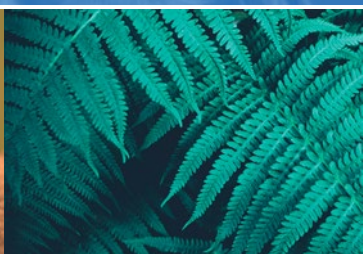
PK Gupta





Concepts and Applications in Veterinary Toxicology

An Interactive Guide

Springer

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Bareilly, Uttar Pradesh, India

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Preface

The book entitled *Concepts and Applications in Veterinary Toxicology: An Interactive Guide* covers a broad spectrum of topics for the students specializing in veterinary toxicology and veterinary medical practitioners. The major emphasis of the book is to briefly highlight specialized topics essential for veterinary specialists. A great attention has been given to common toxicants to which several species, including pet animals, are exposed to a variety of toxicants. The subject of veterinary toxicology is complicated greatly by the wide variations in responses of domestic, companion, aquatic, wild, and zoo species to toxicants. Therefore, emphasis has also been given to species variation and diagnostic toxicology including clinical management that is more relevant to veterinary profession. The author's own experience in different branches of veterinary toxicology has been abstracted in this book. In the last few decades, veterinary toxicologists have faced the enormous task of dealing with a flood of new farm chemicals and household products. Understanding the complete profile (especially mechanisms of toxicity) of each toxicant is the biggest challenge for today's veterinary toxicologists.

This book has 15 chapters that cover several topics, such as general principles of toxicology, current status, factors affecting toxicity, absorption, distribution, metabolism, excretion, mechanism of toxicity, toxic effects of various xenobiotics, poisonings of poisonous and venomous organisms, toxicities from human drugs, bacteria and cyanobacteria (blue-green algae), mycotoxicosis, feed contaminant toxicity, and food hazards in pets and veterinary drug residue hazards. The last chapter is exclusively devoted to veterinary clinical toxicology which deals with the principles of diagnosis, followed by the general management of poisoning of the patients including methods of removal of poisons from the body and treatment of poisoning.

Each chapter in this book starts with the introduction and key points relevant to the topic, then concept and applications, followed by questions and answers that include short questions and answers, multiple choice questions, true/false or correct/incorrect statements, fill in the blanks, and match the statements. It is a unique book in veterinary toxicology that is prepared to offer a comprehensive concepts and application resource to veterinary toxicologists, students, teachers, clinicians, and animal health scientists. This book is more student-teacher-friendly, is targeted primarily for the classroom and practitioners, and is written in a manner to

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stimulate interest on various facets of the subject and make it more exciting. The sample exercises of questions and answers will support active learning because these exercises will not only be a useful tool for the teachers of veterinary toxicology who need inspiration when composing questions for their students but will also help all teachers practicing in medical toxicology and toxicologists engaged in various disciplines. Therefore, the author believes that this book would serve the students, academic institutions, and industry as follows:

- It is a good resourse for veterinary medical practitioners and will be an excellent contribution for the students who need a study aid for veterinary toxicology but want more than a textbook as they need a self-testing regime.
- It will be a useful tool for the teachers of veterinary toxicology who need inspiration when composing questions for their students.
- It will also help the established toxicologists to test their own knowledge of understanding the subject matter.
- It will be useful at universities and colleges and in industry for in-house training courses in veterinary toxicology, which I know exist in some pharmaceutical and chemical companies.
- It is required for all those who want to study for the veterinary toxicology boards and other examinations.

Thus, the main strength of this book is that it reflects the breadth and multidisciplinary nature of veterinary toxicology with the subject needed to improve the engagement and understanding of the subject having a very wide audience.

Toxicology is a rapidly evolving field. Suggestions and comments are welcome to help the author improve the contents of the book. Please also suggest the deficiencies need to be covered at drpkg_brly@yahoo.co.in or drpkg1943@gmail.com if you have any topics you feel should be better covered in any future editions.

Bareilly, Uttar Pradesh, India PK Gupta

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Disclaimer

The information, including text, questions and answers, illustrations, etc., in the book is based on standard textbooks in the area of specialization. However, it is well known that with the advancement of science, the standard of care in the practice of veterinary medicine changes rapidly. Many drugs that were indicated for the treatment of a certain ailment in the beginning get superseded by others. With long-term use, their effects and effectiveness become apparent, or else, the use was advocated for some other problem. Though all the efforts have been made to ensure the accuracy of the information, the possibility of human error still remains. Therefore, neither the author nor the publisher guarantees that the information contained in the book is absolute. Anyone using the veterinary clinical information contained in this book has to be, therefore, duly cautious. It is particularly important to check drug dosages, indications, interactions, and contraindications with the manufacturer's most recent product information. Neither the author nor the publisher should be responsible for any damage that results from the use of the information contained in any part of this book.

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General Principles of Toxicology

1

Abstract

This chapter deals with the general principles and emergence of science-based toxicology and the scope and current status of veterinary toxicology. The future of veterinary toxicologists is very bright because this science will further expand as people and animals will continue to be poisoned by more and different chemicals. Several factors such as age, strain, species variation, pregnancy, physical state, and chemical properties of the toxicant and environmental factors can greatly influence the toxicity of a specific compound. The dose-response relationship, or exposure-response relationship, describes the change in the effect on an organism. Many toxicants/xenobiotics exert their effects by interacting with specific receptors in the body. Therefore, this chapter briefly summarizes a qualitative description of the adverse effect arising from a particular chemical or physical agent irrespective of dose or exposure.

Keywords

General toxicology · Principles of toxicology · Factors affecting toxicity · Dose-response relationship · Interactions · Receptors · Hazards · Risk assessment · Questions and answers bank · Multiple choice questions

1.1 Introduction

This chapter deals with the general principles of toxicology, factors affecting toxicity, emergence of science-based toxicology, and the scope and current status of veterinary toxicology. In addition, this chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements as relevant to general principles of toxicology and their toxic effects on animal health.

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Key Points

- Toxicology assimilates knowledge and techniques from biochemistry, biology, chemistry, genetics, mathematics, medicine, pharmacology, physiology, and physics.
- The word "toxicology" is derived from the Greek word *toxicon* which means "poison" and *logos* which means to study.
- The evolution of veterinary toxicology occurred concurrently with the evolution of its two roots: the profession of veterinary medicine and the science of toxicology.
- Veterinary toxicology involves the evaluation of toxicosis and deficiencies, identification and characterization of toxins and determination of their fate in the body, and treatment of toxicosis.
- Veterinary toxicology in its earliest years had a major focus on poisonous plants and then on antidotes for various toxins.
- Modern toxicology assimilates knowledge and techniques from most branches of sciences such as biochemistry, biology, chemistry, genetics, mathematics, medicine, pharmacology, physiology, and physics.
- After the World War II, the mid-1950s witnessed the strengthening of various laws in the United States and other developed countries in the world.
- The future of veterinary toxicologists is very bright because this science will further expand as people and animals will continue to be poisoned by more and different chemicals.
- Several factors such as age, strain, species variation, pregnancy, physical state, and chemical properties of the toxicant and environmental factors can greatly influence the toxicity of a specific compound.
- The dose-response relationship, or exposure-response relationship, describes the change in the effect on an organism.
- Many toxicants/xenobiotics exert their effects by interacting with specific receptors in the body.

1.2 Roots in Veterinary Medicine and Toxicology

The adjective veterinary is derived from Latin: veterinary, beasts of burden. Obviously, the modern field of veterinary medicine extends beyond the "beasts of burden" to include all the domesticated animal species, both livestock and companion animals, as well as non-domesticated species. Indeed, it has expanded to include nonmammalian species. Veterinary toxicology has now grown into a multifaceted discipline that utilizes many diverse sources of toxicologic information. Veterinary toxicologists can be involved in basic toxicology research, clinical toxicology, regulatory toxicology, chemical risk assessment, and chemical food safety in private, academic, clinical, government, and commercial settings, among others. Like many areas of science, veterinary toxicology information is being generated at rates much

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higher than most professionals can access it and incorporated its principles into practice. Veterinary toxicologists need access to a wide variety of information sources to remain abreast with current toxicologic information and to make sound clinical choices. The Internet has provided the veterinary toxicologist with a valuable tool to access both historical and cutting-edge research information in a timely and cost-effective manner.

The father of modern toxicology is generally acknowledged to be Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541), who referred to himself as Paracelsus, from his belief that his work was beyond the work of Celsus, a first-century Roman physician. Paracelsus is credited with the well-known statement:

> All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

Paracelsus advanced many views that were revolutionary for his time that are now accepted as fundamental concepts for the field of toxicology.

Since then, the evolution of veterinary toxicology occurred concurrently with the development of its two roots: the profession of veterinary medicine and the science of toxicology. The veterinary medicine profession was initially focused on domestic animals, particularly those used for food, fiber, and transportation and those used to provide power for agricultural endeavors and transportation. With the growth of more specialized agriculture and production practices, the profession, with its linkage to domestic livestock, stimulated growth of veterinary toxicology. Veterinary toxicology in its earliest years had a major focus on poisonous plants and then on antidotes for various toxins. By the mid-twentieth century, three movements transformed veterinary medicine:

(i) The first was related to the traditional roots of the profession in animal agriculture and related to the increasing emphasis given to large-scale highly specialized domestic livestock endeavors. This movement was a major factor in the growth of Colleges of Veterinary Medicine at land-grant universities in the United States, followed by some other countries.
(ii) The second was related to the increased attention given to providing veterinary medical services to a growing population of companion animals—a population that included horses, dogs, and cats.
(iii) The third movement—the emergence of the comparative medicine character of veterinary medicine—became more apparent and was enhanced.

During this period, veterinary toxicologists began to play an important role in veterinary medical diagnostics. The expansion of the various facets of toxicology has been the outcome of the need of an affluent society to protect itself from injurious effects resulting from introduction of new chemicals, physical agents, and various industrial and consumer products. Therefore, application of the discipline of toxicology in the safety evaluation and risk assessment is of utmost importance in today's modern life.

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1.3 Toxicology and the Risk Paradigm

As indicated earlier, toxicology, like veterinary medicine, was also rapidly changing and evolving in the mid-twentieth century. These changes in the veterinary medical profession and the emergence of toxicology as a science emerged during a period when the general population was paying increased attention to the health risks and, its counterpoint, safety of new technologies and products.

The mid-1950s witnessed the strengthening of the US Food and Drug Administration's commitment to toxicology under the guidance of Arnold Lehman. Lehman, Fitzhugh, and their co-workers formalized the experimental program for the appraisal of food, toxicant, and cosmetic safety in 1955, updated by the US FDA in 1982. The Delaney clause (1958) of these amendments stated broadly that any chemical found to be carcinogenic in laboratory animals or humans could not be added to the US food supply. Regardless of one's view of Delaney, it has served as an excellent starting point for understanding the complexity of the biological phenomenon of carcinogenicity and the development of risk assessment models.

The end of the 1960s witnessed the "discovery" of TCDD as a contaminant in the herbicide Agent Orange (the original discovery of TCDD toxicity, as the "chick edema factor," was reported in 1957). The expansion of legislation, journals, and new societies involved in toxicology was exponential during the 1970s and 1980s and shows no signs of slowing down. At present, there are several dozens of professional, governmental, and other scientific organizations with thousands of members and over 120 journals dedicated to toxicology and related disciplines in the world. As an example of this diversification, one now finds toxicology graduate programs in medical schools, schools of public health, and schools of pharmacy as well as programs in environmental science and engineering. Now there are undergraduate programs in toxicology at several institutions. Surprisingly, courses in toxicology are now being offered in several liberal arts undergraduate schools as part of their biology and chemistry curricula.

In the 1970s, several federal legislations passed by various countries focused on health impacts of environmental and occupational exposures and led to more formalized approaches to evaluating the risks and safety of various exposures. The risk paradigm built on the long-standing pattern of linking sources of dose exposure to adverse health outcomes had guided toxicology from its earliest days. The original key elements of the risk paradigm were as follows:

(i) Hazard identification
(ii) Exposure-response assessment
(iii) Exposure assessment
(iv) Risk assessment

The information developed in the risk assessment process is utilized in the risk management where decisions are made as to the need for, the degree of, and the steps to be taken to control exposures (the four major elements) of the chemical of concern (Fig 1.1).

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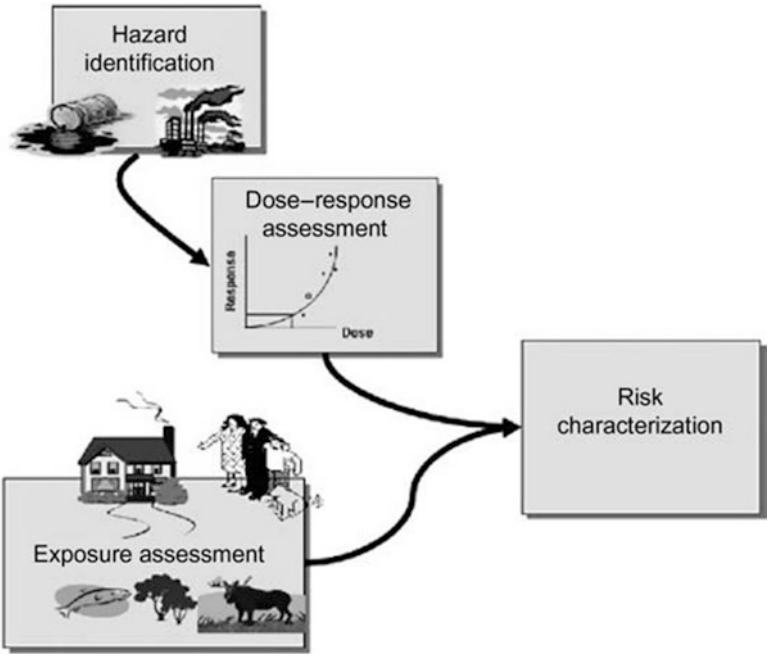


Fig. 1.1 The information developed in the risk assessment. Process is utilized in risk management, whereby decisions are made based on the need for and degree of the steps that should be taken to control exposures of chemicals of concern. (Source: NRC, 2007. Models in Environmental Regulatory Decision Making. The National Academies Press, Washington, D.C. Available from: http://www.nap.edu/read/11972/chapter/4)

Subsequently, in 1994, the United States emphasized the importance of a fifth element: using the results of the risk analysis to guide future research and, thus, reduce uncertainty in future risk estimates. The hazard identification element has been a source of contention and confusion for both the public and the scientific community, especially with regard to cancer.

1.4 Scope of Toxicology

Modern toxicology is a multidisciplinary science. It has expanded largely in the past few decades to cope with the pressure created by the addition of numerous manufactured chemicals through food additives, industrial wastes, toxicants, radioactive substances, pesticides, and other chemicals. The future of veterinary toxicologist is very bright because this science will further expand as mankind, animals, and other creatures continue to be poisoned by more and different chemicals. The contribution and activities of toxicologists are diverse and widespread. Modern toxicology contributes to physiology and pharmacology, environmental sciences, clinical medicine, legal medicine, occupational medicine and hygiene, veterinary medicine,

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experimental pathology, and safety evaluation. Therefore, over the years, various specialized subdisciplines of toxicology have been recognized, and many new are being added every year.

1.5 Current Status

Today, toxicity testing of a chemical, for the purposes of animal, human, or environmental health risk assessment, as might be expected, is not a routine aspect of toxicology. It is actually one of the most controversial subjects as large quantities of animals are needed. Among the many areas of controversy is the use of animals for experimental purposes. Extrapolation of animal data to humans, extrapolation from high-dose to low-dose effects, and the increasing cost and complexity of testing protocols may not be beneficial. Therefore, to reduce the use of animals, some alternative approaches have been developed by each country. For example, the United States, European countries, Japan, and other countries avoid unnecessary animal tests; in particular, data sharing, the use of alternative test methods, and other approaches are used to predict the properties of substances. Over the past few years, a number of alternative approaches have been developed, for example:

(i) Use of test systems of in vitro test methods that are suitable for test purposes have been adopted and incorporated in the test methods' regulation. However, there are currently no in vitro tests, ex vivo tests, or test batteries that can act as a like-for-like replacement of higher-tier toxicology studies, such as those investigating carcinogenicity, ex vivo mutagenicity, or reproductive toxicity.
(ii) Use of computer models, sometimes referred to as in silico methods such as using the quantitative structure activity relationship (QSAR) or the structure activity relationship (SAR) approach. At present, such in silico predictions cannot be used alone to predict a number of the toxicological properties (long-term toxicity, carcinogenicity, mutagenicity, and reproductive toxicity). Detailed discussion on the use of chemoinformatics is beyond the scope of this chapter.
(iii) Properties of substances can be predicted using information from tests on analogs by the "read-across" approach or for a group of substances using the "category" approach. The registrant is responsible for making the scientific arguments that these predicted properties are adequate for Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) in terms of providing comparable information of the animal studies on the registered substance. "Read-across: and "category" are the most promising approaches to predict the long-term toxicological and carcinogenic, mutagenic, and reprotoxic (CMR) properties of substances for REACH and Constraint Logic Programing (CLP). However, it should be noted that sufficient information must be available to support these predictions.

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Furthermore, newly developed alternative in vitro test methods undergo validation to assess their relevance and reliability. The European Centre for the Validation of Alternative Methods (ECVAM) validates alternative methods that replace, reduce, and refine the use of animals in scientific procedures. Regulatory acceptance of validated alternative methods will be facilitated and streamlined by the new mechanism of "preliminary analysis of regulatory relevance" (PARERE). These consultation networks of the European Commission involve EU member state contact points and relevant agencies and committees, such as the European Chemicals Agency (ECHA).

In addition, recently, use of nanomaterial toxicology (nanotechnology) has gained significant development over the past decades, which led to the revolution in the fields of information, medicine, industry, food security, and aerospace aviation. Nanotechnology has become a new research hot spot in the world. According to available literature, the continuing evaluation of the health implications of exposure to nanomaterials is essential before the commercial benefits of these materials can be fully realized. A detailed discussion on this topic is beyond the scope of this book.

1.6 Definitions, Classification, and Toxicity Rating

Veterinary toxicology is the specialty of veterinary medicine dealing with the study, diagnosis, and treatment of effects of natural and man-made chemicals; forms of energy; and gasses in the animal kingdom. The importance of veterinary toxicology in the modern era cannot be overemphasized. Thus, veterinary toxicology involves the evaluation of toxicosis and deficiencies, identification and characterization of toxins and determination of their fate in the body, and treatment of toxicosis.

A toxic agent is referred to as a toxicant or poison. The term toxin refers to a poison produced by a biologic source (e.g., venoms, plant toxins); the redundant term biotoxin is occasionally used. Toxicosis, poisoning, and intoxication are synonymous terms for the disease produced by a toxicant. Toxicity (sometimes is incorrectly used instead of poisoning) refers to the amount of a toxicant necessary to produce a detrimental effect.

Acute toxicosis refers to effects during the first 24-h period. Effects produced by prolonged exposure (≥3 months) are referred to as chronic toxicosis. Terms such as subacute and sub-chronic are used to cover the large gap between acute and chronic.

All toxic effects are dose dependent. A dose may cause undetectable, therapeutic, toxic, or lethal effects. A dose is expressed as the amount of compound per unit of body weight and toxicant concentration as part per million or part per billion. These quantitative expressions are also used for feedstuffs, water, and air as well as for tissue levels.

LD_{50} is the dose that is lethal to 50% of a test sample. It is an estimator of lethality and the most common expression used to rate the potency of toxicants. Other terms used for prediction of illness or lethality include no adverse observed effect

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level (NOAEL), maximum nontoxic dose (MNTD), and maximum tolerated dose or minimum toxic dose (MTD).

These toxic agents are classified in number of ways depending on the interests and needs of the classifier. There is no single classification applicable for the entire spectrum of toxic agents, and hence combinations of classification systems based on several factors may provide the best rating system. Classification of poisons may take into account both the chemical and biological properties of the agent; however, exposure characteristics are also useful in toxicology.

1.7 Toxicity Rating

Assignment to a toxicity class is based typically on results of acute toxicity studies such as the determination of LD_{50} values in animal experiments, notably rodents, via oral, inhaled, or external application. The experimental design measures the acute death rate of an agent. The toxicity class generally does not address issues of other potential harm of the agent, such as bioaccumulation, issues of carcinogenicity, teratogenicity, mutagenic effects, or the impact on reproduction.

Regulating agencies may require that packaging of the agent be labeled with a signal word, a specific warning label to indicate the level of toxicity. For example, World Health Organization (WHO) names four toxicity classes for pesticides (Table 1.1):

Class I – a: extremely hazardous
Class I – b: highly hazardous
Class II: moderately hazardous
Class III: slightly hazardous

European Union
There are eight toxicity classes in the European Union's classification system.

Class I: very toxic
Class II: toxic
Class III: harmful
Class IV: corrosive

Table 1.1 World Health Organization (WHO) classification of toxicity

	LD_{50} for the rat (mg/kg body weight)	
WHO class	Oral	Dermal
Ia Extremely hazardous	<5	<50
Ib Highly hazardous	5–50	50–200
II Moderately hazardous	50–2000	200–2000
III Slightly hazardous	Over 2000	Over 2000
U Unlikely to present acute hazard 5000 or higher		

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Class V: irritant
Class VI: sensitizing
Class VII: carcinogenic
Class VIII: mutagenic

Very toxic and toxic substances are marked by the European toxicity symbol.

United States
The US Environmental Protection Agency (EPA) uses four toxicity classes in its toxicity category rating. Classes I–III are required to carry a signal word on the label. Pesticides are regulated in the United States primarily by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Toxicity Class 1 (most toxic; requires signal word: "Danger-Poison," with skull and crossbones symbol, possibly followed by: "Fatal if swallowed," "Poisonous if inhaled," "Extremely hazardous by skin contact—rapidly absorbed through skin," or "Corrosive—causes eye damage and severe skin burns"). Class I materials are estimated to be fatal to an adult human at a dose of less than 5 g (less than a teaspoon).
Toxicity Class II (moderately toxic: requires signal word: "Warning," possibly followed by: "Harmful or fatal if swallowed," "Harmful or fatal if absorbed through the skin," "Harmful or fatal if inhaled," or "Causes skin and eye irritation"). Class II materials are estimated to be fatal to an adult human at a dose of 5–30 g.
Toxicity Class III (slightly toxic: requires signal word: Caution, possibly followed by: "Harmful if swallowed," "May be harmful if absorbed through the skin," "May be harmful if inhaled," or "May irritate eyes, nose, throat, and skin"). Class III materials are estimated to be fatal to an adult human at some dose in excess of 30 g.
Toxicity Class IV (practically nontoxic: no signal word required since 2002)

General Versus Restricted Use
Furthermore, the EPA classifies pesticides into those anybody can apply (General Use Pesticides) and those that must be applied by or under the supervision of a certified individual. Application of restricted-use pesticides requires that a record of the application be kept.

1.8 Sources of Poisoning

Exposure of animals and other organisms to toxicants may result from many activities such as intentional ingestion, environmental exposure, as well as accidental and malicious poisoning. The toxicity of a particular compound may vary with the portal of entry into the body, whether through the alimentary canal, the lungs, or the skin.

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1.8.1 Malicious Poisoning

It is the unlawful or criminal killing of human beings or animals by administering certain toxic/poisonous agents. Incidence of such poisoning is more prevalent in human beings and less in animals.

1.8.2 Accidental Poisoning

Accidental poisoning may occur when human beings or animals take the toxicant accidentally or is added unintentionally in food or through the feed, fodder, or drinking water. Such toxicants come from either natural sources or man-made sources. The natural sources include ingestion of toxic plants, biting or stinging by poisonous reptiles, ingestion of food contaminated with toxins, contaminated water with minerals, etc. Man-made sources include therapeutic agents, household products, and agrochemicals, and so on.

1.9 Factors Affecting the Activity of Toxicants

Toxicosis potential is usually determined more by the multitude of related factors than by actual toxicity of the toxicant. Exposure-related, biologic, or chemical factors regulate absorption, metabolism, and elimination and, thus, influence observed clinical consequences.

1.9.1 Host Factors (Biologic Factors)

Various species and strains within species react differently to a particular toxicant because of variations in absorption, metabolism, or elimination. Functional differences in species may also affect the likelihood of toxicosis, for example, species unable to vomit can be intoxicated with a lower dose of some agents. Such differences are most common and of greatest magnitude when functions which are phylogenetically divergent between species, such as digestive functions (ruminant vs. non-ruminant, carnivore vs. herbivore, etc.), are involved after exposure to toxicants. Interspecies differences also exist in toxic response, but these are generally more limited, except when a particular targeted function has evolved, as is the case for reproductive physiology (mammals vs. birds vs. fishes; annual vs. seasonal reproductive cycle in mammals, etc.). Interspecies difference due to metabolism is a major factor accounting for species differences in pharmacokinetic (PK) and also in pharmacodynamics (PD). Recent and future advances in molecular biology and pharmacogenomics will enable a more comprehensive view of interspecies differences and also between breeds with existing polymorphism. Finally, the main message of this chapter is that differences between species are not only numerous but also often unpredictable that no generalizations are possible. Instead, each toxicant

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must be investigated on a species-by-species basis to guarantee its effective and safe use, thus ensuring the well-being of animals and safeguarding of the environment and human consumption of animal products. Well-established examples are as follows: rabbit can survive even after eating Atropa belladonna (belladonna leaves) because they contain the enzyme atropinase, which destroys atropine (Fig. 1.2).

Similarly, some dog breeds of animals are more susceptible to the toxic effects of chemicals. For example, in Koolies, vermectin easily crosses blood-brain barrier and causes neurological symptom (Fig. 1.3). Mink (species) is highly sensitive to polychlorinated biphenyls (PCBs) than other species (Fig. 1.4).

The sex of an animal often has an influence on the toxicity of chemical agent. The variation in toxicity due to sex is well known; the chemical agents or toxicants must be used with special care during pregnancy because they could lead to



Fig. 1.2 Rabbit can survive after eating poisonous belladonna leaves. (Reproduced from https://en.wikipedia.org/wiki/File:Kostya2.jpg)



Fig. 1.3 Koolie breed of dog—more susceptible to ivermectin toxicity. (Reproduced from https://en.wikipedia.org/wiki/Border_Collie#/media/File:Blue_merle_Border_Collie.jpg)

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Fig. 1.4 Mink—most susceptible to PCB poisoning than other animal species. (https://encrypted-tbn2.gstatic.com/images?q5tbn:ANd9GcTkXDdI_DKRsLlDws6JTDgE6md1AUouVMc33CHtZKfTVLrXiMWVA)

teratogenic effects in females, and the differences are shown to be under direct endocrine influence. During lactation, it is important to remember that some chemicals or toxicants may be excreted in milk and may even act on the offspring. Thus, it is desirable to measure acute toxicity on both male and female animals of any species.

Young animals are uniquely susceptible to chemicals that are relatively safer at a later period of life. The difference in response during early life is a consequence of the relative inefficiency of various metabolic and excretory pathways. Differences in strain of animals also induce a variation in response to chemical agents, and such differences have been detected in acute toxicity measurement of various inbred strains of mice. Likewise, age and size of the animal are primary factors in toxicosis. Metabolism and translocation of xenobiotic agents are compromised by the underdeveloped microsomal enzyme system in young animals. Membrane permeability and hepatic and renal clearance capabilities vary with age, species, and health. The amount of toxicant required to cause pathology is generally correlated to body weight, but with greater body weight, a disproportionate increase in toxicity (per unit body weight) of a compound often occurs. Body surface area may correlate more closely with the toxic dose. No measurement parameter is consistent for every situation. Nutritional and dietary factors, hormonal and health status, organ pathology, stress, and sex all affect toxicosis. Nutritional factors may directly affect the toxicant (i.e., by altering absorption) or indirectly affect the metabolic processes or availability of receptor sites. The copper-molybdenum-sulfate interaction is an example of both.

Greyhounds (Fig. 1.5) are more susceptible to the toxic effects of barbiturates (used as anesthetics) as they mainly distribute in adipose tissue. Since greyhounds have little body fat, it results in higher circulating concentration of barbiturates causing toxicity.

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Fig. 1.5 Greyhound dog breed—more susceptible to barbiturate toxicity. (Reproduced from https://commons.wikimedia.org/wiki/File:GraceThe.g.reyhound.jpg)

1.9.2 Factors Related to Exposure

Several factors such as dose, routes and rates of toxicant administration, physical state and chemical properties of the toxicant, previous or coincident exposure to other toxicants/chemicals (toxicant-chemical interactions), etc. influence the response of various chemicals.

Dose is the primary concern; however, the exact intake of a toxicant is seldom known. Duration and frequency of exposure are important. The route of exposure affects absorption, translocation, and perhaps metabolic pathways. Exposure of a toxicant relative to periods of stress or food intake may also be a factor. After ingestion of some toxicants, emesis may occur if the stomach is empty, but if partly filled, the toxicant is retained and toxicosis can occur. Environmental factors, such as temperature, humidity, and barometric pressure, affect rates of consumption and even the occurrence of some toxic agents. Many mycotoxins and poisonous plants are correlated with seasonal or climatic changes. For example, the ischemic effects of ergot toxicosis are more often seen during the winter cold, and plant nitrate levels are affected by rainfall amounts.

1.9.3 Chemical Factors

The chemical nature of a toxicant determines solubility, which in turn influences absorption. Nonpolar or lipid-soluble substances tend to be more readily absorbed than polar or ionized substances. The vehicle or carrier of the toxic compound also affects its availability for absorption. Isomers, including optical isomers, vary in toxicity. For example, the γ isomer of hexachlorocyclohexane (lindane) is more toxic than other isomers.

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Adjuvants are formulation factors used to alter the toxicological effect of the active ingredient (e.g., piperonyl butoxide enhances the insecticidal activity of pyrethrins). Binding agents, enteric coating, and sustained-release preparations influence absorption of the active ingredient. As absorption is delayed, toxicity decreases. Flavoring agents affect palatability and thus the amount ingested.

1.10 Natural Law Concerning Toxicity

1.10.1 Dose-Response Relationship

The dose-response relationship, or exposure-response relationship, describes the change in the effect on an organism caused by differing levels of exposure (or doses) to a stressor (usually a chemical) after a certain exposure time. This may apply to individuals (e.g., a small amount has no significant effect; a large amount is fatal) or to populations (e.g., how many people or organisms are affected at different levels of exposure). The relationship between dose and response is usually established when the chemical/toxicant effect at a particular dose has reached a maximum or is constant. The chemical effects do not develop instantaneously or continue indefinitely; they change with time level (Fig. 1.6). Thus, the magnitude of a chemical effect at any given moment is a function not only of the dose but also of the amount of time elapsed since the chemical made contact with the reactive tissues. This curve represents several important features (there are three distinct phases and a fourth phase that may be present or pronounced with some chemicals while absent with others), which include the following:

- Time of onset of action (Ta)
- Time to peak effect (Tb)
- Duration of action (Tc)
- Residual effects (Td)

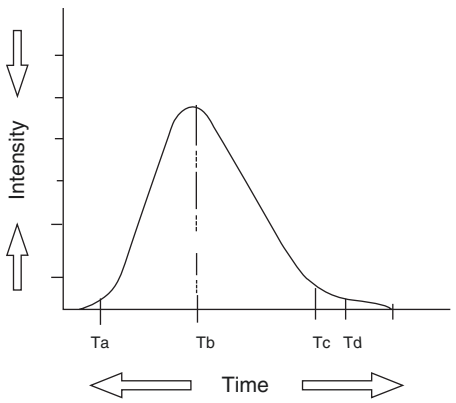


Fig. 1.6 Hypothetical curve showing time-effect relationship of a toxicant. Ta, latency time; Tb, peak time; Tc, persistence time; Td, residual effect

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Phase I: Time of onset of action (Ta)—Following the administration of a chemical agent to a system, there is a delay in time before the first signs of chemical effects are manifested. The lag in onset is of finite time, but for some chemicals, the delay may be so short that it gives the appearance of an instantaneous action. There are various reasons responsible for the chemical effect to reach an observable level.

Phase II: Time to peak effect (Tb)—The maximum response will occur when the most resistant cell has been affected to its maximum or when the chemical has reached the most inaccessible cells of the responsive tissue.

Phase III: Duration of action (Tc)—The duration of action extends from the moment of onset of perceptible effects to the time when an action can no longer be measured. It will depend upon the rate at which it is metabolized, altered, or otherwise inactivated or removed from the body.

Phase IV: Residual effects (Td): Even after its primary actions are terminated, many chemicals are known to exert a residual action. It is not always possible to determine whether the residual effect is caused by a persistence of minute quantities of the chemical or by persistence of subliminal effects.

1.10.2 Types of Dose-Response Relationship

Dose-response relationship is of two types:

(a) Graded or gradual
(b) Quantal (all-or-none) such as death

Graded or gradual dose-response describes the response of an individual organism to varying doses of a chemical, is often referred to as a "graded" response because the measured effect is continuous over a range of doses, whereas, quantal dose-response relationship is one involving an all-or-none response, i.e., on increasing the dose of a compound, the response is either produced or not. This relationship is seen with certain responses that follow all-or-none phenomenon and cannot be graded, e.g., death. The quantal dose-response is used to determine lethal dose (LD) values of a particular toxicant.

1.10.3 Variables of Dose-Response Curves

The dose-response curve has four characteristic variables:

(a) Efficacy
(b) Potency
(c) Slope
(d) Biological variation

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The maximal effect or response produced by an agent is called its maximal efficacy or efficacy (Fig. 1.7).

Potency is the dose of toxicant/toxicant required to produce a specific effect of given intensity as compared to a standard reference. It is a comparative rather than an absolute expression of toxicant activity. Toxicant potency depends on both affinity and efficacy. The compound on the left is more potent compared to the compound depicted on the right because less compound is needed to produce an equivalent response. The slope of a dose-response curve gives the relationship between the receptor/target site and the agent (Figs. 1.8 and 1.9).

Biological variation or variance can be defined as the appearance of differences in the magnitude of response among individuals in the same population given the same dose of a compound.

The margin of safety of a toxicant is the ratio of LD_1/ED_{99} (Fig. 1.9). The farther apart these curves are, the wider the margin of safety.

