contraindications

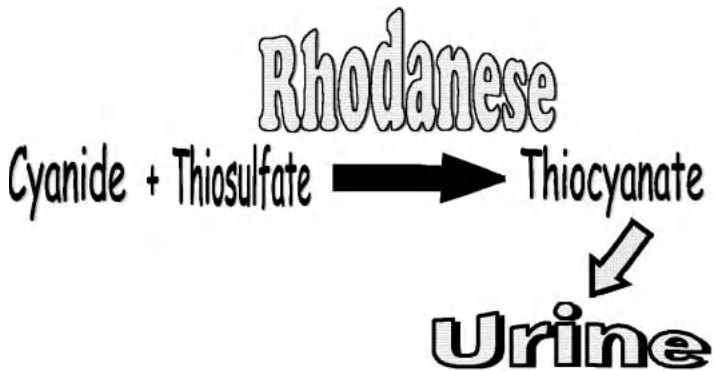


Figure 5-13 Cyanide detoxification with the cofactor thiosulfate by the enzyme rhodanese.

TREATMENT

- Cattle
 - cyanide intoxication
 - 660 mg/kg IV in 30% solution
 - administered with large-gauge needle

ADVERSE EFFECTS

- Not common

Cost of Antidotal Therapy

The following information on the cost of therapy with some of the more common antidotes is from the *2000 Drug Topics Redbook*, edited by Valentine Cardinale and published by Medical Economics, Montvale, New Jersey. The Redbook is a trade publication for pharmacists that is published annually. It is a useful resource for a myriad of drug information. These costs are for human therapeutic agents and are based on the average wholesale price—a nationwide average price for low-volume customers. These costs are very conservative because most practices or pharmacists receive better pricing; however, they give the veterinarian an idea of the cost of therapy. More information is available at <http://www.drugtopics.com>.

Antidote	Cost per Unit	Cost of Therapy
<i>N</i> -Acetylcysteine (Mucomyst)	\$0.004/mg	\$22.4 for a 5-kg cat
Antivenin polyvalent (Crotalidae)	\$630.62/kit	
Atropine sulfate	\$0.44/mg	\$8.80/dose for a 20-kg dog \$13.2/dose for a 300-kg steer
Calcitonin	\$0.08/IU	\$76.8/day for a 20-kg dog
Calcium disodium edetate (Versenate)	\$0.04/mg	\$320.00/day for a 20-kg dog \$1440.00/day for a 300-kg steer
Cyanide kit (amyl nitrate, sodium nitrite, sodium thiosulfate)	\$274.60/kit	
Deferoxamine (Desferal)	\$0.03/mg	\$24.00/day for a 20-kg dog
Dimercaprol (BAL)	\$0.25/mg	\$270.00 for entire course for a 10-kg dog
Ethanol	Very inexpensive	
Fomepizole (Antizol-Vet)	\$667.00/g	\$366.85 for entire course for a 10-kg dog
Methylene blue	\$0.378/g	\$1.13/treatment of a 300-kg steer
D-Penicillamine (Cuprimine)	\$0.004/mg	\$52.80 for entire course for a 10-kg dog
Phytonadione, vitamin K ₁ (Aquamephyton, Mephyton)	\$0.54/mg (inj) \$0.14/mg (tabs)	\$48.60 first 3 days \$88.00 next 21 days \$135 to treat a 10-kg dog
Pralidoxime chloride (Protopam)	\$150.00/g	\$37.50 for a 10-kg dog
Sodium thiosulfate	\$0.02/mg	\$3.96 for a 300-kg steer
Succimer (Chemet)	\$0.04/mg	\$160.00 for entire course for a 10-kg dog

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6

Diagnostic Toxicology

Use of a Clinical Laboratory as a Diagnostic Aid

General

- A clinical laboratory can rapidly provide a veterinarian with information to confirm a clinical impression.
- The results of tests may provide information about the efficacy of therapy.
- Many veterinary clinics can perform some of the following tests.