For example,

$$\text{Safety margin} = LD_1 / ED_{99}$$

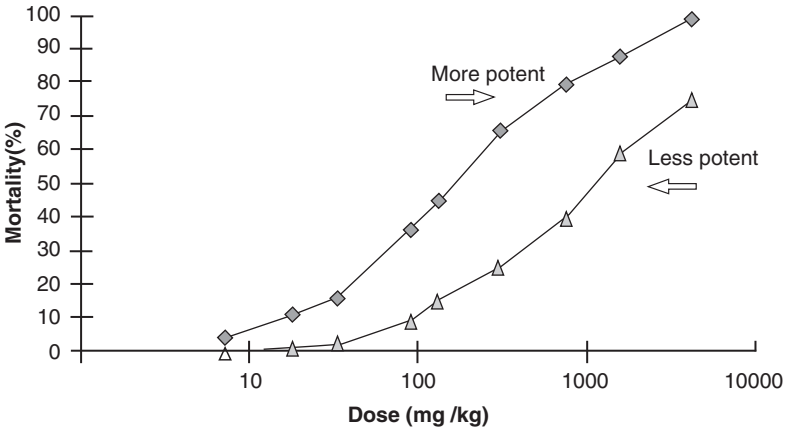
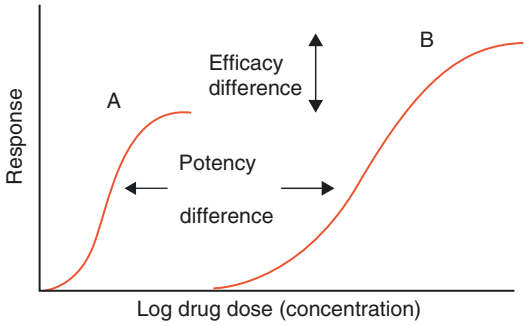


Fig. 1.7 Comparison of potency of toxicant/toxicant

Fig. 1.8 Typical sigmoid log dose-response curves for two toxicants. Toxicant A is more potent than toxicant B; toxicant B is more efficacious than toxicant A



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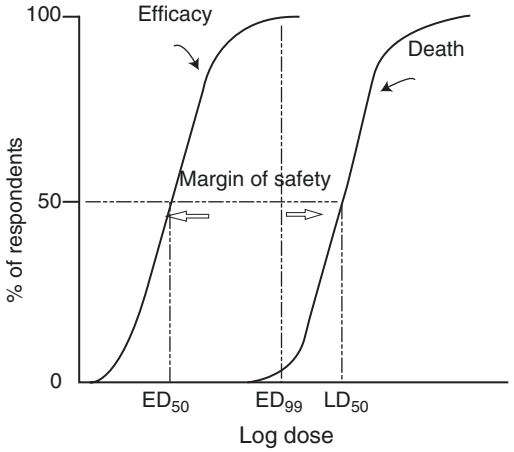


Fig. 1.9 The margin of safety of a toxicant may be determined by comparing the 99% dose-response curve for the efficacy with the curve for a toxic or lethal effect

where LD_1 dose is lethal in 1% of the population and ED_{99} dose is effective in 99% of the population.

Safety margin is a more conservative estimate than therapeutic index as values are derived from extremes of the respective dose-response curves.

1.11 Interaction with Receptors

The main target organs most frequently affected by toxicants are as follows:

(a) Central nervous system
(b) Circulatory system (blood, blood-forming system)
(c) Visceral organs (liver, kidneys, lung)
(d) Muscle and bone

Many toxicants/xenobiotics exert their effects by interacting with specific receptors in the body. This xenobiotic-receptor interaction leads to a change in the macromolecule, which in turn triggers a sequence of events resulting in tissue or organ response. The intensity of response produced by a toxicant/xenobiotic depends on its intrinsic activity, which in turn depends on the chemical structure of the compound.

Toxins are often selective to certain tissues because of the following reasons:

(a) Preferential accumulation: Toxicant may accumulate in only certain tissues and cause toxicity to that particular tissue, e.g., Cd in the kidney, paraquat in the lung.
(b) Selective metabolic activation: Enzymes needed to convert a compound to the active form may be present in highest quantities in a particular organ, e.g., CCl4, nitrosamines in the liver.

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(c) Characteristics of tissue repair: Some tissues may be protected from toxicity by actively repairing toxic damage; some tissues may be susceptible because they lack sufficient repair capabilities, e.g., nitrosamines in the liver.
(d) Specific receptors and/or functions: Toxicant may interact with receptors in a given tissue, e.g., curare—a receptor-specific neuromuscular blocker.
(e) Physiological sensitivity: The nervous system is extremely sensitive to agents that block utilization of oxygen, e.g., nitrite, which oxidizes hemoglobin (methemoglobinemia); cyanide, which inhibits cytochrome oxidase (cells not able to utilize oxygen); and barbiturates, which interfere with sensors for oxygen and carbon dioxide content in the blood.

When two or more xenobiotics are used together, the pharmacological/toxicological response is not necessarily the same as the two agents used individually. This is because one agent may interfere with the action of another agent called xenobiotic/toxicant interaction. The most commonly used terms in relation to interaction with receptors include:

Toxicant affinity: Affinity is the ability of a xenobiotic to combine with its receptors. A ligand of low affinity requires a higher concentration to produce the same effect than ligand of high affinity. Agonists, partial agonist, antagonist, and inverse agonist have the same or similar affinity for the receptor.
Intrinsic activity: Intrinsic activity is defined as a proportionately constant ability of the agonist to activate the receptor as compared to the maximally active compound in the series being studied. It is maximum of unity for full agonist and minimum or zero for antagonist.
Agonist: Agonist (full agonist) is an agent that interacts with a specific cellular constituent (i.e., receptor) and elicits an observable positive response.
Partial agonist: Partial agonist is an agent that acts on the same receptor as other agonists in a group of endogenous ligands or xenobiotics, but regardless of its dose, it cannot produce the same maximal biological response as a full agonist.
Antagonism/antagonistic effect: When the combined effect of two compounds given together is lesser in magnitude to the sum of the effects of each compound given alone, or when one compound having no effect of its own decreases or inhibits the effect of other compound, the interaction is called antagonism and the effect produced is called antagonistic effect. The toxic effect of a chemical, A, the agonist, can be reduced when given with another chemical, B, the antagonist. Antagonists are often used as antidotes (Fig. 1.10).

There are several mechanisms of antagonism:

(a) Functional antagonism: It is simple counterbalancing of the toxic effect (caffeine and phenobarbital).
(b) Chemical antagonism: Chemical antagonist reacts with the toxin to reduce toxicity (dimercaprol chelates toxic heavy metals such as lead).

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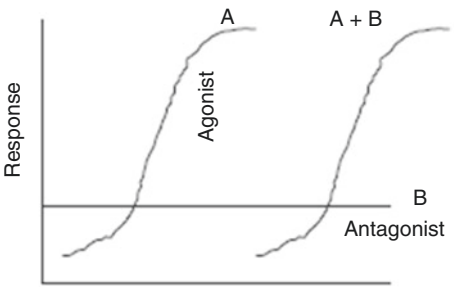


Fig. 1.10 The toxic effect of a chemical, A, the agonist, can be reduced when given with another chemical, B, the antagonist

(c) Receptor antagonism: Receptor antagonist binds to receptor (atropine with organophosphate insecticides).
(d) Dispositional antagonism: In disposition antagonism, fate of the toxin is altered (cholestyramine can prevent the absorption of organic chemicals by binding with them).

Inverse agonist: Inverse agonist is a compound that interacts with the same receptor as the agonist, but it produces a response just opposite to that of the agonist.

Addition/additive effect: When the combined effect of two compounds given together is equal in magnitude to sum of the effects of each compound given alone, the interaction is called an addition and the effect produced is called an additive effect. In this case, no specific interactions occur (Fig. 1.11).

Potentiation/potentiative effect: When one compound having no effect of its own increases the effect of another compound, the interaction is called potentiation and the effect produced is called potentiative effect. For example, if a dose of a compound A is toxic to animals in vivo and another chemical B is not toxic when given at doses several orders of magnitude higher, the toxic response is greater than that of the given dose of A alone when the two are given together. This means the compound B has a potentiative effect on compound A. This is known as potentiation.

Synergism/synergistic effect: The combined effect of the administration of two compounds may be greater than the sum of the two effects—this is called synergism (Fig. 1.12). The synergist piperonyl butoxide is added to some insecticides to greatly increase their toxicity to insects.

For example, 1 + 1 = more than 2.

The difference between the two concepts is that synergism is the interaction of two or more substances, while potentiation is about a singular substance and how it may act when in a synergy relationship:

Hormesis dose response phenomenon: Sometime dose-response curves do not follow typical sigmoidal dose-response curve, and *U-shaped dose-response curves* are observed. For example, essential metals and vitamins show U-shaped curves. At low dose, adverse effects are observed since there is a deficiency of these nutrients to maintain homeostasis. As dose

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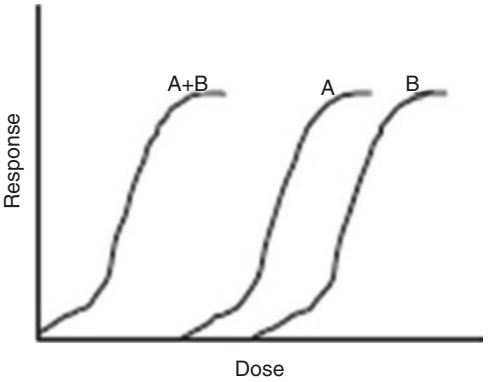


Fig. 1.11 Additive effect

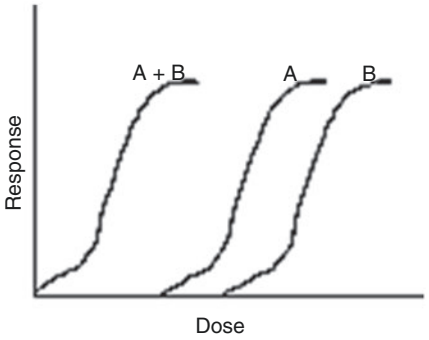


Fig. 1.12 Synergistic effect

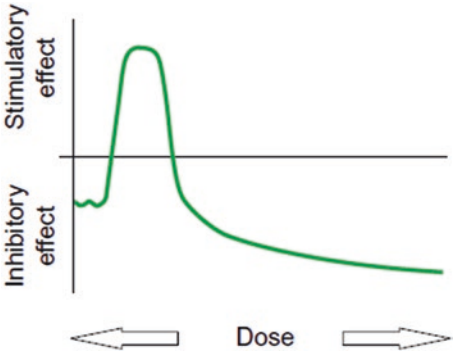


Fig. 1.13 A low dose of a chemical agent may trigger from an organism the opposite response to a very high dose

increases, homeostasis is achieved, and the bottom of the U-shaped dose-response curve is reached. As dose increases to surpass the amount required to maintain homeostasis, overdose toxicity can ensue. Thus, adverse effects are seen at both low and high dose. This phenomenon is called hormesis. Thus, hormesis is a dose-response phenomenon characterized by a low-dose stimulation and a high-dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose response (Fig. 1.13).

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1.12 Questions and Answers

1.12.1 Short Questions and Answers

Exercise 1

Q.1. What do you mean by super toxic?
- Less than 5 mg/kg

Q.2. What do you mean by extremely toxic?
- 5–50 mg/kg

Q.3. What do you mean by very toxic?
- 51–500 mg/kg

Q.4. What do you mean by moderately toxic?
- 501 mg/kg to 5 g/kg

Q.5. What do you mean by slightly toxic?
- 5.1 g/kg to 15 g/kg

Q.6. What do you mean by practically nontoxic?
- More than 15 g/kg

Q.7. What is the duration of exposure for acute toxicosis/ toxicity?
- Less than 24 h (single or multiple)

Q.8. What is the duration of exposure for subacute toxicosis/ toxicity?
- Multiple/continuous: less than 1 month

Q.9. What is the duration of exposure for sub-chronic toxicosis/toxicity?
- Multiple/continuous: more than 1 month and less than 3 months

Q.10. What will be the toxicity rating of a toxic compound having LD_{50} values more than 1000 mg/kg?
- Practically nontoxic

Q.11. What is the duration of exposure for chronic toxicosis/toxicity?
- Multiple/continuous: more than 3 months

Q.12. What is the relationship between various toxicity doses with respect to given compound?
- LD > MTD > NOAEL > NOEL > ADI > MRL

Q.13. What is a dose?
- A dose is the actual amount of a chemical that enters the body. The dose received may be due to either acute, subacute, or chronic (long-term) exposure.

Q.14. What is the threshold dose?
- Threshold dose is the exposure level below which the harmful or adverse effects of a substance are not seen in a population. This dose is also referred to as the no observed adverse effect level (NOAEL) or the no observed effect level (NOEL). These terms are often used by toxicologists when discussing the relationship between exposure and dose. However, for substances causing cancer (carcinogens), no safe level of exposure exists, since any exposure could result in cancer.

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Q.15. What do you mean by lethal dose-50 (LD_{50}) and median lethal dose (MLD)?
- Lethal dose-50 (LD_{50}), also called median lethal dose (MLD), is the dose that is lethal to 50% of animals exposed to a given toxicant under defined conditions.

Q.16. What do you mean by LD_{50}/ED_{50}?
- Therapeutic index

Q.17. What do you mean by LD_1/ED_{99}?
- Margin of safety

Q.18. What do you mean by the terms LD_1, ED_{99}, threshold, threshold dose?
- LD_1 = lethal dose for 1% of the population.
- ED_{99} = effective dose for 99% of the population.
- Threshold = point at which the detoxification pathways and/or the repair mechanisms become saturated/overwhelmed: once threshold is crossed, adverse toxic response is observed.
- Threshold dose = theoretical dose where the dose response curve approaches the x axis (0% response).

Q.19. Which term(s) is (are) used to determine the population dose-response relationship?
(a) LD_{50}
(b) Minimum toxic dose
(c) Median population response to a single dose plus outliers

Q.20. Define margin of exposure (MOE)
- Margin of exposure is defined as the ratio of the no observed adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration

1.12.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none)

Exercise 2

Q.1. "It is the dose that differentiates a substance from drug to poison": this statement was made by the scientist
(a) Paracelsus
(b) Hippocrates
(c) Socrates
(d) Homer

Q.2. The branch of science that deals with assessing toxicity of substances of plant and animal origin and those produced by pathogenic bacteria is _____.
(a) Toxicology
(b) Toxinology
(c) Toxicokinetics
(d) Toxicodynamics

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Q.3. The minimum dose of a drug to produce the desired response is called _____.
(a) Ceiling dose
(b) Threshold dose
(c) Both a and b
(d) None

Q.4. Arthus reaction is seen in hypersensitivity of _____.
(a) Type I
(b) Type II
(c) Type III
(d) Type IV

Q.5. Coolie breeds of dogs are hypersensitive to _____.
(a) Albendazole
(b) Ivermectin
(c) Both
(d) None

Q.6. The measure of margin of safety of a drug is obtained by _____.
(a) LD_{50}/ED_{99}
(b) LD_{1}/ED_{99}
(c) ED_{50}/LD_{50}
(d) LD_{50}/ED_{50}

Q.7. A substance is called as moderately toxic if its median lethal dose is _____.
(a) 1–5 mg
(b) 5–500 mg
(c) 0.5–1 g
(d) >1 g

Q.8. A toxic substance produced by biological system is especially referred to as a _____.
(a) Toxicant
(b) Toxin
(c) Xenobiotic
(d) Poison

Q.9. Allergic contact dermatitis is _____.
(a) A nonimmune response caused by a direct action of an agent on the skin
(b) An immediate type I hypersensitivity reaction
(c) A delayed type IV hypersensitivity reaction
(d) Characterized by the intensity of reaction being proportional to the elicitation dose
(e) Not involved in photoallergic reactions

Q.10. The reference dose (RfD) is generally determined by applying which of the following default procedures?
(a) Applying an uncertainty factor of 100 to the NOAEL in chronic animal studies
(b) Applying a risk factor of 1000 to the NOAEL in chronic animal studies

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(c) Applying a risk factor of 10,000 to the NOAEL in sub-chronic animal studies
(d) Applying an uncertainty factor between 10,000 and 1 million to the NOEL from chronic animal studies
(e) Multiplying the NOAEL from chronic animal studies by 100

Answers

Exercise 2

1. a	6. d
2. b	7. b
3.b	8. b
4.c	9. c
5. b	10. a

1.12.3 Fill in the Blanks

Exercise 3

Q.1. The branch of science which deals with the harmful effects of physical and chemical agents of human and animal life is _____.
Q.2. In the term toxicology, the word "toxicon" (Greek) means _____.
Q.3. The branch of toxicology which deals with the diagnosis, treatment, and management of toxic substances is known as _____.
Q.4. The development and interpretation of mandatory toxicology testing programs is addressed by _____.
Q.5. Investigating and controlling the toxic effects of various substances on the community is dealt by _____.
Q.6. The study of toxicity produced by substances of plant, animal, and microbial origin is termed as _____.
Q.7. A foreign chemical substance which is not normally produced in the body or forms a part of the food is known as _____.
Q.8. The source of adverse effect/damage is known as_____.
Q.9. The likelihood/probability of adverse effect upon exposure to a hazard is known as _____.
Q.10. The statement "all substances are poisons; the dose differentiates poison from a remedy" is associated with _____.

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Answers

Exercise 3

1. Toxicology	6. Toxinology
2. Poison	7. Xenobiotic
3. Clinical toxicology	8. Hazard
4. Regulatory toxicology	9. Risk
5. Toxicovigilance	10. Paracelsus

1.12.4 True or False Statements

Exercise 4

Q.1. Environmental risk is a well-understood entity.
Q.2. Cross-sectional studies look at the exposure and disease at the same time.
Q.3. Bias is a problem primarily in clinical trials.
Q.4. Sub-chronic studies are shorter than acute studies.
Q.5. The lethal dose refers to the dose at which 50% of test animals die.
Q.6. The maximum tolerated dose (MTD) is the level of chemical exposure where 10% of the animals die.
Q.7. Case control studies start with the exposure and follow for the disease.
Q.8. Case control studies are good for rare diseases.
Q.9. Clinical trials look at dose-response in animals.
Q.10. Dose refers to the amount of a substance in the environment.

Answers

Exercise 4

1. F	6. F
2.T	7. F
3.F	8. T
4. F	9. F
5. T	10. F

1.12.5 Match the Statements

(Match the following statements in column A to column B)

Exercise 5

Column A	Column B
Q.1. Hippocrates	a. Corrosive
Q.2. MJB Orfila	b. Less than 5 mg/kg
Q.3. Nutritional toxicology	c. Age

(continued)

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Column A	Column B
Q.4. Genetic	d. Father of medicine
Q.5. Sulfuric acid	e. Father of toxicology
Q.6. Super toxic	h. Food-/feedstuffs
Q.7. Infants	i. Hereditary
Q.8. Tolerance	j. Safety
Q.9. Therapeutic index	k. Receptor
Q.10. Interaction	l. Toxic reaction

Answers

Exercise 5

Q.1	d.	Father of medicine
Q.2	e.	Father of toxicology
Q.3	h.	Food-/feedstuffs
Q.4	i.	Hereditary
Q.5	a.	Corrosive
Q.6	b.	Less than 5 mg/kg
Q.7	c.	Age
Q.8	l.	Toxic reaction
Q.9	j.	Safety
Q.10	k.	Receptor

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Disposition and Fate of Toxicants

2

Abstract

This chapter deals with the study of absorption, distribution, metabolism/biotransformation, and excretion (ADME) of xenobiotics and the study of toxicokinetics of toxicants/xenobiotics in relation to time in animals. Toxicokinetics represents behavior of drugs in the system and extension of kinetic principles to the study of toxicology including applications ranging from the study of adverse drug effects to investigations on how disposition kinetics of exogenous chemicals are derived from either natural or environmental sources that govern their deleterious effects on animals and human beings.

Keywords

Absorption · Disposition · Biotransformation · Metabolism · Excretion · Redistribution · Toxicokinetics · ADME · Multiple choice questions

2.1 Introduction

The disposition of chemicals or xenobiotics is defined as the composite actions of its absorption, distribution, metabolism (biotransformation), and elimination (ADME). This chapter will focus on the contribution of ADME to xenobiotic toxicity in animals. Toxicants exert their effect only when they interact with specific receptor sites, which may be located at distant organs. To reach the target site, the toxicant must be absorbed effectively into the bloodstream, distributed efficiently to the site of action, and subsequently metabolized and excreted from the body. The processes of absorption and distribution are responsible for placement or deployment of these toxicants in the body, and metabolism and excretion for elimination of the toxicant from the body. In addition, a range of factors including age, strain, species, sex, etc. may influence ADME and other aspects of susceptibility to hazards related to a given toxicant. Included among many, these are maturity at birth, time to sexual maturity, and life span of various species of animals. This chapter also briefly focuses on extension of kinetic principles to the study of toxicology and encompasses applications ranging from the study of adverse drug effects to

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investigations on how disposition kinetics of exogenous chemicals are derived from either natural or environmental sources that govern their deleterious effects on organisms including animal health. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple-choice questions, fill in the blanks, and true/false statements as relevant to disposition and fate in an animal exposed to various xenobiotics.

Key Points

- The acronym ADME stands for absorption, distribution, metabolism (biotransformation), and elimination. The acronym is sometimes extended to include toxicant transport (ADME-T) or toxicant toxicity (ADME-Tox).
- Absorption is the transfer of a chemical from the site of exposure, usually an external or internal body surface, into the systemic circulation.
- After absorption, toxicants are removed from the systemic circulation.
- Biotransformation is the metabolic conversion of endogenous and xenobiotic chemicals to more water-soluble compounds and is accomplished by a limited number of enzymes with broad substrate specificities. The enzymes that catalyze xenobiotic biotransformation are often called toxicant-metabolizing enzymes.
- Excretion is the removal of xenobiotics from the blood and their return to the external environment via urine, feces, exhalation, etc.
- Phase I reactions involve hydrolysis, reduction, and oxidation. These reactions expose or introduce a functional group (—OH, —NH2, —SH, or —COOH) and usually result in only a small increase in hydrophilicity.
- Phase II biotransformation reactions include glucuronidation, sulfonation (more commonly called sulfation), acetylation, methylation, and conjugation with glutathione (mercapturic acid synthesis), which usually result in increased hydrophilicity and elimination.
- Toxicokinetics is the study of the modeling and mathematical description of the time courses of disposition (absorption, distribution, biotransformation, and excretion) of xenobiotics in the whole organism.
- The area under the plasma drug concentration-time curve (AUC) is dependent on the rate of elimination of the drug from the body and the dose administered.
- The apparent volume of distribution (Vd) is the space into which an amount of chemical is distributed in the body to result in a given plasma concentration.
- Clearance describes the rate of chemical elimination from the body in terms of volume of fluid containing chemical that is cleared per unit of time.
- The half-life of elimination (T1/2) is the time required for the blood or plasma chemical concentration to decrease by one-half.

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2.2 Absorption

2.2.1 Translocation of Xenobiotics Across Membranes

Absorption may occur through the alimentary tract, skin, and lungs and via the eye, mammary gland, or uterus as well as from sites of injection. Toxic effects may be local, but the toxicant must be dissolved and absorbed to some extent to affect the cell. Solubility is the primary factor affecting absorption. Insoluble salts and ionized compounds are poorly absorbed, whereas lipid-soluble substances are generally readily absorbed, even through intact skin.

Each of the toxicant movements generally relies on cell membranes (transcellular). Membrane barriers may be composed of several layers of cells (e.g., skin, vagina, cornea, placenta) or a single layer of cells (e.g., enterocytes, renal tubular epithelial cells), or they may consist only of a boundary less than one cell in thickness (e.g., hepatic sinusoids). Multilayered tissues each may present different types of barriers, e.g., skin is protected by the dense stratum corneum, which is absent in mucous membranes. Not all toxicants must pass through cell membranes; paracellular movement between cells is an increasingly important movement for some toxicants, e.g., in the GI tract.

Toxicants and other molecules cross cellular membranes by several processes such as bulk flow (e.g., movement with blood, glomerular filtration), passive diffusion, carrier-mediated transport (i.e., active or facilitated transport), and pinocytosis. Of these, passive diffusion is most important for movement of toxicants and other xenobiotics (foreign chemicals), as well as many endogenous compounds.

The rate at which a toxicant passively diffuses through membranes is influenced by several factors, the most important of which is the concentration gradient of diffusible toxicant (e.g., dissolved) across the membrane. However, other host and toxicant factors influence the rate and extent of passive diffusion. Host factors that increase diffusion include permeability and surface area of the membrane; thickness of the membrane negatively impacts diffusion. Toxicant characteristics that influence diffusion include molecular weight, lipophilicity, and degree of ionization. Most toxicants are "small molecules" (<900 daltons), but diffusibility is more likely to occur for toxicants <500 daltons. Toxicants must be sufficiently lipid soluble (lipophilic) to pass through some level of cell membrane lipid bilayer to reach most of the receptors. The lipid-to-water partition coefficient describes the distribution (ratio) of a toxicant (concentration) in a lipid compared with water media. The distribution coefficient also takes into account ionization.

At physiologic pH, toxicants tend to be partially ionized (dissociated) and partially nonionized (undissociated); the ratio of the respective forms depends on the dissociation constant (pKa) of the toxicants, i.e., the pH at which the toxicant is present in equal concentration in ionized and nonionized forms and the pH of the solution in which the toxicant is dissolved. Only nonionized fraction diffuses through lipid membranes. Distribution across any membrane of a toxicant with any given pKa reflects the degree of ionization and thus environmental pH on each side of the membrane. The Henderson-Hasselbalch equation predicts the ratio of ionized

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versus nonionized toxicants. In general, weak acids are nonionized in acidic compared with alkaline environments, and weak bases are nonionized in alkaline compared with acidic environments. The more similar the environmental pH is to that of the pKa of a weak acid or base, the more nonionized is the toxicants/xenobiotic, and the more likely it will diffuse. As long as the ratio of nonionized to ionized toxicant is ≥0.01, the toxicant is considered diffusible.

Buffering and the Henderson-Hasselbalch Equation

Not all toxicants must pass through cell membranes to reach their receptor. Aqueous pores in lipoproteinaceous biologic membranes offer a means of xenobiotic movement through the membrane for predominantly aqueous soluble toxicants. Lipid-insoluble (water-soluble) compounds pass easily through these pores and to a lesser degree directly through the membrane. A hydrostatic or osmotic pressure difference across a membrane facilitates movement by promoting water flow through the aqueous pores. Bulk fluid movement carries or "drags" solute molecules through the pores as long as the solute molecules are smaller than the aqueous channels.

Several specialized transfer processes account for the passage of certain organic ions and other large lipid-insoluble substances across biologic membranes. Active transport, facilitated diffusion, and exchange diffusion are three distinct types of carrier-mediated systems used to move specific substances across cellular membranes. The highly selective carrier-mediated systems are principally used for transporting nutrients and natural substrates across biologic membranes. Among the mechanisms of active transport are transport proteins that move compounds, including toxicants, into or out of cells. Transport proteins are located at portals of entry (e.g., enterocytes of the GI tract or sinusoidal hepatic cells) or "sanctuary" tissues (e.g., brain, CSF, placenta, prostate, eyes, or testicles), where they attempt to ensure that xenobiotics do not enter the protected tissue. As such, transport proteins are able to influence each toxicant movement (absorption, distribution, metabolism, and excretion). The most well-known of the transport proteins is the ATP-binding cassette superfamily of efflux transporters, which includes P-glycoprotein, the multitoxicant resistance protein. Substrates for P-glycoprotein include both xenobiotics and dietary components. Additional transport proteins carry cations, anions, or organic compounds. Competition for transport increases oral absorption or distribution of one of the competing molecules.

Pinocytosis is an important transport process in mammalian cells, particularly intestinal epithelial cells and renal tubular cells. Toxicants that exist in solution as molecular aggregates have large molecular masses themselves or that are bound to macromolecules may be transferred across membranes by pinocytosis. Different mechanisms of transfer of molecules across biological membranes are summarized in Table 2.1.

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Table 2.1 Transfer of molecules across biological membranes

Transfer process	Mechanism	Substrate specificity
Passive diffusion	Diffusion through lipoidal membrane down a concentration gradient	None, most foreign compounds
Filtration	Diffusion through aqueous pores in the membrane down to concentration gradient	Hydrophilic molecules and ions of the molecular weight, e.g., water, urea
Facilitated diffusion	Carrier transport through membrane down a concentration gradient. Saturated by excess substrate	Narrow, mainly for molecules concerned with process of intermediary metabolism, e.g., sugars and amino acids
Active transport	Carrier transport through membrane against a concentration gradient requires metabolic energy. Saturated by excess substrate	Narrow, mainly for molecules concerned with process of intermediary metabolism, e.g., sugars and amino-acids
Pinocytosis	Invaginations of the membrane absorbs extracellular material	Uncertain

2.2.2 Toxicant Absorption

Following are the routes of exposure:

(i) Oral
(ii) Respiratory
(iii) Dermal
(iv) Parenteral

Oral or gastrointestinal (GI), respiratory, and dermal systems are lined with epithelia that present significant barriers to the entry of foreign substances due to tight junctions between their cells or continuous lipid layers in the case of skin. The onset, duration, and intensity of a substance's toxic effects are therefore dependent on the toxicant's ability to permeate lipid cell membranes directly and its interactions with transporter proteins. Dermal penetration is unique in the sense that the outer epithelial cellular layers (corneocytes) are nonviable and do not contain transporter proteins. Absorption, in this case, is therefore dependent on the ability of the toxicants to penetrate the intercellular lipid matrix found between corneocytes. The plasma membranes surrounding all these cells are remarkably similar (such as the stratified epithelium of the skin, the thin cell layers of the lungs or the GI tract, capillary endothelium, and ultimately the cells of the target organ). In fact, the movement of most drug molecules in various tissues is limited only by the rate of blood flow rather than by the capillary wall. However, endothelial cells of sanctuaries, such as the blood-brain or CSF barrier, retina, and testicles, have tight intercellular junctions, thus restricting movement of drugs.

Aqueous solutions of xenobiotics are usually absorbed from an IM injection site within 10–30 min, provided blood flow is unimpaired. Faster or slower absorption

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is possible, depending on the concentration and lipid solubility of the toxicant, vascularity (including number of vessels and state of vasoconstriction), the volume of injection, the osmolality of the solution, and other pharmaceutical factors. Substances with molecular weights >20,000 daltons are principally taken up into the lymphatics.

Absorption of drugs from subcutaneous tissues is influenced by the same factors that determine the rate of absorption from IM sites. Some toxicants are absorbed as rapidly from subcutaneous tissues as from muscle, although absorption from injection sites in subcutaneous fat is always significantly delayed. Increasing blood supply to the injection site by heating, massage, or exercise hastens the rate of dissemination and absorption.

2.2.3 Species Differences in Absorption

Although absorption is dependent on the ability of toxicants to penetrate the intercellular lipid matrix found between corneocytes, however, there are several species differences in absorption, for example, dietary habits of various species groups, as well as the structures and physiologic adaptations that accommodate various diets and affect the material available to bind the toxicant, degree of mastication of the material containing the toxicant, microfloral reactions, acidification, digestion, rate of passage, and rate of absorption. For example, among, mammals:

A. Carnivores have simple digestive tract for easily digesting nutrient-rich food.
B. Omnivores have more complex digestive tracts: e.g., swine and some rodents.
C. Herbivores have much more complex, longer transit times and efficient absorption, e.g., ruminants where structure/function is even more age dependent than in monogastrics.

(i) Rumen dilutes and detoxifies many toxicants but toxifies others. For example, the rumen is a highly anaerobic place which tends to reduce a number of compounds (thus converting nitrate to much more toxic nitrite). Rumen is a reducing environment: Nitrate (NO3) converted to nitrite (NO2); Nitrite then oxidizes hemoglobin (Fe++) to methemoglobin (Fe+++).
(ii) Dilution of xenobiotics in the rumen is greater than in the stomach of a monogastric and occurs immediately after ingestion.
(iii) Binding to fiber (high-fiber diets) can significantly reduce bioavailability of some xenobiotics, e.g., some mycotoxins.
(iv) Microbes in the rumen metabolize many xenobiotics:
    (a) Break epoxides of trichothecenes, which detoxifies these compounds.
    (b) Convert nonprotein nitrogen sources (NPN, e.g., urea, biuret) to ammonia and then ammonia to microbial protein, which is later digested in the abomasum and intestine. The animal is protected from ammonia toxicosis only when the intake of NPN is sufficiently low, the rate of hydrolysis is sufficiently slow, and the rate of microbial protein synthesis is sufficiently high.

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(c) When the rumen contains excess ammonia, the pH increases (ruminal alkalosis) due in part to conversion of ammonia (NH3) to ammonium ions (NH4+). As more ammonia is generated, and fewer protons are available for this reaction, the neutral NH3 is absorbed across the rumen and causes clinical signs of toxicosis. Also, the elevated pH causes a lack of rumen motility, which results in acute bloat. Despite the ruminal alkalosis, the affected animal develops a systemic acidosis and hyperkalemia, which can result in cardiac arrhythmias that terminate in death.

(v) Differences in pH and motility in the upper digestive tract: (1) monogastrics (carnivores and omnivores) tend to have low pH in the stomach (e.g., in the dog and pig, gastric pH range is usually 3–4): ion traps weak bases (adds a proton to form –NH3+ or > NH2+), which delays absorption. Weak acids (adds a proton to form –COOH) are neutral when protonated and therefore are absorbed directly from the stomach. (2) Posterior fermenters (e.g., horses) tend to have a higher gastric pH (of around 5.5) than most other species. The horse's stomach is rarely empty. Because of its small stomach (relative to its body size), the animal is nearly a continuous feeder. (3) Ruminants tend to have a slightly acid ruminal pH (diet dependent—increase in grain lowers pH). In common production systems, ruminal pH may approximately range from 5.5 to 6.5. The rumino-reticular environment does not favor absorption of most toxicants. However, toxicants of sufficient lipid solubility will traverse the stratified squamous epithelium of the mucosa via passive non-ionic diffusion. Well-absorbed toxicants include non-ionized forms of weak acids in the mildly acidic rumen content. Abomasal (true stomach of ruminants) pH is typically around 3, which is similar to that of the stomachs of monogastrics. However, the flow of ingesta through the abomasum is more continuous than in the stomach of most nonruminants.

2.3 Distribution

Distribution or translocation of a toxicant is via the bloodstream to reactive sites, including storage depots. The liver receives the portal circulation and is the organ most commonly involved with intoxication (and detoxification). The selective deposit of foreign chemicals in various tissues depends on receptor sites. Ease of chemical distribution depends largely on its water solubility. While polar or aqueous-soluble agents tend to be excreted by the kidneys, lipid-soluble chemicals are more likely to be excreted via the bile and accumulate in fat depots. The highest concentration of a toxin within an animal is not necessarily found in the organ or tissue on which it exerts its maximal effect (the target organ). Lead may be found in highest concentrations in bone, which is neither a site for toxic effects nor a reliable tissue for toxicologic interpretation. Knowledge of the translocation characteristics of toxicants is necessary for proper selection of organs for analysis.

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2.3.1 Species Differences in Distribution

Unbound compounds in plasma are generally regarded as free to enter the tissues and exert an effect, while bound xenobiotics generally serve as a depot. Therefore, differences in protein binding among species can account for significant differences in potency of certain drugs and other toxicants. Similarly, marked differences exist among species, strains, and individuals with regard to the amount of body fat and its mobilization. Some species of wildlife and domestic animals normally have periods of marked mobilization of lipid stores.

2.4 Biotransformation

Metabolism or biotransformation of toxicants by the body is an "attempt to detoxify." In some instances, metabolized xenobiotic agents are more toxic than the original compound. This is referred to as lethal synthesis. Metabolism of many organophosphorus (OP) insecticides produces metabolites more toxic than the initial (or parent) compounds (e.g., parathion to paraoxon).

There are two phases of metabolism:

(a) Phase I includes oxidation, reduction, and hydrolysis mechanisms. These reactions, catalyzed by hepatic enzymes, generally convert foreign compounds to derivatives for Phase II reactions. Products of Phase I, however, may be excreted as such, if polar solubility permits translocation.
(b) Phase II principally involves conjugation or synthesis reactions. Common conjugates include glucuronides, acetylation products, and combinations with glycine. Metabolism of xenobiotic agents seldom follows a single pathway. Usually, a fraction is excreted unchanged, and the rest is excreted or stored as metabolites. Significant differences in metabolic mechanisms exist between species. For example, because cats lack forms of glucuronyl transferase, their ability to conjugate compounds such as morphine and phenols is compromised. Increased tolerance to subsequent exposures of a toxicant, in some instances, is due to enzyme induction initiated by the previous exposure.

2.5 Excretion

Excretion of most toxicants and their metabolites is by way of the kidneys. Some excretion occurs in the digestive tract and some via milk. Many polar and high-molecular-weight compounds are excreted into the bile. An enterohepatic cycle occurs when these compounds are excreted from the liver via bile, reabsorbed from the intestine, and returned to the liver. Milk is also an excretion pathway for some toxicants. The excretion rate may be of primary concern because some toxicants can

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cause violative residues in food-producing animals. The route of administration, dose, and condition of the animal—to name a few factors—can have a profound effect on excretion rates. Toxicants are removed in the kidney by glomerular filtration, tubular excretion by passive diffusion, and active tubular secretion. The damage to the kidney from the excretion of xenobiotics is specific to the anatomic location where the excretion occurs. Excretion sites are proximal tubules, glomeruli, medulla, papilla, and loop of Henle. The proximal convoluted tubule is the most common site of toxicant-induced injury.

General schematic representation of absorption, distribution, and excretion, after exposure to chemicals/xenobiotics by inhalation, dermal contact, and ingestion is given in Fig. 2.1.

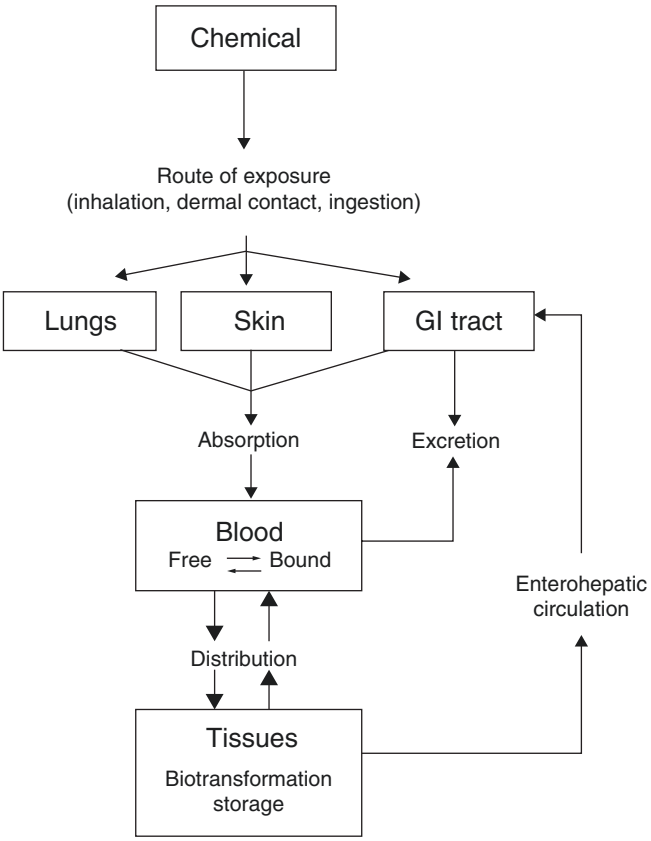


Fig. 2.1 Schematic representation of absorption, distribution, and biotransformation and the possible toxicokinetic fate of a chemical after exposure by inhalation, dermal contact, and ingestion

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2.6 Induction or Inhibition of Metabolizing Enzymes

Several drugs and chemicals have the ability to increase the metabolizing activity of enzymes called enzyme induction. Microsomal enzyme induction by drugs and chemicals usually requires repetitive administration of the inducing agent over a period of several days and the induction, once started, may continue for several days. Metabolizing enzyme induction has great clinical importance because it affects the plasma half-life and duration of action of xenobiotics. Contrary to metabolizing enzyme induction, several drugs and chemicals have the ability to decrease the metabolizing activity of certain enzymes called enzyme inhibition. Enzyme inhibition can be either nonspecific of chromosomal enzymes or specific of some non-microsomal enzymes (e.g., monoamine oxidase, cholinesterase, and aldehyde dehydrogenase).

The inhibition of hepatic microsomal enzymes mainly occurs due to administration of hepatotoxic agents, which cause either rise in the rate of enzyme degradation (e.g., carbon tetrachloride and carbon disulfide) or fall in the rate of enzyme synthesis (e.g., puromycin and dactinomycin). Enzyme inhibition may also produce undesirable xenobiotic interactions.

2.7 Bioactivation and Tissue Toxicity

Formation of harmful or highly reactive metabolic compounds from relatively inert/nontoxic chemical compounds is called bioactivation or toxication. The bioactive metabolites often interact with the body tissues to precipitate one or more forms of toxicities such as carcinogenesis, teratogenesis, and tissue necrosis.

The bioactivation reactions are generally catalyzed by cytochrome P450-dependent monooxygenase systems, but some other enzymes like those in intestinal flora are also involved in some cases. The reactive metabolites primarily belong to three main categories—electrophiles, free radicals, and nucleophiles. The formation of electrophiles and free radicals from relatively harmless substances/xenobiotics account for most toxicities. Formation of harmful or highly reactive metabolic compounds from relatively inert/nontoxic chemical compounds is called bioactivation or toxication. The bioactive metabolites often interact with the body tissues to precipitate one or more forms of toxicities such as carcinogenesis, teratogenesis, and tissue necrosis. The bioactivation reactions are generally catalyzed by cytochrome P450-dependent monooxygenase systems, but some other enzymes like those in intestinal flora are also involved in some cases. The reactive metabolites primarily belong to three main categories—electrophiles, free radicals, and nucleophiles. The formation of electrophiles and free radicals from relatively harmless substances/xenobiotics account for most toxicities.

2.8 Essentials of Toxicokinetic Principles

Toxicokinetics (often abbreviated as “TK”) is the description of both what rate a chemical will enter the body and what occurs to excrete and metabolize the compound once it is in the body.

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It is an application of toxicokinetics to determine the relationship between the systemic exposure of a compound and its toxicity. It is used primarily for establishing relationships between exposures in toxicology experiments in animals and the corresponding exposures in humans. However, it can also be used in environmental risk assessments in order to determine the potential effects of releasing chemicals into the environment. In order to quantify toxic effects, toxicokinetics can be combined with toxicodynamics. Such toxicokinetic-toxicodynamic (TKTD) models are used in ecotoxicology.

Similarly, physiological toxicokinetic models are physiological pharmacokinetic models developed to describe and predict the behavior of a toxicant in an animal body, for example, what parts (compartments) of the body a chemical may tend to enter (e.g., fat, liver, spleen, etc.) and whether or not the chemical is expected to be metabolized or excreted and at what rate.

The elimination or disappearance (by metabolic change) of a chemical from an organ or the body is expressed in terms of half-life (t½), defined as the amount of time required for the disappearance of half of the compound. The rate of elimination usually depends on the concentration of the compound. A constant fraction (e.g., ½) eliminated per unit of time is referred to as first-order kinetics. A metabolic reaction may dictate the rate of elimination. A constant amount eliminated per unit of time is referred to as zero-order kinetics. Different body compartments will likely have different elimination rates. A two-compartment system describes elimination that is initially rapid (e.g., from the central or plasma component) and subsequently slower from the peripheral component (e.g., liver, kidney, or fat). A well designed toxicokinetic study may involve several different strategies and depends on the scientific question to be answered. Controlled acute and repeated toxicokinetic animal studies are useful to identify a chemical's biological persistence, tissue and whole-body half-life, and its potential to bioaccumulate. Toxicokinetic profiles can change with increasing exposure duration or dose. Real-world environmental exposures generally occur as low-level mixtures, such as from air, water, food, or tobacco products. Mixture effects may differ from individual chemical toxicokinetic profiles because of chemical interactions, synergistic, or competitive processes. For other reasons, it is equally important to characterize the toxicokinetics of individual chemical constituents found in mixtures as information on behavior or fate of the individual chemical can help explain environmental, human, and wildlife biomonitoring studies. The details of toxicokinetics is beyond the scope of this book.

2.9 Question and Answers

2.9.1 Short Question and Answers

Exercise 1

Q.1. What do you mean by distribution of xenobiotics?

- Distribution may be defined as a process by which xenobiotics move throughout the body and reach their site of action (extracellular fluid and tissues).

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Q.2. Define ADME?
- ADME is an abbreviation in pharmacokinetics and pharmacology for "absorption, distribution, metabolism, and excretion," and describes the disposition of a pharmaceutical/toxicant compound within an organism.

Q.3. What are the primary routes of exposure for toxic substances?
- Following are the routes of exposure:
  (a) Oral
  (b) Respiratory
  (c) Dermal
  (d) Parenteral

Q.4. What is plasma membrane?
- The biological cell has a fundamental structure, the cell membrane or, as it is often called, the plasma membrane. The thickness of the membranes is of the order of 100 Å.

Q.5. Name at least three important blood organ barriers for transport of xenobiotics.
(a) Blood-Brain Barrier
(b) Placental Barrier
(c) Blood-Testes Barrier

Q.6. What are two main groups of metabolizing enzymes for xenobiotics?
(a) Microsomal enzymes
(b) Non-microsomal enzymes

Q.7. What are two phases or pathways for transformation reactions of biotransformation?
(a) Phase I
(b) Phase II

(a) Phase I Reactions (Non-synthetic or Non-Conjugation Phase)

Phase I reactions modify the compound's structure by adding a functional group. This allows the substance to interact with a reactive group, such as –OH, SH, $–NH_2$ or –COOH. For example, oxidation, reduction and hydrolysis

(b) Phase II Reactions or Conjugation/Synthetic Reactions

Phase II reactions (conjugation/synthetic reactions) includes reactions that catalyzes conjugation of xenobiotics or their Phase I metabolites with endogenous substances with a water-soluble molecule.

Q.8. What do you understand by induction of metabolizing enzymes?
- Several drugs and chemicals have ability to increase the metabolizing activity of enzymes called enzyme induction.

Q.9. What do you understand by Inhibition of metabolizing enzymes?
- Several drugs and chemicals have the ability to decrease the metabolizing activity of certain enzymes called enzyme inhibition. Enzyme inhibition can be either nonspecific of chromosomal enzymes or specific of some non-microsomal enzymes (e.g., monoamine oxidase, cholinesterase and aldehyde dehydrogenase).

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Q.10. What is bioactivation?
- Formation of harmful or highly reactive metabolic compounds from relatively inert/nontoxic chemical compounds is called bioactivation or toxication.

Q.11. Define electrophiles
- Electrophiles are molecules which are deficient in electron pairs with a positive charge that allows them to react by sharing electron pairs with electron-rich atoms in nucleophiles. Important electrophiles are epoxides, hydroxyamines, nitroso and azoxy derivatives, nitrenium ions, and elemental sulfur. These eletrophiles form covalent binding to nucleophilic tissue components such as macromolecules (proteins, nucleic acids, and lipids) or low-molecular-weight cellular constituents to precipitate toxicity. Covalent binding to DNA is responsible for carcinogenicity and tumor formation.

Q.12. Define free radicals
- Free radicals are molecules which contain one or more unpaired electrons (odd number of electrons) in their outer orbit.

Q.13. Define nucleophiles
- Nucleophiles are molecules with electron-rich atoms. Formation of nucleophiles is a relatively uncommon mechanism for toxicants. Examples of toxicity induced through nucleophiles include formation of cyanides from amygdalin, acrylonitrile and sodium nitroprusside, and generation of carbon monoxide from dihalomethane.

Q.14. What are physiochemical properties that affect absorption?
(a) route
(b) duration of exposure
(c) ability to cross cell membrane (passive and active transport, endocytosis)

Q.15. Out of non-ionized or ionized forms of chemicals, which of the forms passively diffuse
- Only non-ionized

Q.16. What are determinants of ionization?
(a) pKa = −log [acid dissociation constant]
(b) pH of the local environment

Q.17. What does it mean when pKa = pH?
- It means 50% ionization

Q.18. What happens to weak acids when they are in an environment where the pH decreases?
- More become non-ionized and are passively diffusible (e.g., diffuse in the stomach).

Q.19. What happens to weak bases when they are in an environment where the pH decreases?
- Becomes more non-ionized (e.g., intestine)

Q.20. What is bioavailability?
- The proportion of a drug or toxicant which enters the circulation when introduced into the body and so is able to have an active effect.

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2.9.2 Multiple Choice Questions

(choose the statement, it may be one, two, or none)

Exercise 2

Q.1. A probe drug for human CYP2C19 activity is _____
(a) Mephenytoin
(b) Valproic acid
(c) Carbamazepine
(d) Warfarin

Q.2. All of the following are true CYP2D6 *except* _____
(a) It converts codeine to morphine.
(b) It is polymorphic.
(c) It is induced by quinidine.
(d) Poor metabolizers have a lower risk of lung cancer.

Q.3. Aryl hydrocarbon receptor agonist includes all of the following *except* _____
(a) TCDD
(b) Benzopyrene
(c) 3-Methylcholanthrene
(d) Benzene

Q.4. Enzyme induction in humans has been associated with _____
(a) Osteomalacia
(b) Hepatocellular carcinoma
(c) cirrhosis
(d) psoriasis

Q.5. In metabolism-dependent inhibition of cytochrome P450, _____
(a) The parent compound is a potent inhibitor.
(b) The metabolite must be a product of P450 catalysis.
(c) The metabolite is a potent inhibitor.
(d) The inhibition is always irreversible.

Q.6. A compound that induces CYP2D6 is _____
(a) Rifampin
(b) Dexamethazone
(c) Ethanol
(d) None of the above

Q.7. All of the following are considered phase I biotransformation reactions *except* _____
(a) Hydrolysis
(b) Conjugation
(c) Reduction
(d) Oxidation

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Q.8. All of the following statements are true *except* _____
(a) Forms of epoxide hydrolase can exist in both microsomes and cytosol.
(b) Gemfibrozil is conjugated with glucuronic acid before it is oxidized by cytochrome P 50.
(c) CYP2D6 and CYP2C9 metabolize over half of the drugs in current use.
(d) Biotransformation can take place in the gut.

Q.9. UDP glucuronyltransferases conjugate all of the following endogenous molecules *except* _____
(a) Thyroid hormone
(b) Bilirubin
(c) Steroid hormones
(d) Parathyroid hormone

Q.10. If codeine were given to a patient who was a CYP2D6 poor metabolizer, the most likely result would be _____
(a) Inadequate analgesia
(b) Higher-than-normal levels of morphine at 2-h post-dose
(c) Higher-than-normal levels of codeine at 4-h post-dose
(d) Higher-than-normal levels of oxycodone at 4-h post-dose

Answers

Exercise 2

1. a	6. d
2. c	7. b
3. d	8. c
4. a	9. d
5. c	10. b.

2.9.3 Fill in the Blanks

Exercise 3

Q.1. The most common process of absorption of xenobiotics across the cell membrane is _____.
Q.2. The important route of excretion for xenobiotics is _____.
Q.3. The process of chemical transformation (conversion from one form to another) occurring in the body is known as _____.
Q.4. The major site for biotransformation of xenobiotics in the body is _____.
Q.5. In a hepatocyte, metabolism of xenobiotics takes place in _____.
Q.6. The most important among microsomal enzymes is _____ or _____.
Q.7. The major biotransformation reaction occurring in Phase I is _____ and in Phase II is _____.
Q.8. Phase I Oxidation reactions are mainly catalyzed by _____.

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Q.9. All Phase II conjugation reactions are catalyzed by non-microsomal enzymes except for _____ which is catalyzed by microsomal enzymes.
Q.10. The ability of certain substances to increase the activity or synthesis of microsomal enzymes is known as _____.
Q.11. The metabolic reaction, which is deficient in dogs is _____; cats are deficient in _____ and pigs are deficient in _____ reactions of biotransformation.
Q.12. The process of conversion of nontoxic substance into a toxic metabolite due to biotransformation is known as _____.

Answers

Exercise 3

1. Passive diffusion
2. Renal excretion
3. Biotransformation
4. Liver
5. Endoplasmic reticulum (ER) or microsomes
6. Monooxygenases or mixed function oxidases (MFO)
7. Oxidation, conjugation
8. Microsomal enzymes (MFO)
9. Glucuronide conjugation
10. Induction
11. Acetylation; glucuronide conjugation and sulfation
12. Lethal synthesis

2.9.4 True or False Statements

Exercise 4
Write T for true and F for false statement.

Q.1. *A water-soluble drug will pass across muscle membranes faster than across brain membranes (assume permeability-rate limitations).*
Q.2. *A neutral, lipophilic drug is likely to be absorbed faster in the intestines than in the stomach. Remember that stomach and intestine differ in their properties.*
Q.3. *Lipophilic drugs are generally taken up fast by highly perfused organs.*
Q.4. *Ionized and lipophilic drugs are most likely to cross most membrane barriers.*
Q.5. *Drugs with a high tissue binding always have a large volume of distribution.*
Q.6. *Compared to the skin, the liver would have a higher rate of uptake of perfusion-limited lipophilic drugs due to its higher blood flow rate.*

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Q.7. *Distribution to a specific tissue for permeability-limited hydrophilic drugs depends on how much and how quickly the blood gets to the specific tissue.*
Q.8. *Perfusion-limited distribution is a type of drug distribution into tissue that occurs when the drug is able to cross membranes easily.*
Q.9. *Assume two drugs (identical molecular weight, same dose given): one neutral drug (Drug A) and one acidic drug (pKa = 7.4, Drug B). Drug A and the unionized form of drug B have the same partition coefficient. The fraction unbound in plasma and tissue is 0.5 for both drugs. Drug B will enter tissues somewhat slower than drug A.*
Q.10. *A weak acid, whose unionized form shows a high partition coefficient is* likely to cross most membrane barriers.

Answers

Exercise 4

1. T	6. T
2. T	7. F
3. T	8. T
4. F	9. T
5. F	10.T

2.9.5 Match the Statements

(Match the following statements in Columns A and B)

Exercise 5

Column A	Column B
Q.1. Metabolizing enzymes	a. P-aminobenzoic acid
Q.2. Dealkylation	b. Oxidation
Q.3. Ethanol	c. Permeability
Q.4. Procaine	d. Conjugation
Q.5. Phase II reaction	e. Liver
Q.6. Aspirin	h. Acetaldehyde
Q.7. Transport	i. Gastrointestinal
Q.8. Facilitated	j. Salicylic acid
Q.9. Membrane	k. Movement
Q.10. Oral	l. Diffusion

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Answers

Exercise 5

Q.1	e. Liver
Q.2	b. Oxidation
Q.3	h. Acetaldehyde
Q.4	a. P-aminobenzoic acid
Q.5	d. Conjugation
Q.6	j. Salicylic acid
Q.7	k. Movement
Q.8	l. Diffusion
Q.9	c. Permeability
Q.10	i. Gastrointestinal

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Mechanism of Toxicity

3

Abstract

This chapter deals with various aspects of mechanism of action of chemical or physical agents, their interaction with living organisms, and how they trigger perturbations in cell function and/or structure or may initiate repair mechanisms at the molecular, cellular, and/or tissue levels including necrosis and apoptosis of different xenobiotics. This process is completely organized whereby individual cells break into small fragments that are phagocytosed by adjacent cells or macrophages without producing an inflammatory response. Knowledge of the mechanism of toxicity of a substance enhances the ability to prevent toxicity and design more desirable chemicals; it constitutes the basis for therapy upon overexposure and frequently enables a further understanding of fundamental biological processes.

Keywords

Mechanism of action · Mechanism of toxicity · Mode of action · Necrosis · Apoptosis · Question and answer bank

3.1 Introduction

This chapter deals with various aspects of mechanism of action including necrosis and apoptosis of different xenobiotics as applicable to mechanism of toxicity. Knowledge of the mechanism of toxicity of a substance enhances the ability to prevent toxicity and design more desirable chemicals; it constitutes the basis for therapy upon overexposure and frequently enables a further understanding of fundamental biological processes. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple-choice questions, fill in the blanks, and true/false statements related to mechanism of action of different xenobiotics in animals.

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Key Points

- Mechanism of toxicity is the study of how chemical or physical agents interact with living organisms that may trigger perturbations in cell function and/or structure or that may initiate repair mechanisms at the molecular, cellular, and/or tissue levels.
- Apoptosis, or programmed cell death, is a tightly controlled, organized process whereby individual cells break into small fragments that are phagocytosed by adjacent cells or macrophages without producing an inflammatory response.
- Sustained elevation of intracellular Ca2+ is harmful because it can result in (1) depletion of energy reserves by inhibiting the ATPase used in oxidative phosphorylation, (2) dysfunction of micro-aments, (3) activation of hydrolytic enzymes, and (4) generation of reactive oxygen and nitrogen species (ROS and RNS).
- Cell injury progresses toward cell necrosis (death) if molecular repair mechanisms are inefficient or the molecular damage is not readily reversible.
- Chemical carcinogenesis involves insufficient function of various repair mechanisms, including (1) failure of DNA repair, (2) failure of apoptosis (programmed cell death), and (3) failure to terminate cell proliferation.

3.2 Mechanism of Action

The term mechanism of action (MOA) refers to the specific biochemical interaction through which a toxicant substance produces its pharmacological effect or toxic response. A MOA usually includes mention of the specific molecular targets to which the toxicant binds, such as an enzyme or a receptor. Receptor sites have specific affinities for toxicants based on the chemical structure of the toxicant, as well as the specific action that occurs there. Toxicants that do not bind to receptors produce their corresponding therapeutic effect by simply interacting with chemical or physical properties in the body. Common examples of toxicants that work in this way are antacids and laxatives.

3.3 Mode of Action

There are two major types of modes of toxic action:

(i) Nonspecific acting toxicants are those that produce narcosis.
(ii) Specific acting toxicants are those that are nonnarcotic and that produce a specific action at a specific target site.

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3.3.1 Nonspecific

Nonspecific acting modes of toxic action result in narcosis; therefore, narcosis is a mode of toxic action. Narcosis is defined as a generalized depression in biological activity due to the presence of toxicant molecules in the organism. The target site and mechanism of toxic action through which narcosis affects organisms are still unclear, but there are hypotheses that support the fact that it occurs through alterations in the cell membranes at specific sites, such as the lipid layers or the proteins bound to the membranes. Even though continuous exposure to a narcotic toxicant can produce death, if the exposure to the toxicant is stopped, narcosis can be reversible.

3.3.2 Specific Type

Toxicants at low concentrations modify or inhibit some biological process by binding at a specific site or molecule have a specific acting mode of toxic action. However, at high enough concentrations, toxicants with specific acting modes of toxic actions can produce narcosis that may or may not be reversible. Nevertheless, the specific action of the toxicant is always shown first because it requires lower concentrations. Different specific modes of toxic actions include:

- Uncouplers of oxidative phosphorylation: The action involves toxicants that uncouple the two processes that occur in oxidative phosphorylation—electron transfer and adenosine triphosphate (ATP) production.
- Acetylcholinesterase (AChE) inhibitors: AChE is an enzyme associated with nerve synapses that is designed to regulate nerve impulses by breaking down the neurotransmitter acetylcholine (ACh). When toxicants bind to AChE, they inhibit the breakdown of ACh. This results in continued nerve impulses across the synapses, which eventually cause nerve system damage. Examples of AChE inhibitors are organophosphates and carbamates.
- Irritants: These are chemicals that cause an inflammatory effect on living tissue by chemical action at the site of contact. The resulting effect of irritants is an increase in the volume of cells due to a change in size (hypertrophy) or an increase in the number of cells (hyperplasia).
- Examples of irritants are benzaldehyde, acrolein, zinc sulfate, and chlorine.
- Central nervous system (CNS) seizure agents: CNS seizure agents inhibit cellular signaling by acting as receptor antagonists. They result in the inhibition of biological responses. Examples of CNS seizure agents are organochlorine pesticides.
- Respiratory blockers: These are toxicants that affect respiration by interfering with the electron transport chain in the mitochondria. Examples of respiratory blockers are rotenone and cyanide.

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3.4 Mechanism of Toxicity

Mechanism of toxicity is the study of how chemical or physical agents interact with living organisms to cause toxicity. Knowledge of the mechanism of toxicity of a substance enhances the ability to prevent toxicity and design more desirable chemicals; it constitutes the basis for therapy upon overexposure and frequently enables a further understanding of fundamental biological processes.

3.4.1 Steps Involved in the Process of Mechanisms of Toxicity

Different steps involved in the process of mechanisms of toxicity include:

- Delivery: site of exposure to the target
- Reaction of the ultimate toxicant with the target molecule
- Cellular dysfunction and resultant toxicity
- Repair or dysrepair

Different steps involved in mechanisms of toxicity are summarized in Fig. 3.1.

3.4.2 Factors Responsible for Cellular Dysfunction

Factors that are responsible for cellular dysfunction include:

- Chemicals that cause DNA adducts can lead to DNA mutations which can activate cell death pathways; if mutations activate oncogenes or inactivate tumor suppressors, it can lead to uncontrolled cell proliferation and cancer (e.g., benzopyrene).
- Chemicals that cause protein adducts can lead to protein dysfunction which can activate cell death pathways; protein adducts can also lead to autoimmunity; if protein adducts activate oncogenes or inactivate tumor suppressors, it can lead to uncontrolled cell proliferation and cancer (e.g., diclofenac glucuronidation metabolite).
- Chemicals that cause oxidative stress can oxidize DNA or proteins leading to DNA mutations and protein dysfunction (e.g., benzene, CCl4).
- Chemicals that specifically interact with protein target chemicals that activate or inactivate ion channels can cause widespread cellular dysfunction and cause cell death and many physiological symptoms. For example, Na1, Ca21, and K1 levels are extremely important in neurotransmission, muscle contraction, and nearly every cellular function (e.g., tetrodotoxin closes voltage-gated Na1 channels).

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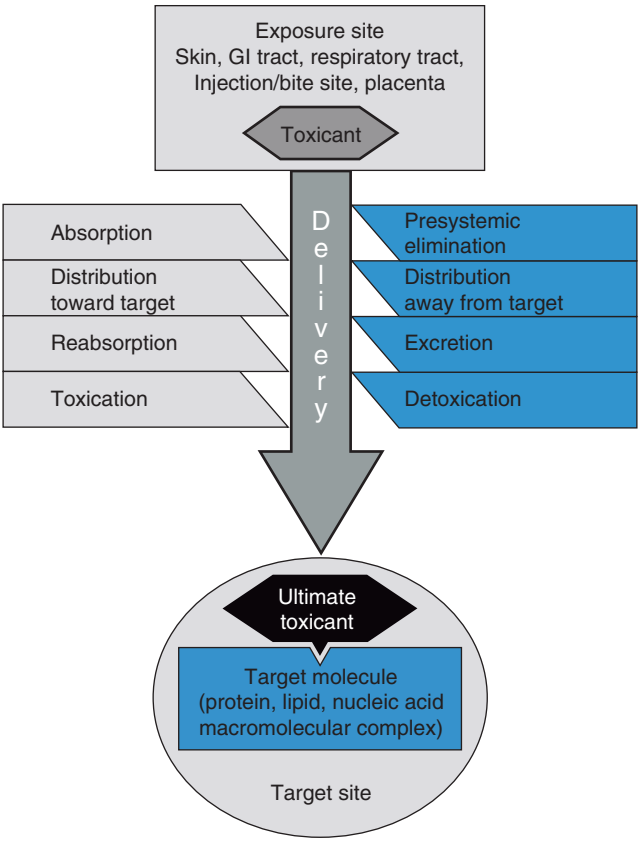


Fig. 3.1 Steps involved in mechanisms of toxicity. (nature.berkeley.edu/Bdnomura/pdf/Lecture6Mechanisms3.pdf)

- Chemicals that inhibit cellular respiration—inhibitors of proteins or enzymes involved in oxygen consumption, fuel utilization, and ATP production will cause energy depletion and cell death (e.g., cyanide inhibits cytochrome c oxidase).
- Chemicals that inhibit the production of cellular building blocks, e.g., nucleotides, lipids, amino acids (e.g., amanitin from death cap mushrooms), alter ion channels and metabolism (e.g., sarin inhibits AChE and elevates ACh levels to active signaling pathways and ion channels).

All of the above can also cause inflammation which can lead to cellular dysfunction.

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3.5 Forms of Cell Deaths

There are two forms of cell deaths.

3.5.1 Necrosis

Necrosis is unprogrammed cell death (dangerous) and is caused by factors external to the cell or tissue, such as infection, toxins, or trauma which result in the unregulated digestion of cell components. A cell that commits homicide is necrosis. Necrosis of the apex of the pedal bone is extremely common in yearling beef calves after transportation over long distances (Fig. 3.2).

Necrosis may be:

(i) Passive form of cell death induced by accidental damage of tissue does not involve the activation of any specific cellular program.
(ii) Early loss of plasma membrane integrity and swelling of the cell body followed by bursting of cell.
(iii) Mitochondria and various cellular processes contain substances that can be damaging to surrounding cells and are released upon bursting and cause inflammation.
(iv) Cells necrotize in response to tissue damage (injury by chemicals and viruses, infection, cancer, inflammation, ischemia—death due to blockage of blood to tissue).



Fig. 3.2 Toe necrosis syndrome, distal phalanx necrosis. (https://www.merckvetmanual.com/-/media/manual/veterinary/images/toe_necrosis_syndrome_distal_phalanx_necrosis_high.jpg?la=en&thn=0&mw=350)

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3.5.2 Apoptosis

Apoptosis is the term used to describe generally the normal death of the cell in living organisms. Since new cells regenerate, cell death is a normal and constant process in the body. It is one of the main forms of programmed cell death (not as dangerous to organism as necrosis).

Apoptosis may be:

(i) Active form of cell death enabling individual cells to commit suicide
(ii) Caspase dependent
(iii) Dying cells that shrink and condense and then fragment, releasing small membrane-bound apoptotic bodies, which are phagocytosed by immune cells (i.e., macrophages)
(iv) Intracellular constituents that are not released where they might have deleterious effects on neighboring cells

Apoptosis has several distinct stages. In the first stage, the cell starts to become round as a result of the protein in the cell being eaten by enzymes that become active. Next, the DNA in the nucleus starts to come apart and shrink down. The membrane surrounding the nucleus begins to degrade and ultimately no longer forms the usual layer. Cell commits suicide by apoptosis (Fig. 3.3).

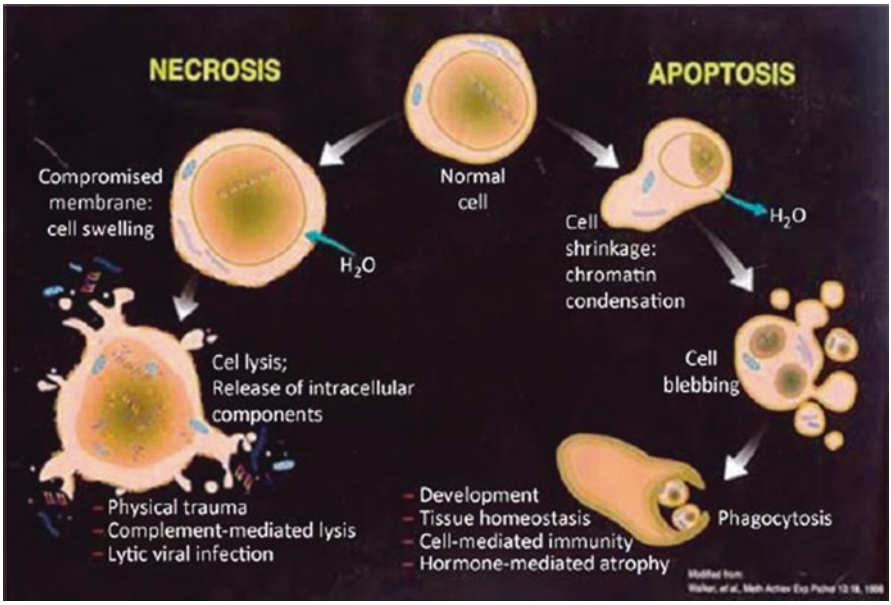


Fig. 3.3 Different steps involved during the process of necrosis and apoptosis. (http://1.bp.blogspot.com/-ftJ7AFYXkmY/TW0q8cK4auI/AAAAAAAAAC-o/AkM8Sgr65Z0/s1600/Necrosis%2BVs%2BApoptosis.png)

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Table 3.1 Differences between necrosis and apoptosis

Necrosis	Apoptosis
Cellular swelling	Cell shrinkage
Membranes are broken	Membranes remain intact
Cell lysis, eliciting an inflammatory reaction	Cell is phagocytosed; no tissue reaction
DNA fragmentation is random, pyknosis	DNA fragmentation into nucleosome size fragments
Mechanism—ATP depletion, membrane injury, free radical damage	Mechanism-caspase activation, endonuclease and proteases
In vivo, whole areas of the tissue are affected	In vivo, individual cells appear affected

The figure shows apoptosis, which is a form of cell death that is generally triggered by normal, healthy processes in the body; necrosis is cell death that is triggered by external factors or disease, such as trauma or infection. Apoptosis, which can also occur as a defense mechanism during healing processes, is almost always normal and beneficial to an organism, while necrosis is always abnormal and harmful. Though necrosis is being researched as a possible form of programmed cell death (i.e., sometimes a natural process), it is considered an "unprogrammed" (unnatural) cell death process at this time. As a usually healthy form of a cell's life cycle, apoptosis rarely demands any form of medical treatment, but untreated necrosis can lead to serious injury or even death. Differences between necrosis and apoptosis is summarized in Table 3.1.