Tests

- Electrolytes
 - sodium, calcium, potassium, chloride, magnesium
- Hepatic function
 - bilirubin, alkaline phosphatase, transaminases
- Renal function
 - blood urea nitrogen, urinalysis, visual examination of urine
- Hemostasis
 - prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen level

- Hemolysis
 - hemoglobin, reticulocytes
- Anemia
 - hemoglobin, hematocrit

Common Diagnostic Procedures to Assist the Clinician

Anion Gap

DEFINITION

- The difference between measured cations and anions (Figure 6–1)

INTERPRETATION

- An increase in the anion gap suggests metabolic acidosis due to unmeasured organic acids.
- The normal anion gap is 10–12 mEq/L.
- Alteration of the anion gap may depend on the stage of intoxication.
- The anion gap can be increased in the following diseases:
 - ketosis
 - uncontrolled diabetic ketoacidosis
 - uremia due to renal failure
 - severe dehydration
 - seizures
- An increase in the anion gap greater than 30 mEq/L is clinically significant.

COMMON TOXINS ASSOCIATED WITH AN INCREASED ANION GAP

- Ethylene glycol
- Ethanol
- Iron

$$\text{Anion Gap} = \frac{(\text{serum sodium} + \text{serum potassium})}{(\text{serum bicarbonate} + \text{serum chloride})}$$

Figure 6–1 Anion gap.

- Methanol
- Salicylates (aspirin)
- Strychnine

Osmolar Gap

- **Definition:** The difference between measured and calculated osmolarity (Figure 6–2)
- Measured by freezing point depression
- Used to assist in the diagnosis of intoxication with alcohol or ethylene glycol
- May not be available in smaller hospitals

General Comments About Samples and Diagnostic Laboratories

- A diagnostic laboratory is a powerful tool that can help veterinarians treat patients and educate owners to prevent further exposures.
- The correct use of the technology and the expertise of a diagnostic laboratory depends on the information and samples submitted—as in computer science, “garbage in, garbage out.”
- There is no substitute for the correct sample, promptly delivered to the diagnostic laboratory. If there is any question about sample collection or submission, *telephone the laboratory before proceeding*.
- A quick telephone call to the laboratory can save time and money and facilitate the return of useful information to the veterinarian.

Elements of Diagnostic Toxicology

- Clinical signs
- Case history

$$\text{Calculated Osmolarity} = 2[\text{sodium}] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

$$\text{Osmolar Gap} = (\text{Measured Osmolarity} - \text{Calculated Osmolarity})$$

Figure 6–2 Osmolar gap.

- Selection of tests
- Sample submission
- Analytical testing
- Histopathologic examination
- Necropsy
- Analysis and diagnosis

Samples

Timing

- Initial presentation—the best time for sample collection
- After emergency treatment and stabilization
- Before antidotal therapy

Suspected Toxin

- Submit labels of commercial products if available
 - bait, pesticide
 - complete samples of feed
 - minimum of 2 kg
 - higher moisture feed (>12%) frozen
 - feed with suspected volatile toxin, such as cyanide, frozen in clean glass
 - feed supplements
 - water source
- Freeze samples.
- Do not overfill sample containers.

Specimens from Live Animals

- Vomitus (refrigerated or frozen)
- Whole blood (EDTA or heparin tube)
- Serum (serum removed from clotted blood)
- Urine (refrigerated)
- Feces (refrigerated or frozen)
- Hair or skin if the route of exposure is dermal

Specimens from Necropsy

- Serum
- Whole blood (refrigerated)
- Ruminal or gastric contents, frozen
- Intestinal contents, frozen
- Feces, frozen
- Urine, frozen
- Tissue
 - part fresh and part fixed in 10% buffered formalin
 - liver
 - kidney
 - part frozen and part fixed in 10% buffered formalin
 - brain
 - eyeball
 - bone
 - fat