3.6 Questions and Answers

3.6.1 Short Questions and Answers

Exercise 1

Q.1. What is mode of toxic action?

A mode of toxic action is a common set of physiological and behavioral signs that characterize a type of adverse biological response. A mode of action should not be confused with mechanism of action, which refers to the biochemical processes underlying a given mode of action.

Q.2. What are the two major types of modes of toxic actions?

(a) Nonspecific: nonspecific acting toxicants are those that produce narcosis.
(b) Specific: specific acting toxicants are those that are nonnarcotic and that produce a specific action at a specific target site.

Q.3. What is specific type of mode of toxic action?

There are several specific acting modes of toxic action: Uncouplers of oxidative phosphorylation. Involves toxicants that uncouple the two processes that occur in oxidative phosphorylation: electron transfer and adenosine triphosphate (ATP) production.

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Q.4. What are the steps involved in the process of mechanisms of toxicity?
(a) Delivery: site of exposure to the target
(b) Reaction of the ultimate toxicant with the target molecule
(c) Cellular dysfunction and resultant toxicity
(d) Repair or disrepair

Q.5. What are two forms of cell deaths?
(a) Necrosis: unprogrammed cell death (dangerous)
(b) Apoptosis: one of the main forms of programmed cell death (not as dangerous to organism as necrosis).

Q.6. What is necrosis of tissues?
Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma which result in the unregulated digestion of cell components. Cell that commits homicide is necrosis.

Q.7. What is apoptosis?
Apoptosis is the term used to describe the generally normal death of the cell in living organisms. Since new cells regenerate, cell death is a normal and constant process in the body.

Q.8. What are the different stages of apoptosis?
Apoptosis has several distinct stages. In the first stage, the cell starts to become round as a result of the protein in the cell being eaten by enzymes that become active. Next, the DNA in the nucleus starts to come apart and shrink down. The membrane surrounding the nucleus begins to degrade and ultimately no longer forms the usual layer. Cell commits suicide by apoptosis.

Q.9. What are the possible toxic mechanisms for chemicals?
(a) Produce reversible or irreversible bodily injury
(b) Have the capacity to cause tumors, neoplastic effects, or cancer
(c) Cause reproductive errors including mutations and teratogenic effects
(d) Produce irritation and sensitization of mucous membranes
(e) Cause a reduction in motivation, mental alertness, or capability
(f) Alter behavior or cause death of the organism.

Q.10. List the variety of processes of absorption including their characteristics.
(a) Diffusion: Molecules move from areas of high concentration to low concentration.
(b) Facilitated Diffusion: Require specialized carrier proteins; no high-energy phosphate bonds are required.
(c) Active Transport: ATP is required in conjunction with special carrier proteins to move molecules through a membrane against a concentration gradient.
(d) Endocytosis: Particles and large molecules that might otherwise be restricted from crossing a plasma membrane can be brought in or removed by this process.

Q.11. How do toxic substances enter the body?
There are several ways in which toxic substances can enter the body. They may enter through the lungs by inhalation, through the skin, mucous membranes or eyes by absorption, or through the gastrointestinal tract by ingestion.

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Q.12. What are the major functions of the skin?
The skin can help to:
(a) Regulate body temperature through sweat glands.
(b) Provide a physical barrier to dehydration, microbial invasion, and some chemical insults.
(c) Excrete salts, water, and organic compounds.
(d) Serve as a sensory organ for touch, temperature, pressure, and pain.
(e) Provide some important components of immunity.

Q.13. What are the three major mechanisms for the harmful effects of environmental toxins?
(a) The toxins' influence on enzymes
(b) Direct chemical combination of the toxin with a cell constituent
(c) Secondary action as a result of the toxins' presence in the system

Q.14. List the four major types of hypersensitivity reactions:
(a) Cytotoxic
(b) Cell-mediated
(c) Immune complex
(d) Anaphylactic

Q.15. What is anaphylaxis?
Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes more than one of the following: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure. These symptoms typically set in within minutes to hours. Common causes include insect bites and stings, foods, and medications.

3.6.2 Multiple-Choice Questions

(Choose the correct statement; it may be one, two, or none)

Exercise 2

Q.1. A possible reason for the selective embryo-fetal toxicity of DES is ___.
(a) Higher concentration of free DES in embryo/fetal compared to adults
(b) Binding to retinoic acid receptors
(c) Lack of placental toxicant metabolism
(d) All of the above

Q.2. The liver and kidney are major target organs of toxicity because ___.
(a) They both receive a high percentage of cardiac output.
(b) They both have substantial xenobiotic metabolizing capacity.
(c) They both have transport systems that can concentrate xenobiotics.
(d) All of the above.

Q.3. Acyl glucuronides are particularly toxic to the liver because ___.
(a) They selectively interact with macrophages releasing active oxygen.

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(b) Active transport systems in the hepatocyte and bile duct system can greatly up concentrate them.
(c) They are resistant to glucuronidase.
(d) They are suitable inhibitors of UGT2B7.

Q.4. The selective renal toxicity of cephaloridine over cephalothin is due to ___
(a) Selective uptake by the organic cation transporter
(b) Selective inhibition of P-glycoprotein
(c) Selective uptake by the organic anion transporter
(d) Significantly less plasma protein binding of cephaloridine

Q.5. All of the following are of alpha-amanitin *except* …
(a) It is less orally available than phalloidin.
(b) It inhibits RNA polymerase II.
(c) It is transported into the hepatocyte by a bile acid transporter.
(d) It is a mushroom toxin.

Q.6. All of the following are true of the toxic mechanism of paraquat *except* ___.
(a) Lungs accumulate paraquat in an energy-dependent manner.
(b) Its energy into the lungs is assumed to be via the polyamine transport system.
(c) Similar molecules with smaller distances between nitrogen atoms do not enter lungs as readily.
(d) Cytotoxicity to alveolar cells is caused by interference with calcium channels.

Q.7. Enzyme induction of phenobarbital is mediated through ___
(a) Aryl hydrocarbon receptor
(b) PPAR-alpha receptor
(c) Constitutively active receptor (CAR)
(d) Estrogen receptor

Q.8. CAR is downregulated by ___
(a) Hypericum extracts
(b) Acetaminophen
(c) Aspirin
(d) Proinflammatory cytokines

Q.9. The pregnane X receptor ___
(a) Is a cytosolic receptor
(b) Is involved in induction of CYP3A4
(c) Is primarily expressed in skin
(d) All of the above

Q.10. Downregulation of receptors is due to continuous exposure of ___
(a) Antagonist
(b) Agonist
(c) Inverse agonist
(d) All the above

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Answers

Exercise 2

1.a	6.d
2. d	7.c
3.b	8.d
4.c	9.b
5.a	10.b

3.6.3 Fill in the Blanks

Exercise 3

Q.1. Nonspecific acting toxicants are those that produce _____.
Q.2. Uncouplers of oxidative phosphorylation uncouple the two processes that occur in _____i.e., electron transfer and adenosine triphosphate (ATP) production.
Q.3. Specific acting toxicants are those that are nonnarcotic and that produce a specific action at a specific _____
Q.4. Irritants are chemicals that cause _____ on living tissue by chemical action at the site of contact.
Q.5. Chemicals that cause DNA adducts can lead to _____ which can activate cell death pathways.
Q.6. Chemicals that cause protein adducts can lead to _____ which can activate cell death pathways.
Q.7. Necrosis can lead to unprogrammed _____.
Q.8. Necrosis is caused by factors external to the cell or tissue, such as _____ and _____.
Q.9. Apoptosis is the term used to describe generally the normal death of the cell in _____.
Q.10. Toxic chemicals can produce _____ or _____ bodily injury.

Answers

Exercise 3

1. Narcosis	6. Protein dysfunction
2. Oxidative phosphorylation	7. Cell death
3. Specific target site	8. Infections, toxins, or Trauma
4. Inflammation	9. Living organisms
5. DNA mutations	10. Reversible, irreversible

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3.6.4 True or False Statements

(Write T for true and F for the false statement)

Exercise 4

Q.1. When lead covalently bonds to an enzyme, its inhibition of enzymes is considered to be irreversible.
Q.2. The exposure of allergens can trigger a diminished immune response in some people.
Q.3. Chemical pollutants such as ozone can depress the immune response by inactivating alveolar macrophages.
Q.4. B cells are the principle agents in cell-mediated immunity.
Q.5. Humoral immune responses are characterized by subcutaneous bleeding.
Q.6. The environmental pollutants such as ozone and fine particulates contribute to the significant rise in the numbers and severity of asthma cases.
Q.7. If absorbed, lead tends to be stored mostly in fatty tissue.
Q.8. Dioxin is considered to be one of the most toxic natural chemicals.
Q.9. The EPA has listed 20 ug/dl as the maximum acceptable blood lead level for fetuses and young children.
Q.10. Lead may impair fertility in both men and women when blood lead levels approach 50 ug/dl.

Answers

Exercise 4

1. T	6. T
2. F	7. F
3. T	8. F
4. F	9. F
5. T	10. T

3.6.5 Match the Statements

Exercise 5

Match the following statements in column A and B

Column A	Column B
Q. 1. Muscimol	a. Serotonin agonist
Q. 2. Benzodiazepines	b. Prevents vesicle dopamine uptake
Q. 3. Clonidine	c. Inhibits norepinephrine uptake
Q. 4. Baclofen	d. Direct nicotine antagonist
Q. 5. Bicuculline	e. Direct dopamine agonist

(continued)

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Column A	Column B
Q.6. Theophylline	f. Direct serotonin antagonist/glycine uptake inhibitor
Q. 7. Nicotine	g. Direct GABA (A) agonist
Q. 8. Clozapine	h. Indirect GABA (A) agonist
Q. 9. Tecadenoson	i. Alpha-2 adrenoceptor agonist
Q. 10. Yohimbine	j. Dopamine antagonist
Q. 11. Cocaine	k. Direct GABA (B) agonist
Q. 12. Alpha-bungarotoxin	l. Adenosine antagonist
Q. 13. Botulinum toxin	m. Direct adenosine agonist
Q. 14. Bromocriptine	n. Alpha-2 adrenoceptor antagonist
Q. 15. Haloperidol	o. Direct GABA (A) antagonist
Q. 16. Reserpine	p. Agonist at neuromuscular junction
Q. 17. Ergonovine	q. Inhibits acetylcholine release

Answers

Exercise 5

Q. 1.	g. Direct GABA (A) agonist
Q. 2.	h. Indirect GABA (A) agonist
Q. 3.	i. Alpha-2 adrenoceptor agonist
Q. 4.	k. Direct GABA (B) agonist
Q. 5.	o. Direct GABA (A) antagonist
Q. 6.	l. Adenosine antagonist
Q. 7.	p. Agonist at neuromuscular junction
Q. 8.	f. Direct serotonin antagonist/glycine uptake inhibitor
Q. 9.	m. Direct adenosine agonist
Q. 10.	n. Alpha-2 adrenoceptor antagonist
Q. 11.	c. Inhibits norepinephrine uptake
Q. 12.	d. Direct nicotine antagonist
Q. 13.	q. Inhibits acetylcholine release
Q. 14.	e. Direct dopamine agonist
Q. 15.	j. Dopamine antagonist
Q. 16.	b. Prevents vesicle dopamine uptake
Q. 17.	a. Serotonin agonist

Further Reading

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Toxic Effects of Pesticides and Agrochemicals

4

Abstract

This chapter deals with the toxic effects of different pesticides such as organochlorine insecticides, organophosphorus insecticides, carbamate insecticides, pyrethroids, formamidines, nicotinamides, botanical insecticides, fumigants, fungicides, herbicides, rodenticides, and various fertilizers used by the farmers. Pesticides and agricultural chemicals are among the most widely used group of chemicals in modern world and have provided immense benefits to mankind by controlling pests, significantly enhancing food production, and improving health. However, their massive and indiscriminate use in crop protection, food preservation, and insect pest control has led to acute or chronic poisoning incidents in human, domestic animals, and wildlife and resulted in widespread ecological adverse effects. Survey indicates that today herbicides and insecticides (organophosphates [OPs] and carbamates [CMs]) are commonly used in agriculture and industry and around homes/gardens throughout the world. Small animals often encounter poisoning with these insecticides via malicious activity or accidental exposure, while livestock may ingest freshly sprayed crop or contaminated feed. Among other pesticides, rodenticide (warfarin), and fumigant (aluminum phosphide) are the common causes of poisoning malicious/suicide poisonings because of their easy availability.

Keywords

Pesticides · Agrochemicals · Organochlorine (OC) insecticides · Organophosphorus (OP) insecticides · Carbamate (CM) insecticides · Pyrethroids · Formamidines · Nicotinamides · Botanical insecticides · Question and answer bank · Multiple choice questions

4.1 Introduction

This chapter deals with the toxic effects of pesticides and agrochemicals in animals and highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions and answers, multiple-choice questions, fill in the blanks, and true or false statements as relevant to their adverse effects on animal health.

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Key Points

- The chlorinated hydrocarbons are neurotoxicants and cause acute effects by interfering with the transmission of nerve impulses.
- Cholinesterase inhibitors fall into two classes—organophosphorus compounds and carbamates. The former has higher toxicity and longer duration of action and more commonly causes CNS toxicity.
- Organophosphorus (OP) and carbamate (CM) insecticides share a common mode of toxicological action associated with their ability to inhibit the ChE enzyme within the nervous tissue at the neuromuscular junction (NMJs).
- Poisoning cases of OP or CM are usually diagnosed based on clinical signs and quantified levels of AChE inhibition in blood.
- Fatalities due to OP compounds occur mainly due to effects on respiration due depression of respiratory drive, paralysis of muscles of respiration, bronchoconstriction, and airway obstruction from profuse respiratory tract secretions.
- OP compounds such as triaryl phosphates (e.g., triorthocresyl phosphate) are weak cholinesterase inhibitors but do inhibit "neurotoxic esterase" (NTE) present in the brain and spinal cord.
- In OP and CM poisoning, antidotal treatment such as the combined use of atropine sulfate and pyridine-2-aldoxime methochloride is used.
- Organochlorine (OC) insecticide toxicosis has no specific treatment. Acute poisoning treatment should mainly be directed toward symptomatic and control of convulsions.
- Piperonyl butoxide is used as a potentiator or synergist in many pesticide formulations.
- Natural insecticides are usually nontoxic to humans and pets and safe for the environment.
- Mixtures of 2,4-D and 2,4,5-T may contain a contaminant, 2,3,7,8-tetrach lorodibenzo-pdioxin (TCDD), that was formed during the manufacturing process which are known to be toxic.
- α-Naphthylthiourea (ANTU), strychnine, thallium salts, zinc phosphide, etc. are other fast-acting poisons.
- All anticoagulants have the basic coumarin or indanedione nucleus. The "first-generation" anticoagulants (warfarin, pindone, coumafuryl, coumachlor, isovaleryl indanedione, and others less frequently used) require multiple feedings to result in toxicity.
- Anticoagulant rodenticides are a common cause of poisoning in pets and wildlife. Intoxications in domestic animals have resulted from contamination of feed with anticoagulant concentrate, malicious use of these chemicals, and feed mixed in equipment used to prepare rodent bait. In acute toxicity with warfarin, Vitamin K_1 is an antidote.
- Phosphine gas, when inhaled, results in acute noncardiogenic pulmonary edema. There is no specific treatment.

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4.2 Definitions and Classifications

The term "agricultural chemicals" has largely been replaced by the term "pesticides." They are among the most widely used group of chemicals in modern world and have provided immense benefits to mankind by controlling significantly in enhancing food production and improving health that is nutrition. However, their massive and indiscriminate use in crop protection, food preservation, and insect pest control has led to acute or chronic poisoning incidents in humans, domestic animals, and wildlife and resulted in widespread ecological adverse effects.

Survey indicates that today herbicides and insecticides (organophosphates [OPs] and carbamates [CMs]) are commonly used in agriculture and industry and around homes/gardens throughout the world. Small animals often encounter poisoning with these insecticides via malicious activity or accidental exposure, while livestock may ingest freshly sprayed crop or contaminated feed. Among other pesticides, rodenticide (warfarin) and fumigant (aluminum phosphide) are the common causes of malicious/suicide poisonings because of their easy availability.

4.2.1 Definitions

Pesticides: They are used to control, kill, or repel pests. They are also known as economic poisons, regulated by federal and state laws.

Acetylcholine: A chemical neurotransmitter found widely in the body. It triggers the stimulation of postsynaptic nerves, muscles, and exocrine glands.

Acetylcholinesterase (AChE) (generally referred to as cholinesterase): An enzyme that rapidly breaks down the neurotransmitter, acetylcholine, so that it does not overstimulate postsynaptic nerves, muscles, and exocrine glands.

ChE inhibitor (generally referred to as cholinesterase inhibitor): A chemical that binds to the enzyme cholinesterase and prevents it from breaking down the neurotransmitter acetylcholine. With toxic doses, the result is that excessive levels of the acetylcholine build up in the synapses and neuromuscular junctions and glands.

4.2.2 Classification

Depending on what a compound is designed to do, pesticides have been subclassified into a number of categories.

Insecticides: organochlorine (OC), organophosphorus (OP), carbamate (CM), pyrethrins and pyrethroids, formamidines, nicotinoids, and natural products (rotenone and nicotine)

Fumigants: inorganic (aluminum phosphide, hydrogen cyanide, carbon disulfide, sulfur dioxide) and organic (methyl bromide, ethylene dibromide, dibromochloropropane)

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Fungicides: inorganic (sulfur, metals) and organic (organomercurial, chlorophenols, phthalimides, etc.)
Herbicides: inorganic (arsenicals, chlorates) and organic (chlorophenoxy and its derivatives, dinitrophenols, bipyridyls, ureas, and other herbicides)
Rodenticide: warfarin

In addition, there are other groups of pesticides such as nematicide, acaricide, algicides, bird repellents, and mammal repellents.

4.3 Toxicity of Insecticides

Approximately 1000 pesticides are available in various preparations such as dusting powder, emulsions, solutions, water-dispensable powders, fumigants, and so on. The pesticides are biocides also capable of killing all forms of life. Due to limited space, pesticides such as insecticides, acaricides, herbicides, fungicides, and so on, that have more relevance in veterinary profession have been discussed. Insecticides are any substance or a mixture of substances intended to prevent, destroy, repel, or mitigate insects. Similarly, acaricides are substances that can destroy mites. A chemical can exert both insecticidal and acaricidal effects. Based on their properties, these chemicals can be classified into four groups: (1) organophosphates; (2) carbamates; (3) organochlorines; and (4) natural products (rotenone and nicotine), pyrethrins, and pyrethroids. Because of worldwide use, these chemicals pose health risks to nontarget species, including people, domestic and companion animals, wildlife, and aquatic species. In large animals, poisoning is often due to inadvertent or accidental use, whereas in small animals (particularly dogs) poisoning is often due to malicious intent. Each exposure, no matter how brief or small, results in some of the compound being absorbed and perhaps stored. Repeated short exposures may eventually result in intoxication because of cumulative effect.

4.4 Herbicide Toxicity

Herbicides control weeds and are the most widely used class of pesticides. This class of pesticide can be applied to crops using many strategies to eliminate or reduce weed populations. Some of the newer families such as the imidazolinones inhibit the action of acetohydroxyacid synthase but have low toxicities to mammals, fish, insects, and birds. The potential for environmental contamination continues to come from families of herbicides that have been used for years. The chlorophenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) are systemic acting compounds to control broadleaf plants and have been in use since the 1940s. The oral toxicities of these compounds are low. However, mixtures of 2,4-D and 2,4,5-T contain a contaminant, 2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD), that was formed during the

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manufacturing process is known to be toxic. TCDD is one of the most toxic synthetic substances known in laboratory animals. In addition, it is toxic to developing embryos in pregnant rats and has been shown to cause birth defects. TCDD is a proven carcinogen in both mice and rats, with the liver being the primary target. This chemical has also been shown to alter the immune system and enhance susceptibility in exposed animals. Another family of herbicides, the triazines, continues to cause concern to environmentalists and toxicologists because of the contamination of surface and groundwater supplies that become public drinking water. The major concern with these types of compounds is their carcinogenic effects. A member of the bipyridylium family of herbicides is the compound paraquat (1,1-dimethyl-4,4-bipyridinium ion as the chloride salt). It is a very water-soluble contact herbicide that is active against a broad range of plants and is used as a defoliant on many crops. The compound binds tightly to soil particles following application and becomes inactivated. However, this compound is classified as a class I toxicant with an oral LD50 of 150 mg/kg (rat).

The bipyridinium compounds such as paraquat and diquat are caustic and irritant agents, which cause ulceration and necrosis of the skin and mucous membranes. They also cause progressive irreversible pulmonary fibrosis. Paraquat is actively taken up by the alveolar cells via a diamine or polyamine transport system where it undergoes Nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction. These are easily reduced to the radical ions, which generate superoxide radical that reacts with unsaturated membrane lipids. The excess of superoxide anion radical O_2^- and H_2O_2 cause damage to the cellular membrane in lungs, which reduces the functional integrity of lung cells, affects efficient gas transport and exchange, and results in respiratory impairment. Diquat is also a very reactive compound and exerts its action in a similar manner but affects liver and kidney but does not cause pulmonary edema or alter lung function. Signs of CNS excitement and renal impairment occur in severely affected patients.

Most poisoning cases, which are often fatal, are due to accidental or deliberate ingestion of paraquat. Toxicity results from lung injury, resulting from both the preferential uptake of paraquat by the lungs and the redox cycling mechanism.

There is no specific treatment for paraquat or diquat poisoning. Treatment is supportive and symptomatic. Oxygen therapy is contraindicated because it will act as a ready source for the formation of more and more superoxides.

4.4.1 Organophosphate and Carbamate Insecticides

4.4.1.1 Mechanism of Action

OP and CM insecticides share a common mode of toxicological action associated with their ability to inhibit the ChE enzyme within the nervous tissue and at the neuromuscular junction (NMJs). Both types of insecticides are known as AChE inhibitors. AChE inhibitors (which, for brevity, have been referred to as cholinesterase (ChE) inhibitors) are chemicals whose primary toxic effect is to block the

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normal breakdown of the neurotransmitter, acetylcholine. This breaking down is done by occupying and blocking the site where the neurotransmitter—acetylcholine—attaches to the enzyme—AChE. Organophosphate (OP) and carbamate CM) insecticides produce their toxicity by inactivation of AChE enzyme at the synapses in the nervous tissue and neuromuscular junctions, and in RBCs. Therefore, the cholinesterase-inhibiting property of organophosphates or carbamates may be used to indicate degree of exposure if the activity of the blood/RBC-AChE is determined during an early period of exposure. These insecticides are known to exert deleterious effects on fish and wildlife as well as on domestic species. In no event should amounts greater than those specifically recommended be used, and maximal precautions should be taken to prevent drift or drainage to adjoining fields, pastures, ponds, streams, or other premises outside the treatment area. A brief mechanism of action of these OP and CM compounds is given under Figs. 4.1, 4.2, 4.3 and 4.4. The first step is the breakdown of ACh to acetic acid and choline (Fig. 4.1).

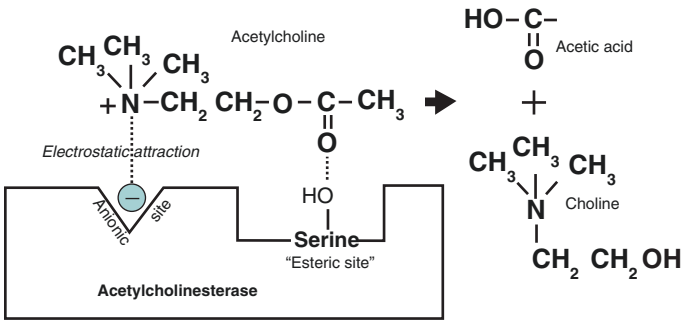


Fig. 4.1 Breakdown of acetylcholine. (https://www.atsdr.cdc.gov/csem/cholinesterase/images/acetylcholinesterase.png)

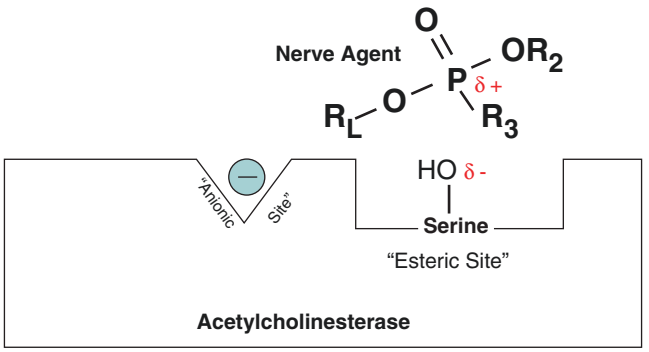


Fig. 4.2 Partially electropositive phosphorus is attracted to partially electronegative serine. δ + Indicates that phosphorus is partially electropositive. δ – Indicates that oxygen is partially electronegative. (https://www.atsdr.cdc.gov/csem/cholinesterase/images/agent_binding.png)

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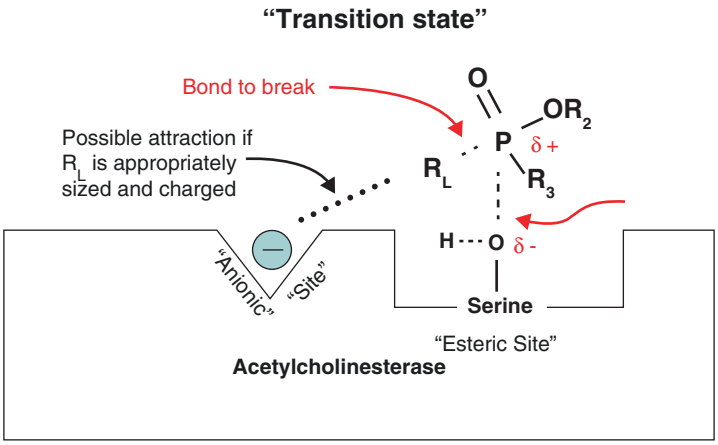


Fig. 4.3 Transition state showing which bonds break and which bonds form. δ + Indicates that phosphorus is partially electropositive. δ – Indicates that oxygen is partially electronegative. (https://www.atsdr.cdc.gov/csem/cholinesterase/images/transition_state.png)

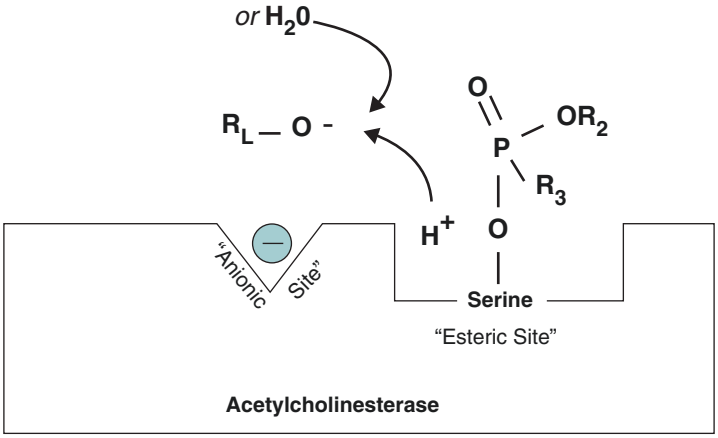


Fig. 4.4 Cholinesterase inhibitor attached to acetylcholinesterase preventing the attachment of acetylcholine. (https://www.atsdr.cdc.gov/csem/cholinesterase/images/esteric_binding.png)

Step 1

Step 2

The second figure (Fig. 4.2) shows how a cholinesterase (ChE) inhibitor (in this case, a nerve agent) attaches to the serine hydroxyl group on ChE. This prevents acetylcholine (ACh) from interacting with the ChE enzyme and being broken down.

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Step 3
The third step shows (Fig. 4.3) how molecular bond changes. The figure shows transition state showing which bonds break and which ones are formed.

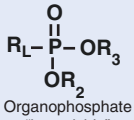
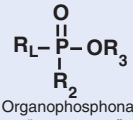
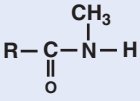
Step 4
In the fourth step, ChE inhibitor gets attached to acetylcholinesterase (AChE), thereby preventing the attachment of ACh (Fig. 4.4). This leads to the buildup of excessive levels of the neurotransmitter ACh, at the skeletal neuromuscular junction and those synapses where ACh receptors are located. Thus, the primary manifestations of acute ChE inhibitor toxicity are those of cholinergic (neurotransmitter) hyperactivity. There are also other delayed and chronic pathological effects of inhibitors of the cholinesterase enzyme which are less well understood. ChE inhibitors can have effects on a variety of non-cholinesterase enzymes and neurotransmitters as well. However, the significance of these effects is not well understood.

4.4.1.2 Differences Between Organophosphate and Carbamate Toxicity

Key differences between two classes of ChE inhibitors (organophosphorus compounds and carbamates) are summarized in Table 4.1.

Action of both OP and CM compounds leads to accumulation of ACh at both muscrinic and nicotinic receptors. Since the cholinergic system is widely distributed within both the central and peripheral nervous systems, chemicals that inhibit AChE are known to produce a broad range of well-characterized symptoms of ACh poisoning (both muscrinic and nicotinic types. OPs and CMs are considered as irreversible and reversible AChE inhibitors, respectively.

Table 4.1 Key differences between two classes of ChE inhibitors (organophosphorus compounds and carbamates)

	Organophosphorus Compounds	Carbamates
Molecular "R" denotes a variety of groups that attach to the basic structure "P = S" of organophosphorus compounds can be substituted for "P = O" "RL" of organophosphates may attach via an "O" to "P"	 Organophosphate "insecticide"  Organophosphonate "nerve agent"	 Carbamate "insecticide"
Toxicity	Higher	Lower
Duration of action	Longer	Shorter
CNS toxicity	More common	Less common

https://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=5

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Table 4.2 OP and CM insecticide-induced muscrinic and nicotinic signs of toxicity

	Site of Action	Physiological Effects
Muscrinic (parasympathetic effects)	Sweat glands	Excessive sweating lead to hypothermia and electrolyte balance
	Pupil	Constricted
	Lacrimal glands	Lacrimation (red tears)
	Salivary gland	Excessive salivation
	Bronchial trees	Wheezing
	GI tract	Cramps, vomiting, diarrhea, and tenesmus
	Cardiovascular	Bradycardia, fall in BP
	Ciliary body bladdery	Blurred vision
	Bladder	Urinary inconsistence
Nicotinic effects	Striated muscles	Fasciculations, cramps, weakness, twitching, paralysis, respiratory distress, and cyanosis/ arrest
	Sympathetic ganglia	Tachycardia, BP raised
	CNS effects	Anxiety, restlessness, ataxia, and convulsions

Muscrinic and nicotinic effects produced by OP and CM insecticides are summarized in Table 4.2. Muscarinic receptor–associated effects are manifested by vomiting; abdominal pain; salivation, lacrimation, urination, and diarrhea (SLUD); miosis (pinpoint pupils); tracheobronchial secretion; lung edema; and cyanosis. The nicotinic receptor–associated effects are produced on autonomic ganglia and skeletal muscles, and the affected animals show twitching of muscles, tremors, followed by convulsions and seizures. This condition may lead to paralysis. The central effects include apprehension and stimulation, followed by depression, restlessness, ataxia, stiffness of the neck, and coma. Onset of death occurs due to respiratory failure and cardiac arrest. However, there are variations in clinical signs (as described earlier) depending upon the OP or CM compound and route of exposure. The poisoned individuals usually recover within 3–6 h with CMs and within 24 h with Ops; some individuals exposed to OP nerve agents may show signs of toxicity for days.

Poisoning cases of OP or CM are usually diagnosed based on clinical signs and quantified levels of AChE inhibition in blood. Inhibition of AChE activity is considered a positive case of poisoning. However, there is great species variability in normal values of AChE activity.

In OP poisoning, antidotal treatment such as the combined use of atropine sulfate and pyridine-2-aldoxime methochloride should be provided. Atropine sulfate acts by blocking the muscarinic receptors from ACh. The use of morphine, aminophyline, phenothiazine, reserpine, and so on. is to be avoided. However, use of respiratory support and correction of dehydration should be maintained.

4.4.1.3 OP-Induced Delayed Neurotoxicity

OP compounds such as triaryl phosphates (e.g., triorthocresyl phosphate) have been used as flame retardants, plasticizers, lubricating oils, and hydraulic fluids. They are weak ChE inhibitors but do inhibit “neurotoxic esterase” (NTE) present in the brain

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and spinal cord. A form of delayed neurotoxicity results from the inhibition and aging of NTE, often referred to as OP-induced delayed neuropathy (OPIDN). Triaryl phosphates have caused accidental poisonings in people and other species (mostly cattle). Some other OPs, including Ethyl p-nitrophenyl (EPN), leptophos, parathion, haloxon, diisopropylphosphorofluoridate, and tetraethyl pyrophosphate, are known to cause OPIDN, and field cases have been seen. The lesions associated with delayed neurotoxicity include demyelination of peripheral and spinal motor tracts due to loss of neurotoxic esterase function. Clinical signs associated with delayed neurotoxicity include muscle weakness and ataxia that progresses to flaccid paralysis. Signs are usually not manifest until 10–14 days after exposure to a neurotoxic triaryl phosphate. There are no specific antidotes.

4.4.2 Chlorinated Hydrocarbon Compounds (Toxicity)

Because of persistent tissue residues and chronic toxicity, use of chlorinated hydrocarbon compounds has been drastically curtailed. Only lindane and methoxychlor are approved for use on or around livestock. Detectable residues of some chlorinated hydrocarbon insecticides, including BHC, heptachlor, heptachlor epoxide, lindane, and oxychlordane, can be found in fatty tissue after acute or chronic exposure.

There are no known specific antidotes to chlorinated hydrocarbon compound poisoning. When exposure is by spraying, dipping, or dusting, a thorough bathing without irritating the skin (no brushes), using detergents and copious quantities of cool water, is recommended. If exposure is by ingestion, gastric lavage and saline purgatives are indicated. The use of digestible oils such as corn oil is contraindicated; however, heavy-grade mineral oil plus a purgative hastens the removal of the chemical from the intestine. Activated charcoal appears to be useful in preventing absorption from the GI tract. When signs are excitatory, a sedative anticonvulsant such as a barbiturate or diazepam is indicated. Residues in exposed animals may be reduced by giving a slurry of activated charcoal or providing charcoal in feed. Feeding phenobarbital, 5 g/day, may hasten residue removal.

4.4.3 Insecticides Derived from Plants (Toxicity)

4.4.3.1 Natural Plant Extracts

Extracts from natural plants have been used for centuries to control insects. The commonly used natural insecticides include (derris) nicotine, pyrethrum, rotenone (derris plant) (Fig. 4.5), and neem extracts, made by plants as defenses against insects. Natural insecticides are usually nontoxic to humans and pets and safe for the environment. Pets are exposed to tobacco by ingesting commercial tobacco products (e.g., cigarettes or chewing tobacco), whereas livestock may consume discarded tobacco stalks or hay contaminated with tobacco plant drippings in the barn.

Affected animals show tremors, incoordination, nausea, disturbed respiration, muscle paralysis, and finally coma and death. Nicotine and related alkaloids from

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Fig. 4.5 (**a**) Nicotine plant. (http://www.thetortoisetable.org.uk/common/files/catalogue/475/large/tobaccoplant_nicotiana%20spp_solanaceae_lr_oct09%201%206.jpg). (**b**) Chrysanthemum flowers—source of natural pyrethrin. (http://flowerinfo.org/wp-content/gallery/chrysanthemum-flowers/chrysanthemum-flower-3.jpg). (**c**) Derris plant—root is the source of rotenone. (Reproduced from https://commons.wikimedia.org/wiki/File:Starr_990106-3021_Derris_elliptica.jpg)

tobacco can cross the placenta and produce teratogenic effects. Recovery from sublethal doses is usually complete within 3 h. Death occurs within a matter of hours from paralysis of thoracic respiratory muscles and cardiac arrest. Necropsy may reveal parts of tobacco leaves or stalks in the rumen contents. Lesions include pale mucous membranes, dark blood, hemorrhages on the heart and in the lungs, and congestion of the brain. Treatment consists of removing the material by washing or by gastric lavage with tannic acid, administering activated charcoal, providing artificial respiration, and treating for cardiac arrest and shock.

4.4.3.2 Pyrethrins

Pyrethrins are insecticides obtained from the flowers of C cinerariaefolium and have been used as insecticides for many years. Pyrethrins and pyrethroids produce toxicity affecting primarily the sodium channel but also chloride and calcium channels of nerve cells. These insecticides also interact with nicotinic ACh receptors. Synergists, such as piperonyl butoxide, sesamex, piperonyl cyclonene, and so on, are added to increase stability and effectiveness. This is accomplished by inhibiting mixed function oxidases, enzymes that detoxify pyrethrins and pyrethroids; unfortunately, this also potentiates mammalian toxicity.

4.4.3.3 D-Limonene

D-Limonene is the major component of the oil extracted from citrus rind. It is used for the control of fleas on cats and for other insect pests. Adult fleas and eggs appear to be most sensitive to D-limonene, which is more effective if combined with the synergist piperonyl butoxide. At recommended dosages, the solution containing D-limonene appears to be safe, but increasing the concentration 5–10-fold in sprays or dips increases the severity of toxic signs, which include hypersalivation, muscle tremors, ataxia, and mild-to-severe hypothermia. The inclusion of piperonyl butoxide in the formulation potentiates the toxicity in cats. Allergies have also been reported in people in contact with D-limonene, and it appears to increase dermal absorption of some chemicals. When orally administered to dogs, D-limonene causes vomiting. No antidote is available.

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4.4.4 Synthetic Pyrethroid Insecticides

Pyrethroids are synthetic derivatives of natural pyrethrins. There are two types of pyrethroids.

(a) Type I compounds that lack an α-cyano substituent include pyrethrin I, allethrin, tetramethrin, kadethrin, resmethrin, phenothrin, and permethrin. Type II compounds that contain a stabilizing α-cyano-3-phenoxybenzyl component include cyfluthrin, cypermethrin, fenpropanthrin, deltamethrin, cyphenothrin, fenvalerate, and fluvalinate. Type I pyrethroids produce a neurologic syndrome through their effects on both the central and peripheral nervous systems, with signs including tremors, incoordination, prostration, seizures, and death.
(b) Type II pyrethroids work primarily through CNS mechanisms to exert the choreoathetosis/salivation syndrome, characterized by hyperactivity, hunched back, salivation, tremors, and incoordination, progressing to sinuous writhing movements.

Diagnosis of pyrethrin/pyrethroid poisoning is based on clinical signs, history of exposure, and determination of insecticide residue in body tissues and fluids. These insecticides do not produce characteristic pathologic lesions.

Generally, symptomatic and supportive treatment is required after ingestion of a dilute pyrethrin or pyrethroid preparation. Toxicity may also be due to the solvent. Induction of emesis may be contraindicated. A slurry of activated charcoal, followed by a saline cathartic (magnesium or sodium sulfate) may be used. Vegetable oils and fats, which promote the intestinal absorption of pyrethrum, should be avoided. If dermal exposure occurs, the animal should be bathed with a mild detergent and cool water. The area should be washed very gently so as not to stimulate the circulation and enhance skin absorption. Initial assessment of the animal's respiratory and cardiovascular integrity is important. Further treatment involves continuing symptomatic and supportive care. Seizures should be controlled with either diazepam, phenobarbital, or pentobarbital can be used if diazepam or methocarbamol are too short acting.

4.5 Fungicides

The fungicide, chlorothalonil (tetrachloroisophthalonitrile), is a broad-spectrum fungicide which is used widely in urban environments. It is relatively cheap and controls some 140 species of organisms. As a result of the popularity of this compound, it is found routinely in surface waters entering public drinking water supplies. In the formulation that can be purchased by the general public, it is relatively nontoxic. Other fungicides such as captan, captafol, folpet, dithiocarbamates, sulfur derivatives of dithiocarbamic acid, and metallic dimethyldithiocarbamates are commonly used. The latter group includes mancozeb (a coordination product of zinc ion and manganese ethylene bisdithiocarbamate), maneb (manganese ethylenebisdithiocarbamate), and

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zineb (zinc ethylenebisdithiocarbamate). All are effective fungicides are used on a variety of crops, including grapes, sugar beets, and ornamental plants. Although relatively nontoxic, they do hydrolyze and produce known carcinogens such as ethylthiourea (ETU). In most cases, there is no specific treatment. Treatment is symptomatic and supportive.

4.6 Rodenticide Poisoning

This class of compounds is used to control rodents that cause yearly losses of 2–30% in grain and other food storage facilities. Rodenticide—fluoroacetamide—is a fast-acting poison with an oral LD_{50} (rat) of 15 mg/kg. This material is supplied as bait pellets or grains. α -naphthylthiourea (ANTU), strychnine, and thallium salts, zinc phosphide, and so on, are other fast-acting poisons and have been on the market for many years. Many poisons have been used against rodent pests. If baits are not well secured, they may be ingested directly by nontarget animal species (farm animals, pets, and wildlife). Sometimes, nontarget species may ingest recently poisoned rodent pests and develop relay or secondary poisoning. Occasionally, baits may be used maliciously or intentionally to kill either domestic animals or wildlife. This chapter discusses only the most commonly used rodenticides currently available in the market: Anticoagulants, bromethalin, cholecalciferol, and zinc phosphide. Strychnine poisoning (see Chap. 11) is discussed separately. There is no specific antidote. Supportive and symptomatic treatment is suggested.

4.6.1 Anticoagulant Rodenticides (Warfarin and Congeners)

Warfarin and Congeners known as anticoagulant rodenticides inhibit the enzyme vitamin K epoxide reductase, which normally reactivates vitamin K, a crucial component in a number of normal clotting factors, after those factors are consumed in normal maintenance. Potentially dangerous to all mammals and birds, anticoagulant rodenticides are a common cause of poisoning in pets and wildlife. Intoxications in domestic animals have resulted from contamination of feed with anticoagulant concentrate, malicious use of these chemicals, and feed mixed in equipment used to prepare rodent bait.

All anticoagulants have the basic coumarin or indanedione nucleus. The “first-generation” anticoagulants (warfarin, pindone, coumafuryl, coumachlor, isovaleryl indanedione, and others less frequently used) require multiple feedings to result in toxicity. The “intermediate” anticoagulants (chlorophacinone and, in particular, diphacinone) require fewer feedings than “first-generation” chemicals, and thus they are more toxic to nontarget species. The “second-generation” anticoagulants (brodifacoum, bromadiolone, difethiolone) are highly toxic to nontarget species (dogs, cats, livestock, or wildlife) after a single feeding. Secondary poisoning in nontarget animal species from anticoagulants has also been documented. Anticoagulants antagonize vitamin K, which interferes with the normal synthesis of

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coagulation proteins (factors I, II, VII, IX, and X) in the liver; thus, adequate amounts are not available to convert prothrombin into thrombin. After ingestion, the affected individuals show signs of hemorrhages of gums, epistaxis, and massive internal bleeding, followed by shock and death.

In acute toxicity with warfarin, Vitamin K_1 is antidote; if the poisoning is severe, blood transfusions should be provided. For poisoning due to other rodenticides, the treatment is supportive and symptomatic.

4.6.2 Nonanticoagulant Rodenticide (Bromethalin)

Bromethalin, a nonanticoagulant, single-dose rodenticide, is a neurotoxin available as bars (blocks), pellets, seed, and worm. Bromethalin and its main metabolite desmobromethalin are strong uncouplers of oxidative phosphorylation. This results in intra-myelin fluid accumulation, leading to long nerve demyelination and intramyelin cerebral edema. The net result is cerebral and spinal edema and increased CSF pressure, leading to neurologic dysfunction. Dogs are more commonly involved. Cats are 2–3 times more sensitive than dogs. Presumptive diagnosis of bromethalin toxicosis is made based on known or suspected history of exposure to the bait, followed by development of neurologic signs within 1–7 days of exposure. Treatment of bromethalin toxicosis is aimed at early decontamination (induction of emesis and administration of activated charcoal) in an asymptomatic animal and controlling CNS signs (seizures) and providing supportive care in a symptomatic animal. Emesis using 3% hydrogen peroxide solution or apomorphine in dogs and xylazine in cats within 4 h of ingestion may remove some bait from the gut. Depending on the ingested dose of bromethalin, administration of activated charcoal is considered an effective method to prevent toxicosis.

4.6.3 Cholecalciferol Toxicosis

Cholecalciferol (vitamin D_3) is used both as a dietary supplement and as a rodenticide. It appears to be toxic at a much lower dose when consumed in a bait form than when ingested as a technical grade agent. Cholecalciferol toxicosis is characterized by hyperphosphatemia and hypercalcemia, leading to renal failure, cardiac abnormalities, hypertension, CNS depression, anorexia, vomiting, diarrhea, and lethargy. The increased calcium and phosphorus can lead to calcification of soft tissue, notably the highly vascular areas of kidneys and lungs, as well as within the walls of the great blood vessels.

Clinical initial signs can include depression, anorexia, polyuria, and polydipsia. Nausea, vomiting, hematemesis, and depression are common as the clinical signs progress. It is important to obtain a baseline biochemistry profile as early as possible after the exposure, so that each animal can be monitored based on individual values.

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Ingestion of vitamin D_3 may require decontamination (induction of emesis and administration of activated charcoal) and monitoring of serum calcium, phosphorus, and renal values. Emesis can be induced with 3% hydrogen peroxide or apomorphine in dogs and xylazine in cats. Activated charcoal may be helpful. In addition, use of cholestyramine, a bile acid sequestrant, may be useful to decrease the body burden of vitamin D_3 that undergoes enterohepatic recirculation with bile acids. However, the efficacy of cholestyramine to reduce vitamin D_3 levels in dogs has not been determined. Calcium and phosphorus levels should be monitored and treated until they return to baseline.

4.6.4 Zinc Phosphide

Among rodenticides, zinc phosphide is a component in a number of animal baits, such as mole, gopher, ground squirrel, and vole, intended for outdoor use only. There is evidently no way to identify this grain mixture, and bait ingestion has resulted in lethal exposure to a number of horses. The clinical effects of aluminum phosphide, used as a grain fumigator, are similar to those of zinc phosphide.

Lethal doses of zinc phosphide vary markedly between species and are much more toxic to species unable to vomit. The phosphide salts are unstable in an acid environment. At gastric pH, they degrade rapidly to form phosphine gas. Presence of food in the stomach, which will trigger release of gastric acid, increases the rate of this transition. Zinc phosphide is thought to block cytochrome C oxidase, leading to formation of highly reactive oxygen compounds, which cause most of the tissue injury; the most severe damage is in tissues with the highest oxygen demand, that is, brain, lungs, liver, and kidney.

Phosphine gas, when inhaled, results in acute noncardiogenic pulmonary edema. Vomiting, often hemorrhagic, is a common presenting sign in animals capable of vomiting. Tachypnea, ataxia, weakness, trembling, collapse, seizures, and death may ensue. Phosphine gas is a public health hazard. Animal owners and veterinary staff members must be cautious while inducing emesis, because they can be exposed to phosphine gas from the presence of zinc phosphide bait in the stomach contents after vomiting. The gas is reported to have a garlic-like or fishy odor.

Management of zinc phosphide ingestion relies on effective decontamination. If the animal has not already vomited, emesis can be induced by use of apomorphine. Decreasing gastric acid may be beneficial, via oral magnesium hydroxide antacid or using famotidine. Intravenous (IV) fluid support is recommended while the animal is under observation. Use of activated charcoal may be considered; although metals are poorly bound by activated charcoal, the larger zinc phosphide molecule may be. If vomiting is ongoing, administration of activated charcoal should be avoided because of the aspiration risk. Use of *N*-acetylcysteine may be beneficial; administration of *S*-adenosyl methionine (SAM-e) may also be beneficial. Seizures should be controlled with diazepam or barbiturates, and other signs should be treated symptomatically.

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4.7 Molluscicide Poisoning

Metaldehyde, a cyclic polymer of acetaldehyde, is the active component in molluscicides used to control slugs and snails. It is commonly used in wet coastal areas worldwide. This neurotoxicant has been associated with poisoning in a variety of domestic and wildlife species, although most poisonings have been reported in dogs and are related to careless placement of bait. Metaldehyde may be combined with other agents such as carbamate insecticides to enhance efficacy. After ingestion, metaldehyde undergoes partial hydrolysis in the stomach to produce acetaldehyde. Both metaldehyde and acetaldehyde are readily absorbed from the GI tract. The nature of the stomach contents and the rate of gastric emptying influence the rate of absorption and the onset of the clinical syndrome. The clinical syndrome is similar in most species. Neurologic manifestations, which predominate, develop within 1–3 h. after ingestion. Severe muscle tremors, anxiety, hyperesthesia, ataxia, tachycardia, and hyperthermia may be evident initially. As the acidosis becomes more severe, depression and hyperpnea may become more evident. As the syndrome progresses, opisthotonos and continuous tonic convulsions that are unresponsive to external stimuli (in contrast to those in strychnine poisoning) are typical manifestations. Emesis, diarrhea, hypersalivation, colic, cyanosis, sweating (horses), mydriasis, and nystagmus (cats) are often reported. There is no specific treatment for metaldehyde poisoning. Supportive and symptomatic treatment such as activated charcoal and cathartics may be administered to assist in decontamination and to reduce enterohepatic cycling of metaldehyde. Diazepam may be used to control neurologic manifestations.

4.8 Solvents and Emulsifier Toxicity

During formulation of pesticide, several types of solvents and emulsifiers such as acetone, isopropyl alcohol, methanol, and so on, are used. These compounds are well known for their toxicity. For example, acetone toxicity leads to GI irritation, narcosis, and kidney and liver damage are the main signs of acetone poisoning. Treatment consists of gastric lavage, oxygen, and a low-fat diet. Additional supportive treatment to alleviate clinical signs may be provided.

Symptoms of Isopropyl alcohol poisoning are GI pain, cramps, vomiting, diarrhea, and CNS depression (dizziness, stupor, coma, and death from respiratory paralysis). The liver and kidneys are reversibly affected. Dehydration and pneumonia may occur. Treatment consists of emetics, gastric lavage, milk, oxygen, and artificial respiration.

Typical signs of methanol poisoning include nausea, vomiting, gastric pain, reflex hyperexcitability, opisthotonos, convulsions, fixed pupils, and acute peripheral neuritis. Large overdoses can lead to blindness. Toxic effects are due in part to the alcohol itself, and in part to formic acid produced by its oxidation. Treatment should include emetics (apomorphine) followed by gastric lavage with 4% sodium

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bicarbonate, saline laxative, oxygen therapy, sodium bicarbonate solution IV, and analgesics; however, the prognosis is poor. Intensive and prolonged alkalinization is the mainstay of treatment. Ethanol retards the oxidation of methanol and may be given as an adjunct therapy.

4.9 Sulfur and Lime-Sulfur

(for details please also see Chap. 5 dealing with metals and micronutrients)

Sulfur and lime-sulfur are two of the oldest insecticides. Elemental sulfur is practically devoid of toxicity, although poisoning has occurred occasionally when large amounts were mixed in cattle feed. Specific toxic dosages are not known but probably exceed 4 g/kg. Lime-sulfur, which is a complex of sulfides, may cause irritation, discomfort, or blistering but rarely causes death. Treatment consists of removing residual material and applying bland protective ointments, plus any supportive measures that may be indicated.

4.10 Questions and Answers

4.10.1 Short Questions and Answers

Exercise 1

Q.1. Which pesticides are commonly used for malicious poisoning in animals?
- (a) Organophosphorus insecticides
- (b) Carbamates
- (c) Rodenticides
- (d) Fumigants such as aluminum phosphide and zinc phosphide
- (e) Pyrethroid insecticides

Q.2. How are animals exposed to pesticides?
- The most common exposure scenarios for pesticide poisoning cases are:
  - (a) Accidental
  - (b) Suicidal poisonings
  - (c) Occupational exposure
  - (d) By exposure to off-target drift
  - (e) Through environmental contamination
  - (f) aerial spray

Q.3. Why is fever observed in atropine poisoning?
- Atropine poisoning causes decreased secretions in the body and, occasionally, therapeutic doses dilate cutaneous blood vessels, particularly in the "blush" area (atropine flush), and it may cause atropine "fever" due to suppression of sweat gland activity, especially in infants and small children.

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Q.4. Describe the mechanism of action of 2-PAM
- In organophosphate poisoning, organophosphates bind to just one end of the ChE enzyme (the esteric site), blocking its activity. Pralidoxime is able to attach to the other half (the unblocked, anionic site) of the acetylcholinesterase enzyme. It then binds to the organophosphate, the organophosphate changes conformation, and loses its binding to the acetylcholinesterase enzyme. The conjoined poison/antidote then unbinds from the site and thus regenerates the enzyme, which is now able to function again.

Q.5. Describe mode of action of paraquat herbicide.
- Paraquat is actively taken up by the alveolar cells via a diamine or polyamine transport system where it undergoes NADPH-dependent reduction. These are easily reduced to the radical ions, which generate superoxide radical that reacts with unsaturated membrane lipids. The excess of superoxide anion radical O_2^- and H_2O_2 cause damage to the cellular membrane in lungs, which reduces the functional integrity of lung cells, affects efficient gas transport and exchange, and results in respiratory impairment including pulmonary fibrosis.

Q.6. Why are OC insecticides being discouraged/banned?
- OC insecticides are not degradable and are persistent in the environment. And due to high lipid solubility, they accumulate in the food chain and enter human and animal bodies. Hence, OC compounds are being discouraged.

Q.7. Why are OP compounds preferred as insecticides for the crops?
- OP compounds are biodegradable and hence are not persistent in environment. Further, they are easily destroyed by sunlight, water, microbes, alkalis, metals, and so on. Hence, within 2–4 weeks of application, OP compounds are destroyed. However, they have considerable toxicity for mammals if consumed directly.

Q.8. Can we use phenothiazine derivatives as treatment in pyrethroid insecticide poisoning?
- No. Use of phenothiazine derivatives is contraindicated.

Q.9. Why is lung tissue primarily affected by paraquat?
(a) Paraquat accumulates up to ten times in lungs.
(b) Lung tissue is deficient in superoxide dismutase (SOD) enzyme, which destroys superoxide radical. Hence, lungs are primarily affected.

Q.10. Despite being highly toxic, why do bipyridyl herbicides not produce toxicity after being sprayed on plants?
(a) Bipyridyl herbicides are used in very low doses, which are not toxic.
(b) They are inactivated immediately upon contact with soil.

Q.11. How do paraquat and diquat differ in their toxicity?
- During paraquat exposure, toxicity results from lung injury, resulting from both the preferential uptake of paraquat by the lungs and the redox cycling mechanism. Pulmonary fibrosis is the usual cause of death in paraquat poisoning.

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During diquat poisoning, renal damage results from both the preferential uptake of diquat by the kidney and the redox cycling mechanism. No progressive pulmonary fibrosis has been noted in diquat poisoning. However, diquat has severe toxic effects on the central nervous system that are not typical of paraquat poisoning.

Q.12. Is the use of oxygen beneficial in paraquat poisoning?
- Use of supplemental oxygen is contraindicated until the patient develops severe hypoxemia.
  High concentrations of oxygen in the lung increase the injury induced by paraquat and possibly by diquat as well.

Q.13. Despite being very specific to rats, why is ANTU banned?
- Due to carcinogenic potential of alpha naphthylamine impurities, ANTU is banned.

Q.14. What is the difference between pulmonary toxicity caused by ANTU (rodenticide) and paraquat (herbicide)?
- ANTU causes pulmonary edema and is fatal, whereas paraquat causes pulmonary fibrosis, which is not fatal.

Q.15. What materials are used as fertilizer?
- Many different materials are used as fertilizers. Fertilizers typically provide, in varying proportions, the three major plant nutrients (nitrogen, phosphorus, and potassium), the secondary plant nutrients (calcium, sulfur, magnesium), and sometimes trace elements (or micronutrients) with a role in plant nutrition: Boron, chlorine, manganese, iron, zinc, copper, and so on. The actual nutrient level can vary, depending on the source.

4.10.2 Multiple Choice Questions

Exercise 2

(Choose the correct statement—it may be one, two or none)

Q.1. Zinc phosphide releases phosphine gas in the following pH:
(a) Acidic
(b) Basic
(c) Neutral
(d) All

Q.2. The following rodenticides require multiple administration to cause death
(a) Zinc phosphide
(b) Anticoagulants
(c) Vitamin
(d) Strychnine

Q.3. OP compounds can inhibit the following enzyme(s)
(a) AChE
(b) BuChE
(c) NTE
(d) All

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Q.4. The following type of toxicity caused by OP compounds is irreversible even with treatment
(a) Acute
(b) Subacute
(c) Chronic
(d) OPIDN

Q.5. Which of the following insecticides are more specific to arthropods?
(a) OC compounds
(b) OP compounds
(c) Carbamates
(d) Pyrethroids

Q.6. Paraquat and diquat differ substantially in their
(a) Metabolism to a free radical
(b) Ability to initiate lipid peroxidation in vivo
(c) Uptake by the lung
(d) Generation of superoxide anion in vivo
(e) Mechanism of cytotoxicity

Q.7. Toxic injury to the cell body, axon, and surrounding Schwann cells of peripheral nerves are referred to, respectively, as
(a) Neuropathy, axonopathy, and myelopathy
(b) Neuronopathy, axonopathy, and myelinopathy
(c) Neuropathy, axonopathy, and gliosis
(d) Neuronopathy, dying-back neuropathy, and myelopathy
(e) Chromatolysis, axonopathy, and gliosis

Q.8. The following OC insecticides are not persistent in environment
(a) DDT
(b) Aldrin
(c) Methoxychlor
(d) Endosulfan

Q.9. The most commonly used pyrethroid synergist is
(a) Silica
(b) Piperonyl butoxide
(c) Methyl butyl ether
(d) N-octyl bicyloheptene dicarboximide
(e) Toluene

Q.10. The chloronicotinyl compound imidacloprid demonstrates a high insecticidal potency and exceptionally low mammalian toxicity due to
(a) Its high affinity for insect nicotinic acetylcholine receptors and low affinity for mammalian nicotinic acetylcholine receptors
(b) The blood-brain barrier in mammals
(c) The first pass effect in the liver in mammals
(d) The low pH in the stomach of monogastric mammals
(e) The presence of true acetylcholinesterase in mammals

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Answers

Exercise 2

1. a	6. a
2. b and c	7, b
3. d	8. c and d
4. d	9. b
5. d	10. a

4.10.3 Fill in the Blanks

Exercise 3

Q.1. OC compound insecticides act by inhibiting _____ receptors.
Q.2. Hyperthermia in OC insecticide poisoning is due to changes in metabolism of _____ and _____ neurotransmitters.
Q.3. The metabolite of Dichloro-diphenyl-trichloro-ethane (DDT) is _____.
Q.4. DDT acts as agonist for _____ receptors, and DDE acts as antagonist for _____ receptors.
Q.5. DDE, the metabolite of DDT, causes thinning of egg shells due to inhibition of _____ enzyme.
Q.6. The predominant symptoms in OC insecticide poisoning are _____ and _____.
Q.7. The sedatives of choice used in OC insecticide–induced CNS excitation is _____.
Q.8. Death in OC compound poisoning is due to _____ failure.
Q.9. Organic insecticides, which are esters of phosphorus, are _____ compounds.
Q.10. OP insecticides act as irreversible inhibitors of _____ enzyme.
Q.11. The use of oxime reactivators is contraindicated in _____ insecticide poisoning.
Q.12. Voltage-gated sodium channels are more sensitive for _____ type of pyrethroids.
Q.13. The metabolite of zinc phosphide that is produced in the body is _____. (Hypophosphite is excreted in urine).
Q.14. Phosphine gas acts as _____ poison.
Q.15. Bait shyness is not observed with _____ rodenticides.
Q.16. Warfarin inhibits clotting factors, which are dependent on _____ for synthesis.
Q.17. Anticoagulant rodenticides decrease vitamin K synthesis through inhibition of _____ enzyme.
Q.18. Capillary damage seen in warfarin rodenticides is due to the presence of _____ chemical moiety.

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Q.19. The hematological tests used to confirm poisoning from anticoagulants are _____ and _____.
Q.20. The specific treatment for anticoagulant poisoning is _____.

Answers

Exercise 3

1. GABA
2. Serotonin and noradrenaline
3. (DDE)
4. Estrogen, androgen
5. CalciumATPase
6. Behavioral (nervous), hyperthermia
7. Benzodiazepines
8. Respiratory
9. Organophosphate (OP)
10. Acetyl choline esterase
11. Carbamate
12. Two
13. Hypophosphite
14. Protoplasmic
15. Anticoagulant
16. Vitamin K
17. Vitamin K epoxide reductase
18. Benzalactone
19. Clotting time and prothrombin time
20. Phytomendadione (Vitamin K_1)

4.10.4 True or False Statements

Write (T) for true and (F) for false statements

Exercise 4

Q.1. Sodium arsenate is less toxic than sodium arsenite.
Q.2. Synthetic pyrethroids are more toxic than naturally occurring Pyrethrins.
Q.3. Like mammalian species, pyrethroids are less toxic to aquatic organisms.
Q.4. Phosphine released from aluminum phosphide is less acutely toxic than methyl bromide.
Q.5. Specific antidote for diquat poisoning is atropine.
Q.6. Phase I reactions are detoxification reactions in the true sense.
Q.7. Mitochondrial fraction of the cell is a part of the microsomal fraction.
Q.8. Echothiopate is organochlorine compound, which interacts with both anionic and esteric site of AChE to produce stable complex.

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Q.9. Mammals are less susceptible to OP poisoning because of presence of enzyme carboxylesterase.
Q.10. Warfarin is not a coumarone derivative used in rodent control.

Answers

Exercise 4

1. T	6. F
2. F	7. F
3. T	8. F
4. F	9. T
5. F	10. F

4.10.5 Match the Statements

Exercise 5
Match the Column A with Column B

	Column A	Column B
Q.1	OP compound	a. Hemlock
Q.2	Organochlorine compound	b. Pyrethrin
Q.3	Pyrethroid synergist	c. Endosulfan
Q.4	Conium maculatum	d. Hen Test
Q.5	OP-Induced delayed neurotoxicity	e. Piperonyl Butoxide
Q.6	Amitraz	f. Serum
Q.7	Bipyridyl herbicide	. Miosis
Q.8	Rodenticide	h. Paraquat
Q.9	Diagnosis	i. Ziram
Q.10	Dithio-carbamates	j. Warfarin
Q.11	Zinc phosphide	k. Neonics
Q.12	Paraquat	l. Ureas
Q.13	Ammonia	m. Alpha 2 agonist
Q.14	Natural insecticide	n. Nitotinic
Q.15	Amitraz	o. Citric acid
Q.16	Herbicides	p. Lungs
Q.17	Tabun	q. Rotenone
Q.18	Neonicotinoids	r. Rat poison
Q.19	Fluoroacetate	s. Nerve agent
Q.20	Cholinergic receptors	t. Fertilizer

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Answers

Exercise 5

Match the column A with Column B

	Column A	Column B
Q.1	OP compound	g. Miosis
Q.2	Organochlorine compound	c. Endosulfan
Q.3	Pyrethroid synergist	e. Piperonyl Butoxide
Q.4	Conium maculatum	a. Hemlock
Q.5	OP Induced Delayed Neurotoxicity	d. Hen Test
Q.6	Chrysanthemum	b. Pyrethrin
Q.7	Bipyridyl herbicide	h. Paraquat
Q.8	Rodenticide	j. Warfarin
Q.9	Diagnosis	f. Serum
Q.10	Dithio-carbamates	i. Ziram
Q.11	Zinc phosphide	r. Rat poison
Q.12	Paraquat	p. Lungs
Q.13	Ammonia	t. Fertilizer
Q.14	Natural insecticide	q. Rotenone
Q.15	Amitraz	m. Alpha 2 agonist
Q.16	Herbicides	l. Ureas
Q.17	Tabun	s. Nerve agent
Q.18	Neonicotinoids	k. Neonics
Q.19	Fluoroacetate	o. citric acid
Q.20	Cholinergic receptors	n. Nicitinic

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Toxic Effects of Metals and Micronutrients

5

Abstract

This chapter deals with the adverse effects of a wide range of metals and micronutrients such as arsenic, lead, mercury, copper, fluoride, iron, molybdenum, selenium, zinc, salt poisoning, etc. that have an important role in animal practice. These metals have also been used to make utensils, machinery, and so on. These activities increased environmental levels of metals. More recently metals have found a number of uses in industry, agriculture, and medicine. These activities have increased exposure not only to metal-related occupational workers but also to animals through environmental contamination or through other sources. Despite the wide range of metals and their toxic properties, there are a number of toxicological features that are common to many metals. Toxicity of a few of these metals that are of veterinary importance have been briefly discussed.

Keywords

Metals · Micronutrients · Arsenic · Lead · Mercury · Copper · Fluoride · Iron · Molybdenum · Selenium · Zinc · Salt poisoning · Question and answer bank · Multiple choice questions

5.1 Introduction

Metals are certainly one of the oldest toxicants known to humans due to their very early use. Likewise, importance of micronutrients is well known. This chapter covers toxic potential of a wide range of metals and micronutrients such as arsenic, lead, mercury, copper, fluoride, iron, molybdenum, selenium, zinc, salt poisoning, etc. Arsenic was used early on for decoration in Egyptian tombs and as a "secret poison." These metals have also been used to make utensils, machinery, and so on. These activities increased environmental levels of metals. More recently metals have found a number of uses in industry, agriculture, and medicine. These activities have increased exposure not only to metal-related occupational workers but also to animals through environmental contamination or through other sources. Despite the wide range of metal toxicity and toxic properties, there are a number of

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toxicological features that are common to many metals. In this chapter, toxicity of a few of these metals that are of veterinary importance are discussed. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, true/false statements, and match the statements as relevant to toxicity of important metals and micronutrients related to animal health.

Key Points

- Metals are elements that form cations when compounds of it are in solution, and oxides of the elements form hydroxides rather than acids in water.
- Micronutrient is a chemical element or substance required in trace amounts for the normal growth and development of living organisms.
- Metals that provoke immune reactions include mercury, gold, platinum, beryllium, chromium, and nickel.
- Complexation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor, referred to as a ligand. Chelation occurs when bidentate ligands form ring structures that include the metal ion and the two ligand atoms attached to the metal.
- Metal-protein interactions include binding to numerous enzymes, the metallothioneins, nonspecific binding to proteins such as serum albumin or hemoglobin, and specific metal carrier proteins involved in the membrane transport of metals.
- Increased exposure to cadmium in combination with zinc, lead, and/or other metals results in toxicoses.
- All ruminants (including sheep, cattle, and goats) require cobalt in their diet for the synthesis of vitamin B12.
- Arsenic, certain chromium compounds, nickel, beryllium, cadmium, and cisplatin have carcinogenic potential.
- Metals lose electrons easily, and they often corrode easily. The oxides of metals tend to be basic, but the oxides of non-metals tend to be acidic.
- Non-metals show more variability in their properties than do metals. Non-metals if solid generally have a submetallic or dull appearance and are brittle, as opposed to metals, which are lustrous, ductile, or malleable.
- Exposures to non-metals act as irritant poisons and produce inflammation on the site of contact, especially in the GI tract, respiratory tract, and skin.
- Selenium (Se), a non-metal, is sometimes classified instead as a metalloid.
- Sulfur and lime sulfur are two of the oldest insecticides. Acute oral poisoning with elemental sulfur results in the formation of hydrogen sulfide, as well as many other potential metabolites.

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5.2 Arsenic (Sankhyal, Somalkar)

Arsenic is a ubiquitous element with several different forms. The toxicity of arsenic is determined by its form. The prevalent valences are the 13 and the 15 form. Arsenic is found in both an organic form and an inorganic form with valence numbers ranging from 13 to 15. As13, or arsenite, is more toxic than arsenate, or As15. It is found as different ores and rocks, which are mined and then smelted resulting in elemental arsenic and arsenic trioxide. In the environment, arsenic usually exists in the pentavalent form, and soil microorganisms may methylate it. Since it is ubiquitous in many forms, complete avoidance is nearly impossible.