Sample Storage and Packaging

- Place the following submission paperwork in a separate plastic Zip-lock bag and attach the bag to the top of the shipping container.
 - completed submission form
 - written record of the known history
 - date of sample collection
- Double-bag samples before freezing them.
 - Place an identification tag for each organ or sample between the two bags.
- Place formalin-fixed tissue in containers that can be properly sealed.
 - On the label, identify the animal and the tissues or sample.
- Package to prevent cross contamination.
- Package tissue specimens separately.
- If submitting suspect material with tissues, avoid cross-contamination by wrapping the suspect material in aluminum foil or paper.

- Do not send specimens in hypodermic syringes.
- Label tubes with consecutive numbers (1, 2, 3, etc.). Pack blood tubes in order.
- Use shipping ice packs (gel packs), not ice.
- Ship frozen or refrigerated material in a properly insulated leak-proof container, clearly marked on the outside as a frozen or refrigerated laboratory specimen.
- Ship to the diagnostic laboratory by means of overnight courier.
 - Be certain to provide the courier with the correct delivery address, that is, an exact physical address, not a post office box.

Remedies for Common Problems or Submission Errors

- Include a complete case history.
 - clinical signs
 - number of animals affected
 - time of onset and time course
 - treatment provided
 - tentative diagnosis
- Call the laboratory if there are any questions.
- Place blood sample for serum zinc measurement in royal-blue-topped tubes to avoid zinc contamination from the stopper.
- Collect samples of appropriate size.
 - Too large a sample cannot be fixed properly.
- Send unclotted blood samples cooled but not frozen.
- Pour serum off the clot, if possible, and send the serum to the laboratory cold or frozen.
- Cut formalin-fixed tissues no more than $\frac{1}{4}$ inch (6 mm) thick and place them in a wide-mouthed, leak-proof container with 5–10 times the volume of formalin to tissue ratio.
 - Formalin penetrates only $\frac{1}{8}$ inch (3 mm) in the critical first 24 hours of fixation.
 - Tissues fixed for at least 2 days before being sent to the laboratory can be shipped in a smaller volume of formalin.

Specific Diagnostic Samples for Common Veterinary Toxins

The following are the preferred diagnostic samples for common veterinary toxins, as reported in the veterinary literature. It is crucial for veterinarians to ask the diagnostic laboratory about the need for additional samples, specialized handling, and the method of storage. The laboratory can provide guidance about samples for additional testing that may aid in the diagnosis, such as bacteriology, virology, and clinical pathologic studies.

Toxicant	Specimen	Comment
Acute bovine pulmonary edema and emphysema (AIP; 3-methyl indole)	Lung (fresh and in 10% buffered formalin)	Histopathologic and bacteriologic examinations to exclude common pathogens
Aflatoxin	Feed, liver (fixed in 10% buffered formalin)	At least 1 lb (450 g) of feed for chemical analysis Liver for histopathologic examination
Anticoagulant rodenticides	Whole blood, serum, liver, bait	Freeze liver
Arsenic (organic and inorganic)	Inorganic: liver, kidney, urine Organic: optic nerve, brain	Also submit complete feed sample
Blister beetles (cantharidin intoxication)	Serum, urine, stomach contents, hay, beetles	Serum calcium: hypocalcemia
Blue-green algae (Cyanobacteria)	Liver, water samples	Microscopic exam of water Histopathology of liver
Bromethalin	Suspect bait, brain from dead animal	
Cholecalciferol	Serum, kidney, bait	Finding of hypercalcemia confirms the diagnosis
Cholinesterase inhibitors (organophosphorus and carbamate)	Brain (all species) Whole blood (ruminants) Serum (monogastric animals)	Keep samples cool Submit half a brain (right hemisphere and associated brain stem)

(continues)

(Continued)