5.2.1 Mechanism of Action

Arsenite (13) reacts with sulfhydryl groups (-SH) of proteins and inhibits the enzymes by blocking the active groups. The arsenite inhibits alpha-keto oxidases which contain dithiol groups and are involved in oxidation of pyruvate. Lipoic acid, an essential coenzyme for pyruvic acid oxidase, and alpha-oxyglutaric acid oxidase are inhibited by the arsenite. These play an essential role in the tricarboxylic acid cycle. Actively dividing cells having a high oxidative energy requirement are most susceptible to the effects of arsenicals. Arsenites induce vasodilation and can cause capillary damage. The cellular integrity of the capillary is affected by an unknown mechanism. Evidence of vascular instability is seen by the presence of congestion, edema, and hemorrhage in most of the visceral organs of animals with acute poisoning. This same mechanism of action occurs with inorganic arsenicals and with organic trivalent arsenicals, and they may be considered as "vascular poisons." Arsenates (15) are a little different. They are uncouplers of oxidative phosphorylation. The inorganic pentavalents may substitute phosphate in this reaction. The result is an increase in body temperature. Organic pentavalents have an unknown mechanism of action. There is some thought that they may interfere with vitamins B6 and B1, which may allow for the demyelination and subsequent axonal degeneration that occurs.

5.2.2 Toxicity

Inorganic arsenicals are up to ten times more toxic than pentavalent arsenicals. In other metal toxicities, the organics are more toxic, but with arsenicals the inorganics are the more toxic. Arsenic poisoning clinically manifests in three forms, (a) acute (fulminating) type, (b) subacute (gastroenteritis type), and (c) chronic.

Acute (Fulminating Type) Clinical signs caused by either inorganic or trivalent aliphatic arsenicals are similar. Peracute toxicities often result in sudden death within minutes to a few hours if the dose of dissolved arsenic ingestion is high. Acute poisonings have more clinical signs: abdominal pain or colic, vomiting (in

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those animals capable of vomiting), a staggering gait and weakness, incoordination, rapid weak pulse and shock, and diarrhea, followed by collapse and death. If the acute poisoning is through dermal contact, then the arsenic will also be systemic. The skin will have blisters and edema and may be cracked and bleeding, leaving the skin susceptible to secondary infection.

Subacute (Gastroenteritis Type) Those receiving a lower dose over a period of time may have subacute poisonings and will likely live several days, developing depression and anorexia. Movements may be difficult, stiff, and uncoordinated. Diarrhea is dark and possibly hemorrhagic and very fluid. Hematuria may be present, or the urine may contain protein and casts.

Chronic Toxicity Animals suffering chronic poisoning are easily fatigued and have dyspnea when they are moved.

These animals display intense thirst and have a rough dry hair coat as well as dry, brick-red mucous membranes. Cattle are described as having enlarged joints. Clinical signs of phenylarsenic poisoning occur within 3 days of a high dose or after chronic exposure. Most noticeable are the neurological signs. The animal is generally bright and alert but uncoordinated. The animal may or may not be blind, and these animals may have erythema in the skin. Some of the neurological damage may be reversible unless the nerves are damaged.

In cattle, there is hyperemia of the abomasum, and this may be the only finding. This "paintbrush" hyperemic lesion is characteristic of arsenic poisoning. If there are other lesions in cattle, it is often necrosis of the rumen mucosal epithelium. Ruminants have gelatinous serosal edema in the rumen, reticulum, omasum, and abomasum. The GI tract may have indications of irritation and be hemorrhagic. Lesions are indicative of capillary damage, and the liver is usually soft and yellow. In pigs if, the phenylarsonics (15) were previously used in feed additives, and lesions would be expected to be associated with overdoses in the feed mixture. A "downer pig" would have severe abrasions with muscle atrophy. Microscopic lesions indicate there was demyelination in the optic nerve and the posterior cord.

Inorganic arsenicals can be treated. In small animals, if no clinical sigs are evident in a recent exposure, the animal should have its stomach emptied with warm water or a 1% solution of sodium bicarbonate solution for gastric lavage. Emetics and strong cathartics and parasympathomimetic drugs are not recommended as they may cause rupture of the walls of a weakened GI system. Emesis, cathartics, and charcoal have been used when very early in the process and when there are no clinical signs but are used with caution if at all.

In treatment of arsenic intoxication, the efficacy of charcoal is undetermined. Following gastric emptying, provide GI protectants, such as kaolin-pectin. If charcoal has been used, then protectants should follow approximately 1–2 h later in small animals. If the patient is showing clinical signs, then aggressive fluid therapy

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and, if needed, a blood transfusion should be instituted. In cases with clinical signs, British Anti Lewisite (BAL, dimercaprol, or 2,3-dimercaptopropanol) should be used. In large animals, the efficacy of BAL alone is questionable.

Use of sodium thiosulfate, the water-soluble analogs of dimercaprol, 2,3-dimerc aptopropane-1-sulfonate (DMPS) and dimercaptosuccinic acid (DMSA) are considered less toxic, more effective, and may be given orally. D-penicillamine is also an effective chelator, having a wide margin of safety and could be used in animals.

5.3 Cadmium Poisoning

Cadmium is a divalent transition metal with chemical properties that are similar to zinc and is usually found as a mineral in combination with other elements to form cadmium oxide, cadmium chloride, or cadmium sulfate. Since numerous compounds are formed from cadmium, it is used in batteries, solders, semiconductors, solar cells, plastics stabilizers, and to plate iron and steel. All soil and rocks contain some cadmium. It can enter the environment from zinc smelting and refining, coal combustion, mine wastes, iron and steel production, and from the use of rock phosphate and sewage sludge as fertilizers.

5.3.1 Mechanism of Toxicity

Cadmium is present in the circulatory system bound primarily to the metal-binding protein, metallothionein (CdMT), produced in the liver. Following glomerular filtration in the kidney, CdMT is reabsorbed efficiently by the proximal tubule cells, where it accumulates within the lysosomes. Subsequent degradation of the CdMT complex releases Cd12, which inhibits lysosomal function, resulting in cell injury.

5.3.2 Toxicity

Increased exposure to cadmium in combination with zinc, lead, and/or other metals continues to occur in the vicinity of nonferrous metal smelters and processing facilities. These exposures have resulted in toxicoses, although it can be difficult to separate the effects of cadmium from those of lead, zinc, and other metals. In humans, occupational exposure to cadmium has been associated with renal dysfunction and osteomalacia with osteoporosis. One of the earliest effects of chronic cadmium exposure is renal tubular damage with proteinuria. Other chronic effects can include liver damage; emphysema (through inhalation); osteomalacia; neurological impairment; testicular, pancreatic, and adrenal damage; and anemia. Reproductive, developmental, and tumorigenic effects have been reported in experimental animals. In animals, cadmium toxicosis is prevented by minimizing exposure in the environment and in feedstuffs.

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5.4 Cobalt Deficiency (Vitamin B12 Deficiency)

All ruminants (including sheep, cattle, and goats) require cobalt in their diet for the synthesis of vitamin B12. Vitamin B12 is essential for energy metabolism and the production of red blood cells. Normally microorganisms in the rumen are able to synthesize vitamin B12 needs of ruminants if the diet is adequate in cobalt. Cobalt deficiency in soils can cause vitamin B12 deficiency in livestock. Sheep are more susceptible to cobalt deficiency than cattle (Fig. 5.1). It is seen more often in weaners and young animals due to their increased energy demand for growth. Deficiency causes lack of appetite, lack of thrift, severe emaciation, weakness, anemia, decreased fertility, decreased milk and wool production, and weeping eyes, leading to a matting of wool on the face. Sheep are more susceptible to cobalt deficiency than cattle. Cobalt deficiency also impairs the immune function of sheep, which may increase their vulnerability to infection with worms.

Prevention Vitamin B12 injections provide the quickest response in cobalt deficiency. A single injection of vitamin B12 will prevent the development of deficiency for 6–8 weeks. This is the best method for use for lambs at marking and calves preweaning. It can also be used for animals to be sold in the next 2 months (prime lamb, beef weaners). Intraruminal cobalt pellets, given using a "bulleting gun," are better for long-term prevention of deficiency. In sheep, pelleting is best done when lambs are weaned. Pellets are not suitable for lambs less than 8 weeks old. One pellet is effective for 1–3 years. Cobalt licks are available but the intake is highly variable. Cobalt sulfate drenches are available and cobalt is often included in multi-mineral drenches. The protective effect of cobalt given in this form only lasts about 2 weeks so the drench must be given frequently.



Fig. 5.1 Signs of cobalt deficiency in sheep. Affected sheep show weepy eyes with damp matted wool below the eyes, in some cases, wool break; affected ewes may have small lambs. (https://www.agric.wa.gov.au/sites/gateway/files/treated%20versus%20untreated%20sheep%20Co%20deficiency.jpg, https://www.agric.wa.gov.au/livestock-biosecurity/cobalt-deficiency-sheep-and-cattle)

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Cobalt can be added to a fertilizer blend, but this is an expensive option, and the cobalt given in marginal areas may be wasted in drier years. Pasture sprays with cobalt sulfate are also available. It is not necessary to treat the whole property. Grazing stock can be rotated through sprayed paddocks, or strips of spray can be applied in each grazing paddock during winter (July).

5.5 Chromium Toxicity

Chromium is a metallic element that can exist in six valence states, with the trivalent chromium form most commonly found in nature as ferrochromite ores. Both trivalent and hexavalent chromium are widely used in various industrial and manufacturing processes. Chromium is an essential trace element and functions in a number of metabolic processes, including glucose, lipid, and amino acid metabolism. Hexavalent chromium is considered to be more toxic than the trivalent form, which may be a direct result of its increased systemic availability. Both hexavalent chromium and dichromate are easily converted to trivalent chromium in mammalian systems. Oil field contamination with hexavalent chromium has been associated with cases of cattle deaths. Acute chromium toxicosis is associated with severe congestion and inflammation of the digestive tract, kidney damage, and liver damage.

5.6 Iodine Toxicity/Deficiency

Iodine is a non-metallic element of the halogen group that occurs as a purple-black crystalline solid but has several common other forms, including iodide and iodate. Iodine is widely distributed in nature in both organic and inorganic forms, but only in low concentrations, with rare exceptions.

5.6.1 Toxicity

High dietary iodine for a prolonged period of time can reduce the iodine uptake by the thyroid, thus causing a clinical syndrome of iodine deficiency especially when normal levels are subsequently fed. Toxic effects of iodine excess have been reported in cattle consuming iodine-containing feed additives. Clinical signs include decreased feed intake, decreased milk production, rapid breathing, nasal and ocular discharge, dry hair coat, and nonresponsive hock lesions. Puppies have been reported to have depressed thyroid gland function and bone abnormalities when fed diets high in iodine. Removal of the excess iodine from the diet, as well as supportive care, usually results in rapid return to normal.

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5.6.2 Iodine Deficiency (Goiter)

Iodine is essential for the normal synthesis of thyroid hormones, and a deficiency of iodine can result in thyroid enlargement or goiter. Deficiencies may occur from eating feeds grown on iodine-deficient soils or from the presence of goitrogenic substances. Hyperplastic thyroid glands (goiter) occasionally occur in swine. Goiter usually occurs as a result of one of the following:

(a) Iodine deficiency in the pregnant sow
(b) A genetic defect in the sow for the biosynthesis of thyroid hormones
(c) Ingestion by the gestating sow of goitrogenic substances (certain plants, drugs, or chemicals)
(d) Iodine toxicity from dams being fed an excess of iodine

In ruminants, iodine is absorbed primarily in the rumen and in the intestines. Absorption is very efficient, sometimes reaching more than 80 percent. Dairy cows have a higher iodine requirement than beef cattle because they excrete some 10 percent of their iodine intake via the milk. Colostrum is particularly high in iodine. Deficiencies cause abnormalities in the thyroid gland. Symptoms in beef cattle may also include blind and hairless (still-born) calves. Prolonged deficiencies may cause diminished production and reproduction.

In swine and sheep (Fig. 5.2), goiter usually occurs in iodine-deficient regions where iodized salt has not been included in the dam's feed. Deficiency of iodine leads to the birth of weak or dead pigs that are largely devoid of hair. Many of the pigs have a mucinous edema, especially over enlarged foreparts of the body. The skin in these areas is thick and doughy. The tongue is often edematous and may protrude from the oral cavity. Enlarged thyroid glands (goiter) in piglets may not be visible externally but often can be palpated or observed at necropsy. In mature swine, iodine deficiency is not usually a significant disease although gestation may be prolonged by as much as 7 days. Iodine deficiency is easily avoided by using iodized salt in the ration of gestating sows.



Fig. 5.2 Sheep with an abnormally large thyroid gland (goiter). (http://wia.agrosolutions.de/wp-content/uploads/2015/03/sheep.jpg)

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In horses, iodine is an important trace element for regulation of the metabolism. In adult horses, symptoms of an iodine deficiency are a dull or rough coat. The shedding process may also be slower in iodine-deficient animals, and hair loss may be patchy. An iodine deficiency in pregnant mares can result in weaker foals or foals with thyroid gland abnormalities.

The best treatment for iodine deficiency symptoms is prevention. Nutritionists can do this through the diets of animals by insuring that enough of the mineral is contained in the ration. Painting the teats of sows, ewes, goats, and cows with tincture of iodine or an iodophor teat dip once each day for a fortnight will allow the suckling young to obtain enough iodine to limit development of most goiters. Iodine is important in the synthesis of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), that regulate energy metabolism in animals. The thyroid hormones are responsible for setting the basal metabolic rate that is a component of the energy needed for maintenance of the body.

5.7 Phosphorus

Most phosphorus in nature exists in combination with oxygen in the form of phosphates, primarily in igneous and sedimentary rocks. Inorganic phosphates are commonly used as chemical fertilizers and food and feed supplements, and have many industrial uses. Phosphorus, white or yellow, has historically been used as a rodenticide, which is uncommon today.

Phosphorus is abundant in the animal body, primarily as a structural component of crystalline hydroxyapatite in bone and teeth but also as required components of phospholipids, nucleic acids, nucleotides, and enzyme cofactors. Phosphate ions also function in acid-base balance and other essential body functions. Phosphorus is an essential macroelement in nutrition and is an important consideration in the formulation of animal diets. The largest dietary source of phosphate will be in the form of inorganic phosphate supplements, and other dietary sources may include plant-origin feeds, as well as bone, meat, poultry, and fish meals. Normal phosphorus nutrition and metabolism requires adequate calcium in the diet with an appropriate calcium-to-phosphorus ratio (Ca:P). While adverse effects of excess phosphorus are rare, they can occur with either excess dietary phosphates or deficient dietary calcium. If the Ca:P ratio is balanced, usually no wider than 2:1, animals can tolerate a wide range of dietary phosphorus levels.

Excess phosphorus in the diet of ruminants, especially sheep, can result in the formation of urinary calculi in the kidney or bladder. This formation of stones can obstruct or completely block urine flow, especially in males, resulting in the bladder filling with urine and eventually rupturing into the abdominal cavity, causing death. The problem can be prevented by correctly balancing calcium and phosphorus in the diet. Excess phosphorus in the diet of horses has resulted in nutritional secondary hyperparathyroidism, a condition usually associated with a high-grain diet without appropriate calcium supplementation. The high dietary phosphate will depress the intestinal absorption of calcium, with a decrease in plasma calcium and an increase

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in plasma phosphate levels. Low plasma calcium will stimulate the secretion of parathyroid hormone, which will increase bone mineral resorption activity. The skeletal bones will lose calcium, and the demineralized bone will be replaced by fibrous connective tissue, with the facial bones often becoming enlarged, leading to the common term of big head disease in horses. It is also known as bran disease, since feeding high dietary levels of bran, which is high in phosphate and low in calcium, has historically been a cause of the disease. In all animals, optimum animal performance will be closely associated with optimum dietary calcium and phosphorus balance.

5.8 Copper Poisoning/Deficiency

Copper has been shown to be an essential element for both animals and plants but can be toxic under certain conditions.

5.8.1 Toxicity

Copper poisoning is encountered in most parts of the world. Sheep are affected most often, although other species are also susceptible. In various breeds of dogs, especially Bedlington Terriers, an inherited sensitivity to copper toxicosis similar to Wilson disease in people has been identified (Fig. 5.3). Chronic copper poisoning has been reported in other breeds of dogs, including Labrador Retrievers, West Highland White Terriers, Skye Terriers, Keeshonds, American Cocker Spaniels, and Doberman Pinschers. Acute poisoning is usually seen after accidental administration of excessive amounts of soluble copper salts, which may be present in anthelmintic drenches, mineral mixes, or improperly formulated rations. Chronic copper toxicosis is more likely to occur with low dietary intake of molybdenum and sulfur. Reduced formation of copper molybdate or copper sulfide complexes in tissues impairs the excretion of copper in urine or feces.



Fig. 5.3 Bedlington Terrier—genetic predisposition for copper accumulation. (Reproduced from https://commons.wikimedia.org/wiki/File:Boutchie_apres_championnat_004.JPG)

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In sheep, there may be an acute hemolytic crisis, and the animals show clinical signs of weakness, anorexia, icterus, dyspnea, and pale mucous membranes. There may be hemoglobinuria, and death is common among severely affected animals. Postmortem findings include icterus, swollen liver, enlarged spleen, and the kidneys appear dark, often referred to as gunmetal blue or black kidneys.

Acute exposure to excess copper causes GI irritation and can cause erosions of the mucosa as well as a blue-green discoloration of the contents and wall. Normally, the free copper concentration in cells is kept very low by copper-binding proteins such as metallothionein, glutathione, and copper chaperone proteins. An excess of copper can overwhelm these binding proteins and allow free copper ions to exist in the cell, which can directly bind proteins and nucleic acids. Additionally, the free copper can form reactive oxygen species and hydroxyl radicals, causing lipid peroxidation of membranes and damage to nucleic acids and cellular proteins toxicity. As copper is mobilized from the liver, it can accumulate in the kidney. The kidney can be damaged both from the accumulation of copper and the direct toxic effects of hemoglobin following the hemolytic event.

5.8.2 Copper Deficiency

Copper deficiency is likely to occur in winter on free-draining or peaty soils, especially when there has been lots of rain. Young stock suffers poor growth (Fig. 5.4) and loss of coordination of the hind limbs, and adult cattle gets diarrhea (scours).

Treatment Treatment of animals acutely poisoned with copper mainly consists of supportive treatment directed at the shock, dehydration, and damage to the GI tract. Treatment of sheep with severe clinical signs following hemolytic crisis is often unrewarding. Supportive care should include fluid therapy and the consideration of a blood transfusion. Ammonium or sodium molybdate and sodium thiosulfate should be used. Ammonium tetrathiomolybdate has been suggested as a treatment



Fig. 5.4 Copper deficiency in cattle. (http://www.teara.govt.nz/files/p17537pc.jpg)

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but is difficult to obtain. Molybdenum in the diet can be increased to 5 ppm, and zinc can be supplemented at 100 ppm to reduce copper absorption. Dogs affected with chronic copper toxicosis should be fed a low-copper diet, e.g., avoiding organ meats that are usually higher in copper. The use of oral chelating agents such as D-penicillamine and trientine hydrochloride is suggested to enhance urinary excretion of copper.

5.9 Fluoride Toxicoses

Fluorine is rarely found in elemental form in nature but instead exists as fluoride, the monovalent anion, combined with other elements. The most common mineral-containing fluoride is fluorspar, also known as fluorite (CaF2), and soils generally contain calcium fluoride (CaF2). Although now rare, sodium fluoride and sodium fluorosilicate (Na2SiF6) have been used as insecticides and anthelminthics. Sodium fluoroacetate (compound 1080) is another formerly used rodenticide that is rarely seen in the United States today but may be found in other parts of the world (e.g., Australia). Fluoroacetate can also be found naturally in several species of plants (*Gastrolobium* spp., *Oxylobium* spp. and others). The chronic disease which occurs due to continuous ingestion of small doses of fluoride is known as fluorosis and is quite common in human beings and animals. Fluorosis is endemic in at least 22 countries worldwide (Fig. 5.5).

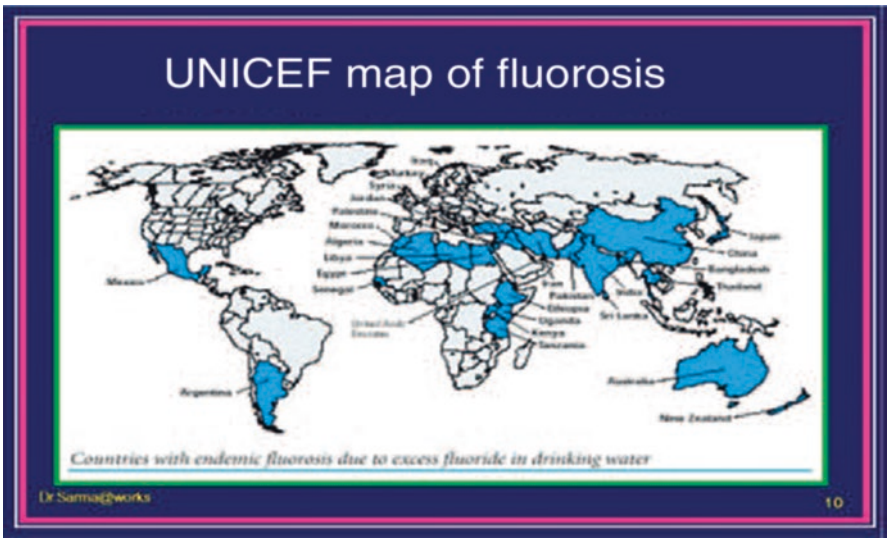


Fig. 5.5 Worldwide distribution of endemic fluorosis—22 counties are affected. (From http://slideplayer.com/224204/1/images/10/UNICEF+Map+of+Fluorosis.jpg)

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5.9.1 Toxicity

There are a number of factors that influence the amount of fluoride required to produce specific lesions and clinical signs including the amount of fluoride ingested, duration of exposure, bioavailability, species, age, and diet of the animal involved. The point where fluoride ingestion becomes detrimental to the animal also varies from animal to animal. Clinical signs develop slowly and can be confused with other chronic problems. Animals often show nonspecific intermittent stiffness and lameness, which appear to be associated with periosteal overgrowth leading to spurring and bridging near joints as well as ossification of ligaments, tendon sheaths, and tendons. In severe cases, affected cattle may become progressively lamer and eventually may refuse to stand or may stand with rear legs upright and be on their knees to graze. Lameness in cattle leads to abnormal hoof wear with elongated toes, especially in the rear legs. In long-term studies with cattle on varying levels of fluoride intake, skeletal neoplasms were not seen even in cattle with severe osteofluoritic lesions.

The major adverse effects of chronic excess fluoride ingestion concern the teeth and bones of affected animals. Fluoride substitutes for hydroxyl groups in the hydroxyapatite of the bone matrix, which alters the mineralization and crystal structure of the bone. Bone changes induced by excess fluoride ingestion, termed skeletal fluorosis or osteofluorosis, include the interference of the normal sequences of osteogenesis and bone remodeling with the resulting production of abnormal bone or the resorption of normal bone. The fluoride content of bone can increase over a period of time without other noticeable changes in the bone structure or function.

In general, severely affected teeth appear with brown or black discoloration, may have enamel defects, and show increased wear including exposure of the pulp cavity, which causes pain while chewing roughage or swallowing extremely cold water. There will be a correlation between lesions on incisor teeth and those cheek teeth that form and mineralize at the same time. Cheek teeth that are abnormally worn cause improper mastication with roughage being difficult for the animal to utilize. The animal will have variable and decreased intake and the decreased production, slowed growth, and general poor health associated with poor nutritional status. Animals with chronic exposure to excess fluorides have dry skin and hair coat. Effects vary from animal to animal. Normally fluoride is required for enamel formation, but excess fluoride before complete formation of enamel can damage tooth due to oxidation. Brown or black discoloration of teeth seen in fluorosis is due to oxidation of enamel (Fig. 5.6).

Some animals often show nonspecific intermittent stiffness and lameness which appear to be associated with periosteal overgrowth leading to spurring and bridging near joints as well as ossification of ligaments, tendon sheaths, and tendons (Fig. 5.7). The clinical presentation may easily be confused with other conditions, such as degenerative arthritis, but the lesions associated with fluorosis are not primarily associated with articular surfaces.

There is no specific antidote or treatment for chronic fluoride toxicosis. Sources of excess fluoride should be identified and removed from the diet.

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Fig. 5.6 Severe form of dental fluorosis (deep yellowish coloration) in a calf. (https://encrypted-tbn3.gstatic.com/images?q5tbn:ANd9GcRotDD6D2TwWd4V09fLD5CO84_EP5a4t6qsZUQW1XfDL4niLc3C)



Fig. 5.7 Fluorosis in animals—skeletal form. (https://upload.wikimedia.org/wikipedia/commons/thumb/c/cf/Fluwor%C3%B4ze_egzostozes1-800h.jpg/220px-Fluwor%C3%B4ze_egzostozes1-800h.jpg)

5.10 Iron Toxicoses

Iron is an essential element for animal and plant life. It works as an oxygen (O_2) carrier in hemoglobin/myoglobin and is involved in numerous biological oxidation reduction reactions, including photosynthesis. Iron is present in cytochrome P450 and is crucial for the metabolism of many chemicals in the liver, kidney, and other organs. The largest amount of iron is incorporated into proteins, hemoglobin, and myoglobin. Within RBCs (erythrocytes), hemoglobin transports O_2 from the lungs to cells throughout the body, while myoglobin binds O_2 for use in muscle cells. Iron present in the serum is bound to the protein transferrin and in milk is bound to lactoferrin. Iron-containing proteins in the mitochondrial electron transport chain are essential for oxidative phosphorylation and energy production. Iron is also

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contained in enzymes of the Krebs cycle and in cytochromes P450, which are necessary for the metabolism of chemicals.

Iron poisoning is not common in animals, although potentially it could occur in any species. Clinical cases of acute iron toxicosis have been reported in dogs, pigs, horses, cattle and goats. In all species, ingestion of a toxic dose (roughly greater than 20 mg/kg in dogs) initially results in necrosis of the GI mucosal cells. This is followed by fluid loss, direct cardiotoxicity, and widespread organ damage through the mechanisms described above. Fluid loss and decreased cardiac output can lead to circulatory shock. Treatment of iron toxicity varies with the inciting cause, dose, and duration of the disease. General therapy is to limit absorption (although activated charcoal is ineffective at binding iron), provide symptomatic and supportive care, remove gastric bezoars of sticky iron-containing pills (surgically if necessary), and increase excretion. Because the body has limited ability to excrete excess iron (other than through bleeding), urinary excretion can be enhanced through the use of a chelating agent. A specific chelator of iron, deferoxamine, has been used in the treatment of iron toxicity.

5.11 Lead Poisoning

The chemical symbol for lead, Pb, is short for the Latin word plumbum, meaning liquid silver. The historical use of lead in gasoline, paint, construction materials, and many other products has resulted in lead being one of the most significant environmental contaminants in the world. Additional sources of lead have included lead weights (e.g., for fishing or curtains), small lead trinkets and toys, lead shot and bullets for weapons, lead arsenate, pesticides, and many other products as well as single source environmental contamination from mining, smelting, and recycling operations. Widespread use of lead has resulted poisoning in animals with greatest frequency compared to any other metal.

Absorbed lead enters the blood and soft tissues and eventually redistributes to the bone. The degree of absorption and retention is influenced by dietary factors such as calcium or iron levels. In ruminants, particulate lead lodged in the reticulum slowly dissolves and releases significant quantities of lead. Lead has a profound effect on sulfhydryl-containing enzymes, the thiol content of erythrocytes, antioxidant defenses, and tissues rich in mitochondria, which is reflected in the clinical syndrome. In addition to the cerebellar hemorrhage and edema associated with capillary damage, lead is also irritating, immunosuppressive, gametotoxic, teratogenic, nephrotoxic, and toxic to the hematopoietic system.

5.11.1 Mechanism of Action

Lead interferes with several biochemical processes in the body by binding to sulfhydryl and other nucleophilic functional groups causing inhibition of several enzymes and changes in calcium/vitamin D metabolism. Lead also contributes to

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oxidative stress within the body. Lead inhibits the body's ability to make hemoglobin by interfering with several enzymatic steps in the heme pathway. Specifically, lead decreases heme biosynthesis by inhibiting delta-aminolevulinic acid dehydratase and ferrochelatase activity. These changes contribute to the anemia that develops in chronic lead poisoning. An increased fragility of red blood cells also contributes to the anemia.

Many of the neurotoxic effects of lead appear related to the ability of lead to mimic or, in some cases, inhibit the action of calcium as a regulator of cell function. At a neuronal level, exposure to lead alters the release of neurotransmitters (dopamine, acetylcholine, and γ-aminobutyric acid) from nerve endings. Spontaneous release is enhanced and evoked release is inhibited. The former may be due to activation of protein kinases in the nerve endings and the latter to blockade of voltage-dependent calcium channels. Lead also inhibits N-methyl-D-aspartate receptors containing NR2A, NR2C, and NR2D subunits, thereby causing decreased calcium influx and reduced brain-derived neurotrophic factor, leading to neuro-inflammation and neuronal injury and death.

Brain homeostatic mechanisms are disrupted by exposure to higher levels of lead. The final pathway appears to be a breakdown in the blood-brain barrier (BBB). Again, the ability of lead to mimic or mobilize calcium and activate protein kinases may alter the properties of endothelial cells, especially in an immature brain, and disrupt the barrier. In addition to a direct toxic effect upon the endothelial cells, lead may alter indirectly the microvasculature by damaging the astrocytes that provide signals for the maintenance of BBB integrity and necrosis in neurons with shrunken cytoplasm, pyknotic nuclei, and increased perineuronal space. Recent studies provide evidence of increased production of reactive oxygen species following lead exposure. Lead induces oxidative damage in several tissues by enhancing lipid peroxidation through Fenton reaction or by direct participation in free radical-mediated reactions, such as inhibition of δ-aminolevulinic acid dehydratase (ALAD) activity or accumulation of ALA, a metabolite that can release Fe_{21} from ferritin and induce oxidative damage.

5.11.2 Toxicity

Mammals, birds, and reptiles have all been found to develop lead poisoning. In general, young animals are more susceptible to lead toxicosis because they are more prone to lead pica and have a higher rate of absorption (about 90%) from the intestinal tract. Cattle have been most widely reported with lead toxicosis, probably because of their propensity to ingest discarded lead acid batteries and construction materials including paints. Dogs are also commonly reported with lead toxicosis, probably because of their chewing habits and ingestion of small lead objects around the house. Both cats and dogs have been exposed to lead by the renovations of older homes containing leaded paints. The major systems affected by lead poisoning are the GI system, central nervous system, and hematological system. Abdominal pain

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and diarrhea can be common clinical signs in animals exposed to excess lead. Anorexia is common as well as vomiting in those species that are able to. Neurological signs including depression, weakness, and ataxia can progress to more severe clinical signs of muscle tremors or fasciculation, head pressing (especially in ruminants), blindness, seizure-like activity, and death. Many animals with chronic lead poisoning will show subtle and nonspecific clinical signs such as abdominal discomfort, vague GI upsets, anorexia, lethargy, weight loss, and behavior changes. Horses develop acute lead toxicosis and show clinical signs of laryngeal paralysis and "roaring," in addition to colic and seizure-like activity. Evidence suggests that horses may be more susceptible to chronic lead toxicosis than cattle. Lead is also a reproductive and developmental toxicant. Chronic lead poisoning, occasionally seen in cattle, may produce a syndrome that has many features in common with acute or subacute lead poisoning. Impairment of the swallowing reflexes frequently contributes to development of aspiration pneumonia. Embryo toxicity and poor semen quality may contribute to infertility. Basophilic stippling of erythrocytes and inhibition of hemoglobin synthesis are characteristic hematological features of lead poisoning (Fig. 5.8).

5.11.3 Treatment

The treatment approach for lead poisoning in animals includes stabilizing and supporting the animal, especially if severe clinical signs are present, preventing additional exposure to lead, and chelation therapy to quickly reduce the body burden of lead. The parenteral use of calcium disodium ethylenediaminetetraacetic acid (CaEDTA) has been commonly used for several decades as a chelation agent in domestic animals. Preceding CaEDTA usage with a chelator that specifically targets lead in the soft tissue (e.g., British Anti-Lewisite or BAL) has been recommended but is difficult to accomplish in most practice settings.

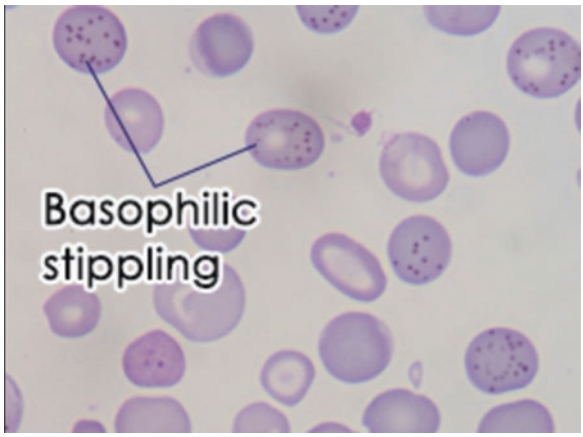


Fig 5.8 Lead poisoning: Showing basophilic stippling of blood cells (https://yaplog.jp/cv/potatos-room/img/391/20224_p.jpg)

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5.12 Manganese Toxicity

Manganese (Mn) is an essential element for maintaining the proper function and regulation of many biochemical and cellular reactions that are critical for humans, animals, and plants. It is required for growth and development and plays a role in immune response, blood sugar homeostasis, adenosine triphosphate (ATP) regulation, digestion, bone growth, reproduction, and lactation. It is a necessary component of numerous metalloenzymes, such as Mn superoxide dismutase, arginase, phosphoenolpyruvate carboxylase, and glutamine synthase. Practically, Mn deficiency occurs more frequently in cattle, pigs, and poultry. In ruminants, Mn deficiency can be linked to silent heat, reduced conception, abortions, reduced birth weight, an increased percentage of male calves, paralysis, and skeletal damage in calves. Mn deficiency can cause delayed estrus, reduced fertility, and spontaneous abortions in mares. Foals are born with skeletal deformities and muscle contractures, such as asymmetry of the skull, curvature of the vertebral column, shortened limb bones, enlarged joints, and contracture of neck muscles. In dogs, Mn deficiency can cause crooked and shortened soft bones. Despite its essentiality, Mn overexposure can cause a variety of toxic effects in humans and animals.