Toxicant	Specimen	Comment
Copper	Liver, kidney, feed, serum, urine	Provide label from complete feed or supplement
Crude oil	Rumen contents, lung (fresh, fixed and frozen), suspect material	Suspect material can be compared with that found in the rumen or lungs
Cyanide	Forage or hay, bait, rumen or stomach contents (frozen)	Store forage or hay in a tightly sealed glass jar
Ethylene glycol	Urine, serum, stomach contents, kidney	Histopathologic examination (kidneys) Urinalysis (crystals)
Fluoride	Bone, urine, forage	
Fumonisin	Feed, brain	Fixed brain for histopathologic examination
Gossypol	Feed containing gossypol, serum, liver (frozen), fixed heart	Histopathology of the heart
Ionophores (lasalocid, monensin, salinomycin)	Feed, stomach or rumen content Cardiac and skeletal muscle	Histopathology of muscles Chromatography of the feed samples
Iron	Whole blood (EDTA or heparin tube), feed, water, liver	
Ivermectin	Feces, gastric content, liver, and fat	Specific tests for ivermectin—call lab first
Lead	Unclothed whole blood, brain liver, kidney	Basophilic stippling in dog Histopathologic examination of brain
Locoweed	Fixed brain	Histopathologic examination often is the definitive diagnostic procedure
Metaldehyde	Stomach contents, bait	
Molybdenum	Feed sample, liver	Feed and liver samples will be analyzed for copper and molybdenum
Mycotoxin screening	Feed	

(continues)

(Continued)

Toxicant	Specimen	Comment
Nitrate	Suspect forage, hay, water, urine, eyeball	
Nonprotein nitrogen (ammonia intoxication)	Suspect feed, rumen content, serum or heparinized blood, eyeball	Freeze rumen content and serum
Organochlorine	Stomach, liver, kidney, brain, fat	Suspect material, feed sample
Petroleum products	Rumen contents, lung, liver	
Poisonous plants	Suspect plant material	Pack in plastic bag and submit for identification
Selenium	Stomach content, urine, feed, liver, kidney, serum or whole blood	
Sodium ion toxicosis, water deprivation	Water from all sources, rumen contents, cerebrospinal fluid, serum, brain	
Strychnine	Stomach content, urine, bait, liver	
Urea	See <i>nonprotein nitrogen</i> .	
Zinc	Blood (serum), feed, liver, kidney	Royal blue-topped tubes Do not allow blood to touch any part of the stopper

Diagnostic Laboratories

The following diagnostic laboratories have access to the services of a veterinary toxicologist certified by the American Board of Veterinary Toxicology. These veterinary toxicologists have undergone additional specialized training, published articles in the field of veterinary toxicology, and have successfully completed a qualifying examination. This additional training allows veterinary toxicologists to provide valuable information concerning the diagnosis and management of veterinary poisoning. The help of a board-certified toxicologist is essential to interpret analytical data and assist the veterinarian in determining

whether findings are important. A board-certified veterinary toxicologist has an extensive network of toxicologists across the country who can aid in establishing the type of intoxication. Additionally, the veterinary toxicologist can serve as a valuable informational resource or expert witness in poisoning cases that involve litigation. Most of the following laboratories are certified by the American Association of Veterinary Laboratory Diagnosticians.

***Veterinary Diagnostic Laboratories with
a Veterinary Toxicologist Who Is a Diplomate
of the American Board of Veterinary Toxicologists***

ARKANSAS

Arkansas Diagnostic Laboratory, Livestock & Poultry Commission,
Little Rock, AR

Phone: (501) 907-2410

CALIFORNIA

University of California at Davis, California Veterinary Diagnostic
Laboratory System

Phone: (530) 752-8700, (530) 752-6322

Fax: (530) 752-6253

<http://sphinx.ucdavis.edu/index.phtml>

COLORADO

Colorado State University, Fort Collins, CO

Phone: (970) 491-1281

Fax: (970) 491-0320

<http://www.cvmb.colostate.edu/dlab/>

<http://www.cvmb.colostate.edu/dlab/webdocs/general/chemist.htm>

GEORGIA

- Athens

Athens Veterinary Diagnostic Laboratory, College of Veterinary
Medicine, The University of Georgia, Athens, GA