5.12.1 Mechanism of Action

Mn is generally described as a neurotoxicant, selectively affecting basal ganglia structures. Although it is known that Mn is a cellular toxicant which can impair the transport system, enzyme activity, and receptors function, the principal mechanism by which Mn neurotoxicity occurs has not yet been clearly established. Since mitochondria are the principal intracellular repository for metals, binding of Mn to inner mitochondrial membrane or matrix proteins directly interacts with proteins involved in oxidative phosphorylation. Mn directly inhibits complex II in brain mitochondria and suppresses ATP-dependent calcium waves in astrocytes, suggesting that Mn promotes potentially disruptive mitochondrial sequestration of calcium. Elevated matrix calcium increases the formation of reactive oxygen species (ROS) by the electron transport chain (ETC) and results in inhibition of aerobic respiration. Recent studies with primary astrocytes and neurons have shown that Mn exposure induces an increase in the biomarkers of oxidative stress. Oxidative stress as an important mechanism in Mn-induced neurotoxicity has also been confirmed in the in vivo model.

5.12.2 Toxicity

Mn is considered to be one of the least toxic of the essential elements. There are no reports of acute toxicity of Mn in animals. Therefore, all toxicity studies described here are chronic in nature. Clinical signs of toxicity include reduced appetite and

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growth rate, anemia and abdominal discomfort. Excess Mn may be associated with abortions and cystic ovaries. In all domestic animals and poultry, excess dietary Mn is known to cause reduced feed intake, growth rate, and lethargy. In dogs, a neurological syndrome of gait disorders is common and indicative of Mn-induced injury to the extrapyramidal motor system in the brain. Mn can have a damaging effect on many body organs, including the brain, liver, pancreas and reproductive system. Young animals might be more susceptible to Mn than adults.

5.12.3 Treatment

The very first step in the treatment of Mn poisoning should be to remove the animals from any further exposure by avoiding contaminated feed, water, or any other source. Several studies suggested that ethylenediaminetetraacetate (EDTA) successfully increased Mn excretion in urine and decreased Mn concentration in blood. However, EDTA cannot effectively chelate and remove Mn ions from brain and damaged neurons, and it appears to be of limited therapeutic value for more advanced cases of Mn intoxication.

5.13 Mercury Poisoning

Mercury (Hg) is a naturally occurring element that exists in several forms, such as elemental (metallic), inorganic, and organic. About 80% of the mercury released into the environment is metallic mercury; it comes from human activities, such as fossil fuel combustion, mining, smelting, and solid waste incineration, as well as from volcanoes and forest fires. Aristotle named it "quicksilver," because it is a silver-colored liquid. Animal poisoning by mercury is rare because of strict federal, state, and local regulations. The most common natural forms of mercury found in the environment are metallic mercury, mercury sulfide, mercuric chloride, and methylmercury.

Methylmercury is of particular concern. Anthropogenic sources, such as coal burning and mining of iron, can contaminate water sources with methylmercury, and it is bioaccumulated and biomagnified in certain edible freshwater and saltwater fish and marine mammals to levels that are many times greater than levels in the surrounding water. As a result, older and predatory fish living in contaminated water build up levels of mercury in their bodies specially in the liver, kidneys, brain, and muscle (Fig. 5.9). Inorganic mercury does not bioaccumulate in the food chain to any extent. The discharge of mercury led to large-scale human methylmercury exposure and toxicity during the 1950s and 1960s. The less toxic inorganic mercury gets converted through biomethylation to more toxic form of mercury. The schematic representation of mercury's environmental cycling, biomethylation, and food chain transfer is shown in Fig. 5.10.

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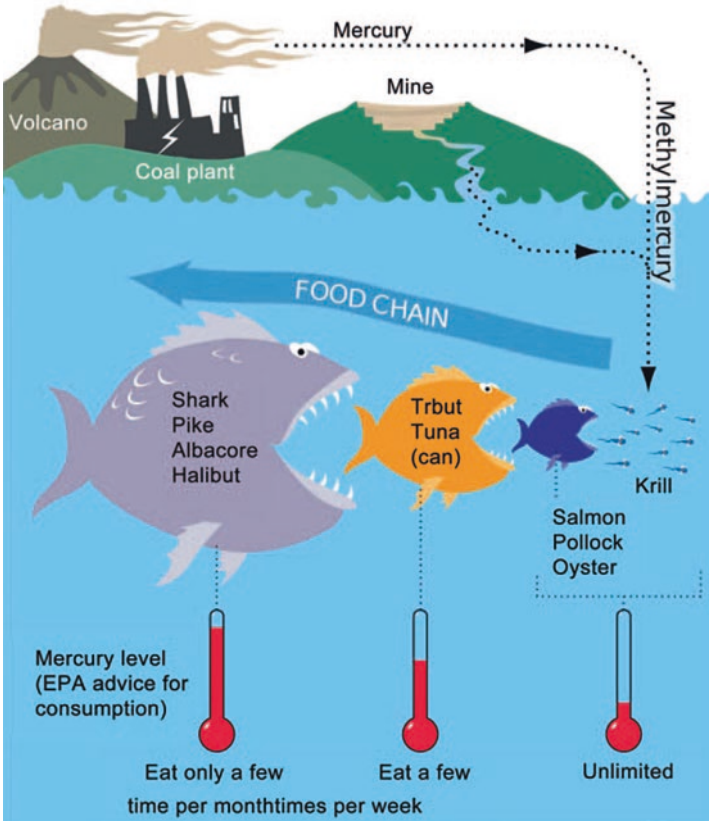


Fig. 5.9 Process of biomagnification of mercury levels in each successive predatory stage in fish. (https://upload.wikimedia.org/wikipedia/commons/thumb/0/07/MercuryFoodChain.svg/1200px-MercuryFoodChain.svg.png)

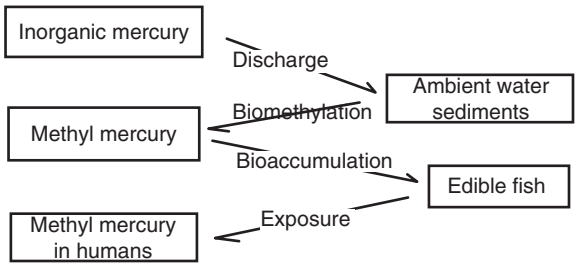


Fig. 5.10 Environmental cycling and conversion of inorganic mercury to methylmercury

5.13.1 Mechanism of Action

High-affinity binding of the divalent cationic mercury to thiol or sulfhydryl groups of proteins is believed to be a major mechanism involved in the toxicity of mercury. As a result, mercury can cause inactivation of various enzymes, structural

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proteins, transport proteins, and alteration of cell membrane permeability by the formation of mercaptides. In addition, mercury may induce one or more of the following effects: increased oxidative stress, mitochondrial dysfunction, changes in heme metabolism, glutathione depletion, increased permeability of the BBB and disruption of microtubule formation, protein synthesis, DNA replication, DNA polymerase activity, calcium homeostasis, synaptic transmission, and immune response. Methylmercury selectively inhibits protein synthesis in the brain (reversibly in neurons from the cerebrum and Purkinje cells; irreversibly in granule cells of the cerebellum), and this effect usually precedes the appearance of clinical signs. This selective action on the brain may be due to the fact that certain cells are susceptible because they cannot repair damage from methylmercury.

5.13.2 Toxicity

The toxic effects of mercury depend upon the form of mercury, the dose, duration, and route of exposure. Mercury, in all forms, has been found to be toxic to both man and animals. There are many similarities in the toxic effects of the various forms of mercury, but there are also differences. Practically, it is organic mercury, which is more toxic and often encountered in poisonings following oral ingestion. The major targets of toxicity to inorganic and organic mercury are the kidneys and the CNS, respectively. In livestock animals, clinical signs of mercury poisoning vary greatly. In cattle, toxicity signs include ataxia, neuromuscular incoordination, and renal failure, followed by convulsions and a moribund state. Average time from ingestion to death is reported to be about 20 days. Ingestion of phenylmercuric acetate may cause sudden death with massive internal hemorrhage, without other signs of toxicity. In horses, signs of acute toxicity include severe gastroenteritis and nephritis. In chronic cases, signs may include neurological dysfunction and laminitis. Mercury poisoning may lead to renal problem, which is characterized by glycosuria, proteinuria, phosphaturia, reduced urine osmolarity, reduced glomerular filtration rate, azotemia, and elevated creatinine and blood urea nitrogen. In sheep, the poisoning is characterized by severe neurological symptoms and tetraplegia. Pigs show incoordination, unstable gait, lameness, recumbency, and death.

5.13.3 Treatment

Activated charcoal is very effective in reducing further absorption of mercury from the GI tract. Specific treatment of mercury poisoning rests with the use of chelators, along with protein solutions to bind and neutralize mercury compounds. Among several chelators, dimercaprol (BAL) has been found to be the most effective against mercury poisoning. Animal studies suggest that antioxidants (particularly vitamin E) may be useful for decreasing the toxicity of mercury.

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5.14 Molybdenum Poisoning

Molybdenum (Mo) was first separated from lead and graphite in 1778. Molybdenum was derived from Greek molybdos meaning "lead-like." As an essential element, molybdenum acts as a cofactor for at least three enzymes in humans: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. Mo exists in five oxidation states but the predominant species are Mo4+ and Mo6+. Mo concentration in food varies considerably depending on the local environment. Mo is an essential nutrient in plants and animals. Mo is commonly found in low concentrations in most dietary constituents, but excess intake can occur from plants grown on soils naturally high in Mo or from areas contaminated by mining or smelting operations. In addition, high molybdenum forages have been identified from contaminated areas associated with mining and industrial operations. Daily dietary requirements for all species are such that requirements are met, even with low intake.

5.14.1 Mechanism of Action

The primary mechanisms by which Mo is toxic are directly tied to its interactions with sulfur and copper. These interactions result in overt or functional copper deficiency, including inhibition of copper-dependent enzyme systems. However, these interactions differ significantly among species, with ruminants being much more susceptible than monogastrics, due to the ruminal production of thiomolybdates. The reducing environment of the rumen converts sulfate or sulfur from sulfur-containing amino acids to sulfide, which then forms mono-, di-, tri-, and tetrathiomolybdates. Thiomolybdates' binding of copper in the digestive tract prevents absorption of ingested copper, while systemic binding renders it non-bioavailable for tissue utilization. These cupric thiomolybdate complexes also result in enhanced copper excretion. It is well known that the ruminal binding is predominantly via tri- and tetrathiomolybdates, while systemic effects are predominantly via di- and trithiomolybdates. In practical terms, the thiomolybdates serve as effective chelators of copper, preventing copper absorption and depleting functional body stores. As the ruminal microbial populations can differ significantly among ruminant species, the relative sensitivity among species could be related to the overall conversion to thiomolybdates or the relative abundances of the mono-, di-, tri-, and tetrathiomolybdates produced.

5.14.2 Toxicity

Mo absorption differs between monogastrics and ruminants. In monogastrics, Mo absorption occurs from the stomach throughout the intestinal tract. In contrast, ruminant absorption likely depends on the chemical form of the molybdenum. Historically, Mo absorption in ruminants was thought to occur in the intestinal tract, as an extensive delay in peak blood concentration would indicate that rumen

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absorption did not occur. Mo is widely distributed in tissues but has highest concentrations in the liver, kidney, and bone. Both acute and chronic toxicity of Mo varies greatly among species. Ruminant animals are much more sensitive than monogastric animals, due to the rumen metabolism of sulfur to sulfides and formation of thiomolybdates. The relative tolerance to Mo has been ranked: horses > pigs > Rats > rabbits > guinea pigs > sheep > cattle, but more recent literature suggests horses may be more sensitive. In total, the toxicity of Mo needs to be evaluated with consideration of dietary sulfur/sulfates and copper. Clinical signs and pathologic lesions in acutely poisoned animals differ from those seen with more chronic poisonings. Acutely or subacutely poisoned cattle and sheep developed feed withdrawal, lethargy, weakness, hind limb ataxia that progressed to the front limbs, and recumbency. The cattle also had profuse salivation, ocular discharge, and mucoid feces. Hydropic hepatocellular degeneration/necrosis and hydropic degeneration/necrosis of the proximal and distal renal tubules were observed in both cattle and sheep.

Most clinical signs of chronic Mo poisoning are associated with induction of overt or functional copper deficiency. Commonly, the first recognized clinical sign of chronic Mo poisoning is severe diarrhea. "Teart" is used to refer to soil or plants that contain unusually high amounts of Mo; thus the term teart scours is commonly used to describe the diarrhea associated with excessive Mo intake. Although the exact mechanism is not well defined, copper supplementation alleviates this clinical sign. Most of the clinical syndromes of Mo poisoning can be tied to deficiencies in copper-containing enzyme system functions via overt deficiencies or inhibition of enzyme systems. Ruminants, especially young cattle, are most susceptible due to Cu deficiency; melanin production is reduced (due to decrease in the activity of Cu-containing enzyme tyrosinase which is responsible for conversion of tyrosine into melanin). Therefore, in buffaloes, spectacle eye is prominently visible due to light-colored hair and depigmentation around eyes in molybdenum poisoning (Fig. 5.11). Although most clinical effects of Mo poisoning are reversed by supplementation of copper, Mo as thiomolybdates can have some direct toxic effects on copper-dependent enzymes.



Fig. 5.11 Spectacle-eye appearance—Molybdenum poisoning. (http://www.toxinfo.co.in/files/spectacled%20appearance.jpg)

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5.14.3 Treatment

The two primary mechanisms for treating Mo toxicosis involve removal from the source of high Mo and copper supplementation, but administration of sulfate to monogastrics will enhance elimination rates. Administration of sulfates to ruminants would not be recommended. Supplementation of copper in Mo-poisoned animals must be done with care, especially in sheep, to prevent excessive copper accumulation and subsequent copper toxicosis.

5.15 Selenium Poisoning

(Selenium toxicity due to plants is also discussed in Chap. 11 dealing with poisonous plants.)

Selenium (Se) was discovered in 1817 and named after the Greek word selene meaning moon. Selenium is an essential nutrient that has a relatively narrow window between ingested amounts that result in deficiencies and those that cause toxicoses. Selenium has four natural oxidation states: −2 (selenides), 0 (elemental), +4 (selenites), and +6 (selenates). Inorganic forms of selenium are the primary form in soil. Only the water-soluble forms are readily available for plant uptake, with the greatest absorption being in the form of selenate via the sulfate transporter. Elemental selenium and precipitated metal selenides are not bioavailable for plant uptake. Some "indicator plants" or "obligatory selenium accumulator plants" can accumulate several thousand ppm selenium and are often found in selenium-rich areas, since they require high selenium for growth. These plants include genera such as *Astragalus* (milk vetch), *Xylorhiza*, *Machaeranthera* (woody aster), *Haplopappus* (golden weed)—formerly known as *Oonopsis*—and *Stanleya* (prince's plume). Although these indicator plants have poor palatability, during times of limited forage, they are eaten. Secondary or facultative accumulating plants can survive with high selenium content, but do not require it for growth. These plants are often more palatable than the indicator plants and include *Aster*, *Atriplex* (salt bush), *Castilleja* (paintbrush), *Gutierrezia* (snakeweed), *Grindelia* (gumweeds), *Sideranthus* (ironweed), *Eurotia* (winter fat), *Mentzelia*, *Machaeranthera*, and *Gyria* sp. as well as some crop plants such as western wheatgrass, barley, wheat, alfalfa, onions, and Swiss chard.

5.15.1 Mechanism of Action

The exact mechanism of the toxic effects in the body are still not clear. However, a few of the following theories seem to be valid:

- 0ne theory is the depletion of intermediate substrates, such as glutathione and S-adenosylmethionine, which disturbs their respective enzyme activities.
- Another potentially interactive theory is the production of free radicals by the reaction of selenium with thiols, causing subsequent oxidative tissue damage.

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- A third theory is the incorporation of selenium compounds in place of sulfur, such as in proteins, in which it disrupts normal cellular functions. This is an especially likely mechanism for the hair and hoof lesions of chronic selenium poisoning, with the loss of disulfide bridges that provide structural integrity to these tissues.

5.15.2 Toxicity

In monogastrics, the relative selenium absorption is greater than in ruminants, ranging from 45% to 95%, and organic forms of selenium are better absorbed. In ruminants, the relative absorption ranges from 29% to 50%. The decreased absorption in ruminants is due to microbial reduction of selenium forms in the rumen to selenides and elemental selenium, which are not bioavailable.

Selenium poisoning cases generally fall into three types of exposure history:

(a) The first is from ingestion of selenium in plants that have accumulated it from naturally seleniferous soils.
(b) The second is from accidental overdoses by injection or errors in feed mixing.
(c) The third is from environmental contamination, which often results in exposure from plant accumulation and/or contaminated waters.

With each of these types of poisonings, one may see acute, subacute, or chronic selenium poisoning, depending upon the daily exposure rate. However, one must understand that an animal's age plays a role in susceptibility to selenium poisoning, as young animals are less tolerant than adults.

Clinical manifestation of acute selenium poisoning includes respiratory distress, restlessness or lethargy, head down, droopy ears, anorexia, gaunt appearance, salivation, watery diarrhea, fever, sweating, tachycardia, teeth grinding, stilted gait, tetanic spasms, and/or death. Clinical signs tend to progress quickly after they are first observed. Gross and histologic lesions include systemic congestion, pulmonary edema, skeletal muscle necrosis, myocardial necrosis, and petechial hemorrhages in and on the myocardium. "Blind staggers" (common in cattle and sheep) has historically been associated with subacute to chronic selenium poisoning. However, this association was due to its occurrence in known seleniferous areas. The areas with seleniferous soils also tend to have highly alkaline soils with high potential for excessive sulfur exposure. It has been stated that blind staggers cannot be reproduced with pure selenium compounds alone and likely involve other factors, such as alkaloid poisoning, starvation, or polioencephalomalacia.

Chronic selenosis, often referred to as "alkali disease," is the result of long-term ingestion of seleniferous forages. High selenium intake is generally for greater than 30 days and, due to plant selenium content, is usually associated with facultative accumulators, not indicator plants, although chronic selenosis can also be reproduced by long-term feeding of high inorganic selenium. Clinical signs of chronic selenosis include depression, weakness, emaciation, anemia, hair loss, hoof abnormalities, anorexia, diarrhea, weight loss, lameness, reproductive failure, and death. Hoof wall abnormalities are frequently identified in cattle, horses, and pigs and

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Fig. 5.12 Chronic selenium toxicosis leads to separation of the hoof wall. (http://www.rockymountainrider.com/articles/2013/images/1013%20Selenium%20photo%205.jpg)

include swelling of the coronary band, hoof deformities, and/or separation and sloughing of the hoof wall (Fig. 5.12).

Hair loss from the base of the tail and switch in cattle, horses, and mules is sometimes referred to as "bobtail disease." Interestingly, sheep do not develop the alopecia or hoof lesions that are seen in cattle, but they have decreased wool growth rates. In pigs, goats and horses, there may be a general alopecia. Pigs also develop neurologic signs of paralysis. Selenosis in poultry and other avian species has major effects in reproduction. Poor hatchability, embryonic deformities, and embryonic death are common sequelae to selenium poisoning.

Pathologic lesions of chronic selenium poisoning are generally related to hoof lesions and to the effects of starvation. Lesions of nephritis, hepatic cirrhosis, and myocardial necrosis can be expected. In pigs, bilateral malacia of the gray matter in the spinal cord can be seen. Reproductive abnormalities are seen in several species when excessive selenium is ingested.

5.15.3 Treatment

There is no specific mechanism of chelation and removal of selenium in animals; the primary treatment is of supportive care with both acute and chronic selenium poisoning.

5.16 Zinc Toxicosis

Zinc (Zn) is a transitional metal and has an essential role in nutrition. The ingestion of some forms of zinc causes the creation of toxic zinc salts in the acidic environment of the stomach. Zinc toxicity has been documented in people as well as in a wide range of large, small, exotic, and wild animals. Exposure typically stems from dietary indiscretion. Household sources of zinc include paint, batteries, automotive parts, zinc oxide creams, vitamin and mineral supplements, zipper pulls, board-game pieces, pet carrier screws and nuts, and the coating on certain types of pipes

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and cookware. One of the most well-known sources of zinc that causes toxicity after ingestion is the US Lincoln penny.

Ingested zinc is primarily absorbed from the duodenum and the intestine by a carrier-mediated mechanism. Zinc absorption is decreased in the presence of phosphates and calcium in the diet. However, the presence of some peptides, amino acids, and ethylenediaminetetraacetic acid disodium (EDTA) may cause an increase in absorption. Generally, the stomach acid provides for rapid release of zinc from ingested metallic objects. The mechanism of action producing clinical signs is not well defined or understood.

Clinical signs vary based on the duration and degree of exposure. Signs progress from anorexia, vomiting, diarrhea, and lethargy to more advanced signs such as intravascular hemolysis, icterus, hemoglobinuria, cardiac arrhythmias, and seizures. Large animals often show decreases in weight gain and milk production, and lameness has been reported in foals secondary to epiphyseal swelling.

With early diagnosis and treatment, the outcome is usually favorable for animals with zinc toxicosis. Eliminating exposure to zinc in the environment is essential to prevent recurrence.

5.17 Salt Poisoning/Deficiency

Salt is a necessary nutrient for the health of animals and many nutrition texts divide it into separate requirements for sodium (Na) and chloride (Cl). Daily requirements for salt will increase due to lactation, exertion, and increases in ambient temperatures. An excess of salt intake can lead to the condition known by various names including salt poisoning, hypernatremia, sodium ion toxicosis, and water deprivation-sodium ion intoxication. The last name in this list is the most descriptive, giving both the result (sodium ion intoxication) and the most common predisposing condition (water deprivation).

5.17.1 Mechanism of Action

As the sodium ion concentration of the serum increases, water will move out of the interstitium and intracellular fluid into the ECF along the osmotic gradient. Sodium will passively diffuse across the blood-brain barrier increasing the sodium concentration of the cerebral spinal fluid above the normal range (135–150 mmol/L). During this developing hypernatremia, the cells of the brain will also increase their intracellular osmolarity to prevent excess water loss to the ECF, which would cause cell shrinkage. If the hypernatremia develops too quickly and this protective mechanism fails, significant cell shrinkage occurs and the entire brain shrinks and pulls away from the calvarium resulting in the disruption of the blood supply to the brain. The brain response to a rapid decrease in serum sodium is delayed and the developing osmotic gradient will cause water to move into the brain causing swelling, cerebral edema, and the development of clinical signs. This can result in subarachnoid, subdural, or intravascular hemorrhages.

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5.17.2 Toxicity

Salt poisoning in dogs and cats results in clinical signs of vomiting, diarrhea, inappetence, lethargy, walking drunk, abnormal fluid accumulation within the body, excessive thirst or urination, potential injury to the kidneys, tremors, seizures, coma, and even death when untreated. Poultry, feeder pigs, and ruminants are more susceptible. Blindness, deafness, or paralysis may result. Clinical signs have best been described in swine and include loss of appetite, thirst, restlessness, pruritus, and constipation. These early clinical signs can progress over several days to aimless wandering, head pressing, circling, or pivoting around a limb. The animal may display seizure-like activity and assume a dog-sitting position, draw its head back in a jerking motion, and fall over on its side. After salt poisoning, pathognomonic histological appearance indicating brain perivascular cuffing of eosinophils in cerebral cortex and meninges known as eosinophilic meningoencephalitis has been reported (Fig. 5.13). Salt deficiency can lead to pica in animals (Fig. 5.14). Pica can be a serious problem because items such as rubber bands, socks, rocks, and string can severely damage or block the intestines.

5.17.3 Treatment

In the dog, acute ingestion of salt can best be treated by allowing the animal full access to water. Emetics may be used. In acute hypernatremia, the use of 5% dextrose solution in combination with a loop diuretic has been suggested. Diuretics such as furosemide can be used to prevent the development of pulmonary edema. The use of slightly hypertonic intravenous fluids has been recommended to reduce the likelihood of cerebral edema developing. The use of slightly hypertonic intravenous fluids has been recommended to reduce the likelihood of cerebral edema developing. If brain edema is suspected, the use of mannitol, dexamethasone, or dimethyl sulfoxide may aid in control.

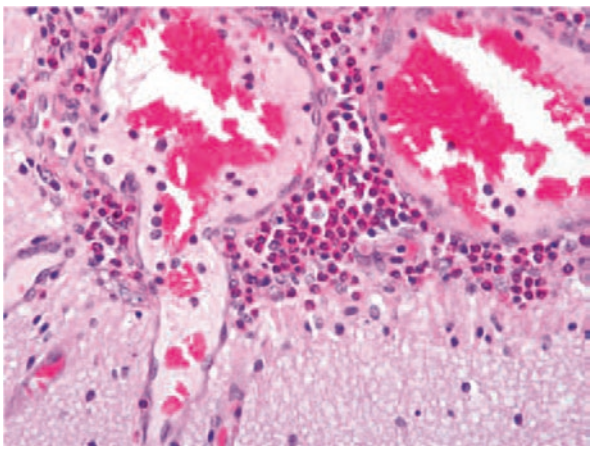


Fig. 5.13 Perivascular cuffing of eosinophils (eosinophilic meningoencephalitis) in the cerebral cortex and meninges after salt poisoning. (https://www.askjpc.org/wsco/wsc/images/2008/082201-1.jpg)

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Fig. 5.14 Pica can be a serious problem because items such as rubber bands, socks, rocks, and string can severely damage or block the intestines. (https://animalwellnessmagazine.com/wp-content/uploads/345.jpg)

5.18 Sulfur and Lime-Sulfur Poisoning/Deficiency

As discussed earlier (Chap. 4), sulfur and lime sulfur are two of the oldest insecticides. Sulfur is a non-metal. It can occur in four different oxidation states: −2 (sulfide), 0 (elemental sulfur), +4 (sulfite), and +6 (sulfate). All valence states, except elemental sulfur, are found in biologic molecules. It is incorporated into many essential molecules, including biotin, chondroitin sulfate, cartilage mucopolysaccharides, coenzyme A, fibrinogen, glutathione, heparin, lipoic acid, mucins, and thiamine. In addition to these biologically active compounds, sulfur is an intricate component of sulfur-containing amino acids, such as methionine, cysteine, cystine, homocysteine, and taurine. With the exception of thiamine and biotin, all sulfur-containing compounds in the body can be synthesized from methionine. Thus, thiamine, biotin, and methionine are essential nutrients in the diet of monogastric animals, but ruminant microbes can synthesize these compounds from inorganic sulfate in the diet. However, ruminants tend to be more sensitive to the toxic effects of dietary sulfur/sulfate due to efficient microbial conversion to bioactive sulfur species in the rumen. Species differences are such that cats cannot synthesize taurine from methionine, making it an essential nutrient in their diets.

5.18.1 Mechanism of Action

Acute oral poisoning with elemental sulfur results in the formation of hydrogen sulfide, as well as many other potential metabolites. The gastric and respiratory effects are postulated to be due to the coagulative effects of rumen-produced sulfurous acids and the irritating effects of hydrogen sulfide, respectively. However, the

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exact mechanisms are not well delineated. Inhaled ruminal sulfide at high concentrations may act in a similar mechanism to high concentrations of exogenous hydrogen sulfide gas, causing acute respiratory paralysis. The mechanism of subacute sulfur poisoning has been more extensively researched. This condition is correlated with the reduction of the sulfate or other forms of sulfur to sulfide in the rumen. The current literature suggests that inhibition of cytochrome C oxidase, which is essential for cellular respiration, is the primary mechanism of poisoning.

The subacute to chronic, indirect effects of excessive sulfur are seen in ruminants, due to the efficient conversion of sulfur compounds to sulfide. The sulfide can form insoluble salts with copper and zinc, but it can also react with molybdenum and form thiomolybdate complexes, which efficiently bind copper making it non-bioavailable.

5.18.2 Toxicity

Acute oral sulfur poisoning is scarce. Important clinical signs include abdominal pain, colic, rumen stasis, fetid diarrhea, dehydration, metabolic acidosis, tachypnea, recumbency, and hydrogen sulfide smell are expected. Other symptoms are irritation, edema, and hemorrhage of the gastrointestinal tract and respiratory tract. In addition, renal tubular necrosis can be seen. Monogastric animals are much less susceptible to the subacute direct and indirect toxic effects of excessive sulfur intake than ruminants because indirect toxic effects of excessive sulfur are related to rumen conversion to sulfides. Subacute ingestion of toxic doses of sulfate/sulfur has been associated with polioencephalomalacia (PEM), a necrotizing lesion of the brain. Gross and histologic lesions are primarily in the brain, but ruminal changes can be observed. Gross pathologic lesions include a darkening of the rumen contents from precipitated sulfide salts, swelling of the cerebral hemispheres, softening of the cerebral hemispheres, and yellow discoloration of the cortical gray matter.

Deficiencies Subacute to chronic sulfur-induced mineral deficiencies can result in severe health problems. Copper deficiency can cause poor growth, weakness, poor immune function, poor reproductive function, and death. In addition, sulfur-induced copper deficiency may play a role in PEM. Severe copper deficiency also causes myelin degeneration (enzootic ataxia) in lambs, deer, and other ruminants. Sulfate-induced selenium deficiency can cause poor growth, weakness, poor immune function, poor reproductive function, damage to the cardiac or skeletal muscles, and death.

5.18.3 Treatment

Treatment for acute sulfur poisoning is predominantly supportive in nature, with removal of the causative material as well as administration of fluids and electrolytes. Treatment of acute hydrogen sulfide poisoning by induction of

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methemoglobinemia with nitrite to allow for the formation of sulfmethemoglobin, similar to therapeutic protocols for treatment of cyanide poisoning, may be useful. This type of therapy may also be beneficial in the treatment of subacute direct sulfur poisoning. The primary treatment of indirect mineral deficiencies resultant from high sulfur intake would also include enhanced supplementation of copper and potentially selenium.

5.19 Questions and Answers

5.19.1 Short Questions and Answers

Exercise 1

Q.1. What is Burtonian line?
- The Burton line or Burtonian line is a clinical sign found in patients with chronic lead poisoning. It is a stippled blue line seen at the junction of the gums usually nearer to tooth caries, especially in the upper jaw. This is due to the deposition of lead sulfide formed by the action of the combination of lead sulfide formed by the action of the combination of lead with hydrogen sulfide which had evolved from the decomposed food debris in the caries tooth.

Q.2. What is the effect of lead on bone?
- Lead can accumulate in bones.

Q.3. Why milk from lead-affected animals is dangerous for young ones?
- Considerable amount of lead is excreted in milk (about 5% of blood concentration). Since young animals have greater capacity to absorb lead than adults, milk from lead-affected animals is dangerous to young ones.

Q.4. Why lead poisoning is more common in veterinary cases?
- Lead is ubiquitous in nature. Most of the animals live at a closer level to soil and hence get more exposure. Further, habits like frequent digging of soil seen in dogs and cats increase exposure. Ultimately, increasing vehicular and industrial pollution is the major reason for lead toxicosis.

Q.5. What is Minamata disease?
- Minamata disease was identified in Japan. This disease is caused due to the consumption of fish contaminated with methylmercury. Children born during an outbreak of Minamata disease had severe mental problems.

Q.6. Why young animals are more susceptible for mercury poisoning?
- Developing nervous system is more susceptible to mercury. Hence young ones are more susceptible.

Q.7. Which form of arsenic is nonpoisonous?
- Arsenic is a heavy metallic inorganic irritant poison. Metallic arsenic is not poisonous as it is insoluble in water and cannot be absorbed from the GI tract.

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Q.8. What is the mode of action of arsenic?
- Arsenic compounds act by inactivating the sulfhydryl enzymes, which in turn interfere with the cellular metabolism, in the liver, lungs, intestinal wall, and spleen. Arsenic can replace phosphorus in the bones where it may remain for years. It also gets deposited in the hairs.

Q.9. What are Meese's lines?
- Meese's lines are *lines* of discoloration across the nails of the fingers and toes (whitish lines 1 to 2 mm breadth) across the nail of the finger and toes. These symptoms represent chronic arsenic poisoning as a result of high sulfhydryl content of the keratin.

Q.10. In arsenic poisoning, why milk is considered unfit, whereas meat is passed for human consumption?
- Arsenic gets methylated and gets rapidly excreted through urine, milk, sweat, etc. Hence, milk is considered unfit for consumption. As arsenic tends to accumulate only in visceral organs and not in muscles, flesh of surviving animal is considered fit for human consumption.

Q.11. Is arsenic cumulative in animals?
- No; arsenic is rapidly detoxified and is completely eliminated in few days.

Q.12. In which species of animals, organic arsenicals cause nervous symptoms?
- Swine are mostly affected. Nervous symptoms include ataxia, incoordination, etc.

Q.13. Which form of arsenic is more toxic?
- Arsenite (As3+ or trivalent) is 5–10 times more toxic than Arsenate (As5+ or pentavalent) due to higher solubility.

Q.14. Malicious poisoning is very common with which arsenic compound?
- Arsenic trioxide

Q.15. What is half-life of cadmium?
- Half-life of cadmium is about 30 years.

Q.16. In which form chromium is available?
- Chromium occurs in a number of oxidation states from Cr + 2 to Cr + 6, but only the trivalent (Cr + 3) and hexavalent (Cr + 6) forms are of biological significance.

Q.17. Which form of chromium is toxic?
- The trivalent compound is the most common form found in nature. The hexavalent form is of greater industrial importance. In addition, hexavalent chromium, which is not water soluble, is more readily absorbed across cell membranes than is trivalent chromium. In vivo the hexavalent form is reduced to the trivalent form, which can complex with intracellular macromolecules, resulting in toxicity. Chromium is a known human carcinogen and induces lung cancers among exposed workers.

Q.18. What is selenium toxicity?
- Selenium is a non-metal that functions as both toxicant and an essential element. Selenium poisoning occurs when animals ingest excessive amounts of selenium. In its most severe form, it causes blindness and staggering. It can also cause cracked hooves and lameness.

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Subacute toxicity is called blind staggers and caused by the accumulation of 2–5 ppm of selenium in dry matter content

Q.19. What is fluorosis?
- Fluorosis is a chronic condition caused by excessive intake of fluorine compounds, marked by mottling and staining of the teeth and, if severe, calcification of the ligaments and abnormalities of the skeleton are observed.