Phone: (706) 542-5568

Fax: (706) 542-5977

<http://www.vet.uga.edu/vetdiag.html>

- Tifton

Veterinary Diagnostic Investigational Laboratory, Tifton, GA

Phone: (912) 386-3340

Fax: (912) 386-7128

<http://www.vet.uga.edu/erc/diagnostic/html/tifton.html>

IDAHO

Department of Food Science and Toxicology, University of Idaho,
Moscow, ID

Phone: (208) 885-7081, (509) 335-9696

ILLINOIS

Veterinary Diagnostic Laboratory, University Diagnostic Laboratory,
University of Illinois, Urbana, IL

Phone: (217) 333-1620

Fax (217) 333-4828

<http://www.cvm.uiuc.edu/vdl/>

<http://www.cvm.uiuc.edu/vdl/diag1.htm>

INDIANA

Animal Disease Diagnostic Laboratory, School of Veterinary Medicine,
Purdue University, West Lafayette, IN

Phone: (765) 494-7448

Fax: (765) 494-9181

<http://www.addl.purdue.edu/>

IOWA

Veterinary Diagnostic Laboratory, College of Veterinary Medicine,
Iowa State University, Ames, IA

Phone: (515) 294-1950

Fax: (515) 294-3564

<http://www.vdpam.iastate.edu/VDL/default.htm>

KANSAS

Veterinary Diagnostic Laboratory, College of Veterinary Medicine,
Kansas State University, Manhattan, KS

Phone: (785) 532-5650

Fax: (785) 532-4481

<http://www.vet.ksu.edu/depts/dmp/service/toxiclgy/index.htm>

MICHIGAN

Animal Health Diagnostic Laboratory, Michigan State University,
Lansing, MI

Phone: (517) 355-0281

Fax: (517) 353-5096

<http://www.ahdl.msu.edu/>

MINNESOTA

Veterinary Diagnostic Laboratory, College of Veterinary Medicine,
University of Minnesota, St. Paul, MN

Phone: (612) 625-8787, (800) 605-8787

Fax: (612) 624-8707

<http://www.mvdl.umn.edu/mvdlhome.htm>

MISSISSIPPI

College of Veterinary Medicine, Mississippi State University,
Mississippi State, MS

Phone: (662) 325-1104

<http://gabriel.cvm.msstate.edu/VetMedResearch/ReschEdHandbookContents/DiagnosticLabServices.htm>

MISSOURI

Veterinary Medical Diagnostic Laboratory, PO Box 6023,
Columbia, MO

University of Missouri–Columbia College of Veterinary Medicine

Phone: (800) 862-8635, (573) 882-6811

Fax: (573) 882-1411

<http://www.cvm.missouri.edu/vmdl/index.html>

NEBRASKA

Veterinary Diagnostic Center, University of Nebraska–Lincoln,
Lincoln, NE

Phone: (402) 472-1434, (402) 472-8462

Fax: (402) 472-3094

<http://ianrwww.unl.edu/ianr/nvdl/index.htm>

OHIO

Animal Disease Diagnostic Laboratory, Reynoldsburg, OH

Phone: (614) 728-6220

Fax: (614) 728-6310

<http://www.state.oh.us/agr/addl/>

OKLAHOMA

Oklahoma Animal Disease Diagnostic Laboratory, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK

Phone: (405) 744-6623

Fax: (405) 744-8612

<http://www.cvm.okstate.edu/~groups/oaddl/www/oaddl.htm>

TENNESSEE

College of Veterinary Medicine, University of Tennessee, Knoxville, TN

Phone: (423) 974-5638

<http://web.utk.edu/~vetmed/toxser.html>

TEXAS

<http://www.tvmdl.tamu.edu/>

- **Amarillo**

Texas Veterinary Medical Diagnostic Laboratory, Amarillo, TX

Phone: (806) 353-7478, (888) 646-5624

Fax: (806) 359-0636

- **College Station**

Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, Texas A&M University, College Station, TX

Phone: (979) 835-3414, (888) 646-5623

Fax: (979) 845-1794

UTAH

Utah Veterinary Diagnostic Laboratory, Utah State University,
Logan, UT

Phone: (435) 797-0238

Fax: (435) 797-2805

WYOMING

Wyoming State Veterinary Laboratory, Department of Veterinary
Sciences, Laramie, WY

Phone: (307) 742-6638

Fax: (307) 721-2051

<http://www.uwyo.edu/VETSCI/vetlab.htm>

***Diagnostic Laboratories Accredited by the American
Association of Veterinary Laboratory Diagnosticians***

ARIZONA

Arizona Veterinary Diagnostic Laboratory

Phone: (520) 621-2356

Fax: (520) 626-8696

CONNECTICUT

Connecticut Veterinary Diagnostic Laboratory, Department of
Pathobiology, University of Connecticut, Storrs, CT

Phone: (860) 486-3738

Fax: (860) 486-3936

<http://www.lib.uconn.edu/pathobiology/cvdl9.html>

FLORIDA

State Diagnostic Laboratories

- Kissimmee

Phone: (407) 846-5200

Fax: (407) 846-5204

- Live Oak

Phone: (904) 362-1216

Fax: (904) 364-3615

<http://doacs.state.fl.us/~ai/5c13x.htm#Toxicology>

GEORGIA

Diagnostic Assistance Laboratory, University of Georgia, College of Veterinary Medicine, Athens, GA

Phone: (706) 542-5568

Fax: (706) 542-5977

ILLINOIS

Animal Disease Laboratory, Illinois Department of Agriculture, Centralia, IL

Phone: (618) 532-6701

Fax: (618) 532-1195

Animal Disease Laboratory, Illinois Department of Agriculture, Galesburg, IL

Phone: (309) 344-2451

Fax: (309) 344-7358

KENTUCKY

Livestock Disease Diagnostic Center, University of Kentucky Coldstream Research Campus, Lexington, KY

Phone: (606) 253-0571

Fax: (606) 255-1624

<http://www.ca.uky.edu/lddc/>

Veterinary Diagnostic & Research Center, Murray State University, Hopkinsville, KY

Phone: (502) 886-3959

Fax: (502) 886-4295

LOUISIANA

Veterinary Medical Diagnostic Laboratory, Baton Rouge, LA

Phone: (225) 346-3193

Fax: (225) 346-3390

<http://www.vetmed.lsu.edu/lvmdl.htm>

MISSISSIPPI

Mississippi Veterinary Diagnostic Laboratory, Jackson, MS

Phone: (601) 354-6089

Fax: (601) 354-6097

MONTANA

State of Montana Animal Health Division, Department of Livestock, Veterinary Diagnostic Laboratory, Bozeman, MT

Phone: (406) 994-4885

Fax: (406) 994-6344

NEW YORK

Veterinary Diagnostic Laboratory, College of Veterinary Medicine, Cornell University, Ithaca, NY

Phone: (607) 253-3900

Fax: (607) 253-3943

http://diaglab.vet.cornell.edu/dl_home.html

NORTH CAROLINA

Rollins Animal Disease Diagnostic Laboratory, North Carolina Department of Agriculture, Raleigh, NC

Phone: (919) 733-3986

Fax: (919) 733-0454

NORTH DAKOTA

Veterinary Diagnostic Laboratory, North Dakota State University, Fargo, ND

Phone: (701) 237-8307

Fax: (701) 237-7514

<http://www.cc.ndsu.nodak.edu/instruct/devold/vetdiag/index.htm>

PENNSYLVANIA

Department of Agriculture, State Veterinary Laboratory, Harrisburg, PA

Phone: (717) 772-2852

Fax: (717) 772-2870

<http://adls20.nbc.upenn.edu/padls2.html>

SOUTH CAROLINA

Clemson University Veterinary Diagnostic Center, Columbia, SC

Phone: (803) 788-2260

Fax: (803) 699-8910

SOUTH DAKOTA

Animal Disease Diagnostic Laboratory, South Dakota State University, Brookings, SD

Phone: (605) 688-5172

Fax: (605) 688-6003

<http://www.vetsci.sdstate.edu/>

TENNESSEE

CE Kord Animal Disease Diagnostic Laboratory, Nashville, TN

Phone: (615) 837-5125

Fax: (615) 837-5250

WASHINGTON

Washington State University, Animal Disease Diagnostic Laboratory, Pullman, WA

Phone: (509) 335-9696

Fax: (509) 335-7424

http://www.vetmed.wsu.edu/depts_services/waddl/waddls.html

WISCONSIN

Wisconsin Animal Health Laboratory Wisconsin Department of Agriculture, Madison, WI

Phone: (608) 266-6687

Fax: (608) 267-0636

Other Sources of Information

National Animal Poison Control Center

- <http://www.napcc.asPCA.org/>

A nonprofit animal poison control center, the National Animal Poison Control Center is staffed by veterinarians 24 hours a day. A fee-based service—the fee is paid by the veterinarian, the owner, or the product manufacturer.

PHONE: (888) 426-4435

- \$45.00 per case charged to major credit cards

PHONE: (900) 680-0000

- \$45.00 per case
- The center will answer follow-up calls as necessary.
- No cost if the poisoning or exposure involves a product covered by manufacturer contracts. The center can inform the caller concerning the drugs or chemicals that are covered by this arrangement.

Regional Human Poison Control Centers

Poison control centers can be a valuable source of information about pharmaceuticals and over-the-counter products used by humans. They have access to informational databases that are not commonly found in a veterinarian's office. The following are certified poison control centers. Other poison control centers may be suggested by the local pharmacist or another health professional.

Alabama (800) 462-0800

Alaska (800) 478-3193

Arizona (800) 362-0101

Arkansas (800) 376-4766

California (800) 876-4766

Colorado (800) 332-3073

Connecticut (800) 343-2722

Delaware (800) 722-7112

Florida (800) 282-3171
Georgia (800) 282-5846
Hawaii (808) 941-4411
Idaho (800) 860-0620
Illinois (800) 942-5969
Indiana (800) 382-9097
Iowa (800) 352-2222
Kansas (800) 332-6633
Kentucky (502) 589-8222
Louisiana (800) 256-9822
Maine (800) 442-6305
Maryland (800) 492-2414
Massachusetts (800) 682-9211
Michigan (800) 764-7661
Minnesota (800) 764-7661
Mississippi (601) 354-7660
Missouri (800) 366-8888
Montana (800) 525-5042
Nebraska (800) 955-9119
Nevada (800) 446-6179
New Hampshire (800) 562-8236
New Jersey (800) 764-7661
New Mexico (800) 432-6866
New York (800) 252-5655; (800) 336-6997
North Carolina (800) 848-6946
North Dakota (800) 732-2200
Ohio (800) 872-5111
Oklahoma (800) 764-7661
Oregon (800) 452-7165
Pennsylvania (800) 521-6110; (800) 722-7112
Rhode Island (800) 682-9211
South Carolina (800) 922-1117
South Dakota (800) 764-7661

Tennessee (800) 288-9999

Texas (800) 764-7661

Utah (800) 456-7707

Vermont (877) 658-3456

Virginia (800) 451-1428

Washington (800) 732-6985

West Virginia (800) 642-3625

Wisconsin (800) 815-8855

Wyoming (800) 955-9119

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