Q.20. What is molybdenum poisoning?
- It is caused by imbalance in copper/molybdenum ratios in soil. Ruminants, especially young cattle, are most susceptible.

5.19.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. Exposure to fumes of which of the following metals is most likely to cause acute chemical pneumonitis and pulmonary edema?
(a) Lead
(b) Zinc
(c) Cadmium
(d) Copper
(e) Magnesium

Q.2. Deficiency of which element in the sow predisposes baby pigs to toxicosis by injectable iron preparations?
(a) Copper
(b) Chromium
(c) Magnesium
(d) Selenium
(e) Zinc

Q.3. Which of the following is NOT commonly associated with mercury vapor poisoning?
(a) Acute, corrosive bronchitis
(b) Interstitial pneumonitis
(c) Tremor
(d) Increased excitability
(e) Vomiting and bloody diarrhea

Q.4. Which form of mercury was the predominant cause of Minamata Bay disease?
(a) Metallic mercury.
(b) Mercuric salts.
(c) Mercurous salts.
(d) Organic mercury compounds.
(e) Mercury was not the causative agent.

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Q.5. Which is the only arsenical that can cause blindness?
(a) Arsenic trioxide
(b) Arsenic pentoxide
(c) Arsine
(d) Arsinilic acid

Q.6. Copper has inverse interrelationship with the following element(s):
(a) Iron
(b) Molybdenum
(c) Sulfur
(d) Both b and c

Q.7. In lead poisoning, basophilic stipplings (BS) are commonly seen in this species:
(a) Cattle
(b) Sheep
(c) Dog
(d) Horse

Q.8. Which of the following chelating agent(s) that is/are used for treating mercury poisoning?
(a) Dimercaprol (BAL)
(b) D-Penicillamine
(c) DMSA (Succimer)
(d) Na-thiosulfate.

Q.9. Which of the following nutrient(s) can counteract toxicity of organic mercurial?
(a) Vitamin A
(b) Vitamin D
(c) Vitamin E
(d) Selenium

Q.10. Which is the only arsenical that can cause blindness?
(a) Arsenic trioxide
(b) Arsenic pentoxide
(c) Arsine
(d) Arsinilic acid

Answers

Exercise 2

1. c	6. d (Both b and c)
2. d	7. c
3. e	8. a, b, c, and d (all)
4. d	9. c and d
5. d	10. d

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5.19.3 Fill in the Blanks

Exercise 3

Q.1. The type of climates in which selenium toxicity is more common is _____ climates.
Q.2. The pH of the soil, which favors selenium accumulation, is _____.
Q.3. The metabolite of selenium excreted through urine is _____.
Q.4. Cytotoxicity of selenium is due to the generation of _____ at cellular level.
Q.5. The nonenzymatic antioxidant depleted by selenium is _____.
Q.6. In selenium poisoning, the characteristic odor observed is _____.
Q.7. The vitamin that can aggravate selenium poisoning is _____.
Q.8. Subacute toxicity of selenium is also known as _____.
Q.9. Chronic selenium toxicity is also called as _____.
Q.10. In cattle, cracked and overgrown hooves are the main symptoms of _____ poisoning.

Answers

Exercise 3

1. Arid and semiarid	6. Garlic-like
2. Alkaline (>7.0)	7. Vitamin E
3. Trimethyl-selenonium	8. Blind staggers
4. Free radicals	9. Alkali disease
5. Glutathione (GSH)	10. Selenium

5.19.4 True or False Statements

Write (T) for true and (F) for false statement.

Exercise 4

Q.1. Chelating agent used to treat copper poisoning is sodium nitrate.
Q.2. The species of animal which is more susceptible of copper poisoning is sheep.
Q.3. The species which is highly resistant to copper poisoning is cattle.
Q.4. The ratio of copper to cadmium in feeds should ideally be 6:1.
Q.5. The breed of dog that is highly susceptible to copper toxicosis due to genetic predisposition is Bedlington Terrier.
Q.6. The deficiency of molybdenum micro-mineral predisposes to copper toxicity.
Q.7. The specific transport proteins for copper in the body are transcuperin and ceruloplasmin.

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Q.8. The primary organ for accumulation (storage) of copper in the body is bone.
Q.9. The major route of elimination for copper from body is urine.
Q.10. Molybdenum and sulfur reduce toxicity of copper by increasing excretion.

Answers

Exercise 4

1. F	6. T
2. T	7. T
3. F	8. F
4. F	9. F
5. T	10. T

5.19.5 Match the Statements

(Match the following statements in Columns A and B)

Exercise 5

Column A	Column B
Q.1. Burton line	a. Minamata disease
Q.2. Methylmercury	b. Arsenic
Q.3. Raindrop pigmentation	c. Lead
Q.4. Metallothionein	d. Overgrown hooves
Q.5. Selenium	e. Phosphorus
Q.6. Aluminum phosphide	f. Cadmium
Q.7. Sodium thiosulfate solution	g. Sulfur
Q.8. Beauty mineral	h. Iodine
Q.9. Teeth and bones	i. Copper
Q.10. Molybdenum	j. Fluoride

Answers

Exercise 5

Q.1	c. Lead
Q.2	a. Minamata disease
Q.3	b. Arsenic
Q.4	f. Cadmium
Q.5	d. Overgrown hooves
Q.6	e. Phosphorus
Q.7	h. Iodine
Q.8	g. Sulfur
Q.9	j. Fluoride
Q.10	i. Copper

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Toxicologic Hazards of Solvents, Gases, Vapors, and Other Chemicals

6

Abstract

This chapter deals with toxicologic hazards of solvents (alcohols, glycols, and petroleum), toxic gases and vapors (carbon monoxide, hydrogen sulfide, oxides of nitrogen, cyanide gas, gaseous ammonia, smoke inhalation, phosphine gas, etc.), organic compounds, brominated flame retardants, perfluorinated agents, persistent halogenated aromatic products, coat tar products, pentachlorophenols, and household products (chlorine bleaches, detergents, soaps and shampoos, etc.) In animals, among these chemicals, household chemicals (e.g., products containing alcohols, bleaches, or corrosives) found in the home represent a risk of toxicosis if companion animals are exposed to concentrates or undiluted products, but casual exposure to areas in which these compounds have been used appropriately rarely causes any serious problems. However, hydrogen sulfide (H_2S; "sewer gas," "swamp gas," "sour gas," and "stink damp") is most commonly encountered as a by-product of the decomposition of sulfur-containing organic material. In general, the toxic effects of multiple solvents are additive; solvents may also interact synergistically or antagonistically.

Keywords

Toxic solvents · Vapors · Toxic gases · Household products · Alcohol toxicity · Inhalants · Question and answer bank · Multiple choice questions

6.1 Introduction

This chapter deals with toxicologic hazards of solvents (alcohols, glycols, and petroleum), toxic gases and vapors (carbon monoxide, hydrogen sulfide, oxides of nitrogen, cyanide gas, gaseous ammonia, smoke inhalation, phosphine gas, etc.), organic compounds, brominated flame retardants, perfluorinated agents, persistent halogenated aromatic products, coat tar products, pentachlorophenols, and

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household products (chlorine bleaches, detergents, soaps and shampoos, etc.). This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true or false statements as relevant to toxicity of important solvents, gases, and chemicals in animals.

Key Points

- The toxic effects of multiple solvents are additive; solvents may also interact synergistically or antagonistically.
- The toxicology of gases is also broadly applicable to the toxicology of vapors. Depending on their physicochemical properties, gases can produce site-of-first-contact effects or systemic toxicity following absorption.
- Both acute lethal and sublethal CO poisonings are well-known problems in intensive pig operations, particularly those relying on gas heating systems.
- Household chemicals (e.g., products containing alcohols, bleaches, or corrosives) found in the home represent a risk of toxicosis if companion animals are exposed to concentrates or undiluted products, but casual exposure to areas in which these compounds have been used appropriately rarely causes any serious problems.
- Hydrogen sulfide (H_2S; "sewer gas," "swamp gas," "sour gas," and "stink damp") is most commonly encountered as a by-product of the decomposition of sulfur-containing organic material.
- Exposure to organic compounds such as PBBs, PCBs, PCDDs, and PCDFs has been linked with a broad spectrum of effects. For example, exposure to TCDD during pregnancy causes prenatal mortality in several animal species.
- A variety of coal-tar derivatives such as cresols (phenolic compounds), crude creosote (composed of cresols, heavy oils, and anthracene), and pitch are toxic.
- Several brominated flame retardants and perfluorinated chemicals containing bromine- and fluorine-containing organohalogens pose a threat on the global scale for present and future adverse health effects in animals and humans.
- Household chemicals (e.g., products containing alcohols, bleaches, or corrosives) found in the home represent a risk of toxicosis if companion animals are exposed to concentrates or undiluted products, but casual exposure to areas in which these compounds have been used appropriately rarely causes any serious problems.

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6.2 Solvent Toxicity

A solvent is a liquid organic chemical that has the ability to dissolve, suspend, or extract other materials, without chemical change to the material or solvent, and has variable lipophilicity and volatility, small molecular size, and lack of charge. Solvents are readily absorbed from the gastrointestinal tract and across the skin.

Commercial solvents are frequently complex mixtures and may include nitrogen- or sulfur-containing organics—gasoline. Most solvents produce some degree of CNS depression.

The common solvents fall into the following groups:

- Aliphatic hydrocarbons, such as hexane. These may be straight or branched-chain compounds and are often present in mixtures.
- Halogenated aliphatic hydrocarbons. The best-known examples are methylene dichloride, chloroform, and carbon tetrachloride, although chlorinated ethylenes are also widely used.
- Aliphatic alcohols. Common examples are methanol and ethanol.
- Glycols and glycol ethers. Ethylene and propylene glycols (PG), for example, in antifreeze give rise to considerable exposure of the general public. Glycol ethers, such as methyl cellosolve, are also widely used.
- Aromatic hydrocarbons. Benzene is probably the one of greatest concern, but others, such as toluene, are also used.

Our knowledge of the toxicity of solvent mixtures is rudimentary relative to the toxicology of individual solvents. While the assumption is frequently made that the toxic effects of multiple solvents are additive, solvents may also interact synergistically or antagonistically.

The commonly used solvents include isopropanol, toluene, xylene, and solvent mixtures such as white spirits and the chlorinated solvents, methylene chloride, trichloroethylene (TCE), and perchloroethylene. In the recent past, 1-bromopropane has been introduced, to replace ozone-depleting agents such as 1,1,1-trichloroethane (methylchloroform).

In general, the majority of systemic absorption of inhaled volatile organic compounds (VOCs) occurs in the alveoli, although limited absorption has been demonstrated to occur in the upper respiratory tract. Gases in the alveoli are thought to equilibrate almost instantaneously with blood in the pulmonary capillaries. Usually they have low toxicity, but like the petroleum products (which many are), they must be considered as possible causes of poisoning. Due to limited space, only a few selected solvents have been discussed below.

6.2.1 Alcohols and Glycols

6.2.1.1 Ethanol Toxicosis

Clinical findings in dogs and cats with ethanol intoxication can be correlated with blood-ethanol concentration (BEC). Clinical signs include ataxia, lethargy, sedation, hypothermia, metabolic acidosis, vomiting, diarrhea, and poor breathing.

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Levels of 2–4 mg/mL in adult dogs have produced clinical signs ranging from ataxia and coma. The time of onset of clinical signs is dependent on the dose ingested and the amount of food present in the GI tract, but it usually occurs within an hour of ingestion.

Mechanism of Action The mechanism of action of alcohol on the CNS is related in part to its interactions with biomembranes and its probable inhibition of gamma-aminobutyric acid receptors.

Treatment The animal has to be treated based on clinical signs. However, patients must be given ADH inhibitors such as 4-methylpyrazole to prevent the formation of toxic metabolites. Respiratory depression may require the administration of doxapram (a respiratory stimulant) or in severe cases mechanical ventilation. Emesis should not be induced in dogs or cats with severe ataxia or CNS depression as the animal could become recumbent or comatose.

6.2.1.2 Methanol Toxicosis

Methanol (methyl alcohol or wood alcohol, CH_3OH) is widely used as a solvent, fuel (Sterno), gasoline additive, antifreeze, and windshield washer fluid (30–40% methanol). Ingested methanol is absorbed quickly from the GI tract, and peak methanol concentrations occur within 30–60 min following ingestion. Toxicosis has also been reported following inhalation or dermal absorption. The rate of elimination of methanol from the blood is slower than that of ethanol. Methanol is metabolized by ADH to formaldehyde, which is oxidized to formic acid by formaldehyde dehydrogenase. In mammals other than primates, formic acid is detoxified relatively rapidly to yield carbon dioxide and water. Formic acid is metabolized less efficiently in primates. This may lead to the accumulation of formic acid, which plays a major part in the development of acidosis observed in primates. Consequently, methanol is more toxic to humans and nonhuman primates than it is to other mammals.

Mechanism of Action Formic acid is responsible for ocular and CNS lesions in primates as a result of the inhibition of cytochrome oxidase. Blindness and permanent neurological abnormalities are common sequelae in primates.

Toxicology Clinical signs in animals other than primates are similar to those seen with ethanol toxicosis and are primarily related to CNS depression. Vomiting and abdominal pain may be seen. In primates, following the initial nausea and CNS depression, a latent period of approximately 12–24 h is followed by metabolic acidosis and impaired visual function. Coma, other CNS signs, and death (20–30 h) may follow after significant exposures.

Treatment in non-primates is symptomatic and similar to treatment for ethanol toxicosis.

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6.2.1.3 Glycol Toxicity

Ethylene glycol (EG) (1,2-dihydroxyethane) is a constituent of antifreeze, deicers, hydraulic fluids, drying agents, and inks and is used to make plastics and polyester fibers. Diethylene glycol (DEG) is used as an excipient in a liquid sulfanilamide preparation. Propylene glycol (PG) is used as an intermediate in the synthesis of polyester fibers and resins, as a component of automotive antifreeze/coolants, and as a deicing fluid for aircraft. Rare cases of poisoning may be observed in dogs or cats. Exposure to glycols and their metabolites are mainly responsible for CNS toxicity. The accumulation of glycolic acid and glyoxylic acid leads to metabolic acidosis. Acidosis is also thought to lead to altered levels of consciousness and cerebral damage.

Therapy for EG poisoning is aimed at preventing absorption, increasing excretion, and preventing metabolism of EG. Supportive care to correct fluid, acid base, and electrolyte imbalances is also helpful.

6.2.2 Petroleum Toxicity

Intoxication of birds and animals with petroleum and chemicals used by the petroleum industry does occur. This chapter essentially focuses on terrestrial animals and especially livestock. Numerous reports that exist in the scientific literature show that cattle ingest crude petroleum and other oilfield substances. Cattle are attracted to and will ingest several gallons of petroleum. Deaths have occurred after cattle drank tractor paraffin and vaporizing oil. Heifers drank gasoline and cattle greedily ingested diesel oil flowing from a storage tank. Cattle have drunk from petroleum puddles near a tank battery, from slush pits, and from puddles of volatile petroleum and petroleum distillate.

Toxicity The sick cattle had petroleum distillate dripping from the nostrils and oil in their feces. Surviving animals had varied signs including anorexia and weight loss, and some of these animals died. Some reports indicate abortions to ingestion of petroleum products. Loss of body condition can also result from petroleum ingestion-linked chronic pneumonia and pleural adhesions. Animals exposed to high levels of some petroleum products have developed liver and kidney tumors. Whether specific petroleum products can cause cancer in humans is not known; however, there is evidence that occupationally exposed people in the petroleum refining industry have an increased risk of skin cancer and leukemia. Petroleum toxicity is more common in domestic and wild animals. Crude petroleum can be released into the environment during well blowouts, leaks at wellheads, pipeline leaks, land and sea shipping disasters, and other events and activities. Emissions can be from venting storage tanks, blowouts of gas wells, burning petroleum that has been spilled, or burning unwanted gaseous material. In general, chemicals associated with petroleum intoxication in cattle are the gaseous, liquid, and solid crude petroleum that contain natural gas, crude oil, and bitumen. Natural gas contains H_2S, other sulfur compounds, methane, and other petroleum hydrocarbons and is

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known as sour gas. Sour gas is extremely irritating to the eyes and respiratory tract. Many of the chemicals used have limited toxicological information, and the toxicology of chemical mixtures is unknown.

Cattle attracted to an area saturated with petroleum condensate can have sore feet mimicking signs of laminitis.

Treatment Treatment is symptomatic and supportive.

6.3 Toxic Gases and Vapors

Gas is defined as a state of matter consisting of molecules that have neither a defined volume nor shape at standard temperatures and pressures. A vapor is the gaseous phase of substances that are either solid or liquid at standard temperatures and pressures. Some of the toxic gases that are of veterinary clinical and veterinary occupational relevance include carbon monoxide (CO), hydrogen sulfide, oxides of nitrogen (silo filler's disease), gaseous ammonia (including anhydrous ammonia), and smoke inhalation). As a general rule, the toxicology of gases is also broadly applicable to the toxicology of vapors. Depending on their physicochemical properties, gases can produce site-of-first-contact effects or systemic toxicity following absorption. The usual driving force for the systemic absorption (i.e., entry into the central circulation) and tissue distribution of inhaled gases is diffusion down concentration gradients Metabolism of gases can occur locally in the respiratory tract or at other distant sites. Generally, biotransformation of gases within the respiratory tract primarily occurs at two main locations: within the olfactory and respiratory epithelia of the nasal cavity and within the club cells of the lung.

6.3.1 Carbon Monoxide (CO)

CO is colorless, odorless, and virtually undetectable without the use of gas detection technologies, hence its reputation as a "silent killer." Veterinarians, farm workers, and animals are at risk of exposure to CO in intensive animal production units that are heated by hydrocarbon combustion. Both acute lethal and sublethal CO poisonings are well-known problems in intensive pig operations, particularly those relying on gas heating systems.

Mode of Action The principal mode of action of CO is tissue hypoxia secondary to reduced blood oxygen-carrying capacity, i.e., it acts as a chemical asphyxiant. Reduced blood oxygen-carrying capacity occurs because of the preferential binding of CO rather than oxygen to hemoglobin (Hb). The presence of COHb also results in a left shift of the oxygen: Hb dissociation curve, further exacerbating tissue hypoxia. Organs and tissues with poorly developed anastomotic networks and high metabolic rates (e.g., the heart and brain) are especially susceptible to CO-induced

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hypoxia. Venous blood has a high level of COHb and is classically described as being "cherry red" in color. Myoglobin also has a higher affinity for CO compared with oxygen. Cardiac myoglobin is particularly vulnerable to this effect, and the result is direct myocardial depression. CO-myoglobin is described as having a bright pink to red coloration.

Toxicity The most common clinical presentation is that the animal is found either unconscious or dead following acute high-level CO exposure. Nonpigmented mucous membranes, nails, and skin may have "cherry red" color. When CO is used as a euthanasia agent in dogs, short periods of vocalization and agitation can occur, even when the animal is apparently unconscious. With nonlethal exposures, any body system, organ, or tissue can be affected. Most commonly, clinical signs pertain to hypoxic central nervous system (CNS) damage and may include apparent weakness, fatigue, depression, transient loss of consciousness, and seizure disorders. Cardiovascular signs and effects usually pertain to the effects of reduced blood oxygen-carrying capacity, tissue hypoxia, and direct effects on the myocardium and may include exercise intolerance, dyspnea, syncope, and cardiac arrhythmias and CNS injury. In pigs, the most common clinically observable effects are abortion storms, stillbirth, increases in perinatal mortality, and reduced neonatal growth rates. Reduced hatching rates may be observed in poultry. There is no specific antidote for CO poisoning. Resuscitation combined with oxygen is the only known effective approach to treatment. Rescue and treatment of individuals with CO poisoning is a matter for properly equipped and trained professionals.

6.3.2 Hydrogen Sulfide

Hydrogen sulfide (H_2S; "sewer gas," "swamp gas," "sour gas," and "stink damp") is most commonly encountered as a by-product of the decomposition of sulfur-containing organic material, particularly with manure tanks, septic tanks, sludge pits, cesspools or settling ponds, or enclosed spaces containing decomposing feed. Exposure of confined cattle to H_2S liberated by agitation of a manure pit has resulted in significant mortality. H_2S is rapidly absorbed through the lungs, although respiratory excretion is minimal. Metabolic detoxification to sulfate within erythrocytes and hepatocyte mitochondria occurs relatively rapidly. Sulfate is primarily eliminated in urine. Approximately 85% of an acutely lethal dose is eliminated per hour.

Mode of Action Hydrogen sulfide produces histotoxic anoxia. H_2S binds to the ferric moiety of cytochrome c oxidase, thus disrupting the mitochondrial electron transport chain and blocking of cellular aerobic energy generation. Anaerobic metabolism then predominates, resulting in lactate accumulation and metabolic acidosis.

Toxicity The H_2S toxicity is characterized by apnea, sudden collapse, loss of consciousness, and death. Individuals may occasionally recover from H_2S knockdown if exposure ceases, although permanent neurological damage is the usual sequel.

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Acute respiratory distress due to pulmonary edema occurs following prolonged exposures to greater than 250 ppm. At lower levels of exposure, upper respiratory and ocular irritation ("gas eye") effects may dominate the clinical picture. Sulfur deposits may be detectable on the eye lashes. Reactive airway disease, bronchiolitis obliterans, and pulmonary interstitial fibrosis have been reported in humans with chronic irritant exposures. Cardiac arrhythmias, nausea, vomiting, diarrhea, and abdominal pain are also common. There is currently no effective antidote for hydrogen sulfide poisoning. Resuscitation combined with oxygen is the only known effective approach to treatment. Rescue and treatment of individuals with hydrogen sulfide poisoning is a matter for properly equipped and trained professionals.

6.3.3 Oxides of Nitrogen (Silo Filler's Disease)

The main gas involved is nitrogen dioxide (NO_2), although other reactive oxides of nitrogen may also be present. NO_2 has a bleach-like odor, a reddish-brown to yellow color, and leaves a yellow stain on silage, wood, or other contact materials. It is heavier than air. The most commonly encountered source in veterinary medicine is from silos that have been recently filled with fresh organic material (notably corn or other grains) or from silage pits. NO_2 is formed when NO in fresh silage or silo contents comes in contact with oxygen in the air. Silage gas also typically contains carbon dioxide. Silo gas has been a cause of mortality in dairy cattle.

Mode of Action NO_2 dissolves in water to produce nitrous and nitric acids, which are irritant and corrosive. Free radical generation and associated damage are also important parts of the pathophysiology. The acids are also immunosuppressive and result in a reduced resistance to infection. With prolonged or high levels of exposure, NO_2 is absorbed. Absorbed NO_2 binds with high affinity to hemoglobin, forming nitrosyl hemoglobin, which is further oxidized to methemoglobin. This results in chemical asphyxia. Methemoglobinemia produces a left shift of the hemoglobin:oxygen disassociation curve, further impairing tissue oxygen delivery.

Toxicity Clinical disease is usually with harvest season, and the presentation depends on the concentration and duration of exposure. High-level exposures can produce sudden death due to bronchiolar spasm, laryngeal spasm, reflex respiratory arrest, and/or asphyxia. Lower exposures may be asymptomatic, or produce mild, self-limiting effects, or result in eye irritation, pulmonary edema, and/or acute respiratory distress syndromes. Mucous membrane irritation is uncommon because NO_2 also results in bronchiolitis obliterans, particularly in the small airways and alveolar ducts, and permanent restrictive lung disease. Bronchiolitis obliterans can develop weeks or months following the initial exposure. There is no specific antidote for nitrogen dioxide poisoning. Treatment requires specialist medical care.

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6.3.4 Gaseous Ammonia

Ammonia (NH_3) is most commonly encountered where swine and poultry production is common. Ammonia is lighter than air and will thus tend to rise from manure pits and from certain burning materials. The concentration of NH_3 in well-ventilated animal production facilities should remain below 30 ppm.

Mode of Action NH_3 is irritant and/or corrosive depending on the concentration. NH_3 reacts with tissue water to produce ammonium hydroxide, a strong alkali. The reaction is exothermic and capable of producing significant tissue burns. Ammonium hydroxide produces typical alkaline liquefaction necrosis. Alkali liquefaction necrosis results in deeper tissue damage than that caused by an acid of similar pH reserve. In addition, ammonium hydroxide tissue breakdown liberates water, aiding the further conversion of NH_3 to ammonium hydroxide.

Toxicity NH_3 is highly water soluble and thus tends to primarily affect the upper respiratory tract, mucous membranes, and the eye; however, deeper structures may be affected if the upper respiratory tract scrubbing is overwhelmed. Clinical signs associated with relatively low-level exposures pertain to eye and upper respiratory tract irritation: shallow breathing, excessive lacrimation, nasal discharge, keratoconjunctivitis, corneal opacity, atrophic rhinitis, dyspnea, hemoptysis, hoarse voice, dysphagia, reduced production values, and possibly increased rates of respiratory infections. Higher exposures can result in severe pulmonary disease and possibly acute respiratory distress. In animal production facilities, the best treatment is to improve ventilation and to reduce the accumulation of animal wastes within the facilities.

6.3.5 Smoke Inhalation

Smoke inhalation injury results from a combination of exposure to gaseous combustion products, particulate matter (which may be superheated), and superheated air. Thus, the syndrome results from a combination of thermal, gas, and particle effects. Smoke inhalation always involves some degree of CO and cyanide poisoning. Combustion of various materials leads to the production of cyanide gas. Other combustion products may include acrolein and other reactive aldehydes (organic combustion) and also chlorine, ammonia, ketones, hydrocarbons, and various acids (combustion of rubber and plastics).

Mode of Action Thermal damage primarily occurs in the upper respiratory tract, particularly in the oropharyngeal area, due to the poor heat conductivity of air and high dissipation of heat in the upper airways. Both pulmonary irritation and systemic effects occur. Systemic effects occur primarily due to direct and chemical asphyxiation. Chemical asphyxiation most commonly occurs as a result of a

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combination of CO and cyanide (CN) poisoning. Methemoglobinemia occurs due to direct heat denaturation of hemoglobin, as well as the inhalation of nitrites.

Toxicity Common early clinical signs of respiratory tract injury include hoarseness and a change in voice, carbonaceous nasal discharge or sputum, coughing, tachypnea, and use of accessory respiratory muscles. Later clinical signs are related to progressive pulmonary decline and acute respiratory distress.

Treatment, Control, and Prevention There is no specific treatment. The immediate treatment is the prompt removal of the patient from the source of exposure, maintenance of the airway, and aggressive management of acute respiratory distress using bronchodilation with a β_2-agonist (e.g., albuterol, terbutaline, epinephrine) which is an important aspect of treatment. Suppression of inflammation and prevention of secondary infections with broad-spectrum antibiotics are useful. Severe carbon monoxide poisoning combined with significant smoke inhalation is almost uniformly fatal. Hydroxocobalamin can be combined with thiosulfate administration. Methemoglobinemia after smoke inhalation is uncommon and can be managed with methylene blue treatment if required. The effectiveness of corticosteroids after smoke inhalation is contentious. Corticosteroids are notably beneficial in cases of metal fume fever.

6.3.6 Phosphine Gas Sources

Phosphide salts (commonly zinc and aluminum) release phosphine gas in the presence of acids and have been extensively used as vertebrate pesticides. Veterinarians are most commonly exposed to phosphine via inhalation when attempting to decontaminate and treat animals that have been poisoned with zinc or aluminum phosphide rodenticides or during necropsy/sample collection procedures on animals that died from these poisonings. Phosphine gas is also used as a fumigant for grain and other agricultural products. Phosphine is described as a "general protoplasmic poison," and it is extremely and acutely toxic after inhalation.

Toxicity Acute inhalation exposure to phosphine can result in respiratory, neurologic, and GI effects. Signs and symptoms may include headaches, dizziness, fatigue, drowsiness, burning substernal pain, nausea, vomiting, GI distress, cough with fluorescent green sputum, labored breathing, chest tightness, pulmonary irritation, pulmonary edema, tremors, and convulsions (may occur after apparent recovery). Skin contact with phosphides may result in numbness and paresthesia. Chronic occupational exposure effects include upper respiratory tract inflammation, weakness, dizziness, nausea, jaundice, liver effects, increased bone density, and symptoms referable to the GI, cardiorespiratory, and central nervous systems.

Treatment There is no antidote for phosphine poisoning, and emergency treatment requires specialist care.

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6.4 Organic Compounds

A number of organic compounds such as polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) are well-known for their contamination in the global environment. These chemicals can bioaccumulate and biomagnified in the food chains and exert toxic effects in wildlife, animals, and human beings. There are a number of ways by which animals can be, and have been, exposed to PCBs, PCDDs/PCDFs, and PBBs. Some of the scenarios involve ingestion of low concentrations of these chemicals through consumption of environmentally or accidentally contaminated feed or feed components. It is difficult to accurately assess their absorption, distribution, metabolism, and elimination.

Toxicity Exposure to these organic chemicals has been linked with a broad spectrum of effects, which vary depending on method/age of exposure, sex of the individual, and dose/duration of exposure. Fetal and early developmental exposures to these chemicals are particularly devastating and can have different outcomes from adult exposure. For example, exposure to TCDD during pregnancy causes prenatal mortality in the mouse, rat, guinea pig, hamster, rabbit, mink, and monkey, PCBs may produce adverse effect through their actions via neuroendocrine disruption. Several epidemiological studies have indicated that exposure to PCBs can contribute to hyperactivity and may contribute to the prevalence of attention deficit hyperactivity disorder (ADHD) in humans. Exposure to PCBs during brain development has been shown to increase activity levels in rats and mice, indicating that PCB exposure could potentially lead to ADHD-like symptoms.

6.5 Brominated Flame Retardants (BFRs) and Perfluorinated Compounds (PFCs)

Bromine- and fluorine-containing organohalogens are emerging as new pollutants that pose a threat on the global scale for present and future adverse health effects in animals and humans. Polybrominated diphenyl ethers (PBDEs) along with brominated bisphenols and cyclododecanes are three major groups of chemicals of BFRs predominantly used in numerous industrial and consumer products to make these materials more fire resistant. PFCs such as perfluorooctane sulfonate/sulfonic acid (PFOS) and related compounds are used as surfactants and have a wide range of industrial and commercial applications. Unlike chlorinated compounds such as DDT (1,1,1-trichloro-2,2-bis[p-chlorophenyl]-ethane) and other pesticides (hexachlorobenzene, hexachlorocyclohexanes, etc.) that are used as agricultural/public health insecticides, use of BFRs and/or PFCs has never resulted in direct exposure to farm, domestic, and/or pet animals. However, due to their unique physicochemical and biochemical properties, both BFRs and PFCs persist and pervade every component of the global ecosystem, leading to exposure of animals and humans and contributing to adverse health effects.

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Toxicity Laboratory animal studies and accidental poisoning case studies have shown that exposure to BFRs and/or PFCs may result in serious health effects, including endocrine disruption leading to reproductive and immune dysfunction, birth defects, neurotoxicity, and certain types of cancers. Although some BFRs have been banned or voluntarily withdrawn by manufacturers, human/animal exposure to these chemicals will continue for a long time, as is the case with chlorinated organic chemicals that exist in large quantities in our biosphere.

6.6 Persistent Halogenated Aromatic (PHAs) Poisoning

PHAs are a complex mixture of chemicals with differing molecular composition and persist in the environment. Important groups of PHAs include polybrominated diphenyl ethers (PBDEs), polychlorinated dibenzo-p-dioxins, dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), DDT, and triclosan. Exposure to PHAs results from contamination of the indoor environment, especially house dust, atmospheric deposition of PHAs, amending agricultural lands with sewage sludge and industrial wastes, industrial incidents, and feed contamination including by-product ingredients. Indoor dust is an important route of exposure of companion animals to PBDE fire retardants. PHAs can be biomagnified in body fat and liver, translocated to the fetus, and secreted in milk and eggs. PHAs can be present in feedstuffs fed to dogs and cats. For example, fish oil, which may be used in formulated diets, generally is twofold higher in PCDD/Fs than in meat and bone meal.

Mode of Action PHA groups and individual PHAs are potent up- and downregulators of enzyme systems by interaction with immunotoxic nuclear receptors; some PHAs interact with an assortment of endocrine receptors.

Toxicity PHAs are readily absorbed from the gut, lungs, and through the skin and can result in acute and chronic toxicity in domestic and wild animals. The general toxicology includes disruption of the immune and endocrine systems and associated organs/functions. Immunotoxicity is considered a sensitive parameter for some PCBs and TCDD/Fs congeners. The overall immune effect is reduced native resistance to infectious disease and a likely increased risk of neoplasia. Cats with lower capacity to metabolize PCBs have increased risk of acromegaly. Some PHAs are known to have an effect on thyroid endocrinology. Exposure to PCBs and brominated biphenyls can delay onset of parturition in cattle. PHAs can also be promoters of carcinogens.

In chickens, acute exposure to PHAs may cause a sudden drop in egg production followed by reduced egg hatchability, and altered thyroid function is associated with anomalous development in birds and mammals. In cats, acromegaly appears to be linked to a decreased ability to metabolize PCB congeners. Hyperthyroidism in cats is associated with high levels of PBDEs in house dust.

Treatment There is no known treatment. Supportive care is recommended. Attention should be given to the indoor environment.

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6.7 Coal-Tar Product Poisoning

Coal-tar derivatives such as cresols (phenolic compounds), crude creosote (composed of cresols, heavy oils, and anthracene), and pitch are toxic. Phenol is the most important toxicant in coal-tar products and is found in antiseptics, creosote, germicides, cleaners, and disinfectants.

Toxicity The cresols and phenols are readily absorbed orally and through the skin. These products are locally corrosive, causing necrosis and scarring of the skin, mouth, and esophagus. Signs may progress to weakness, CNS stimulation, tremors, and incoordination and cardiovascular depression and shock. Secondary anemia may develop. Capillary damage and hepatic or renal damage can occur. Icterus can result from intravascular hemolysis and hepatic damage. Death can occur from 15 min to several days after exposure. The first sign of pitch poisoning often is several dead animals. Other problems have included stillbirths in pigs and hyperkeratosis in calves. Cats are more susceptible because of limited ability to form glucuronides and excrete phenols.

Treatment There is no specific antidote for coal-tar product poisoning. Emetics and gastric lavage are not recommended for recent oral exposure. Activated charcoal and egg white help to dilute and bind the phenols and may reduce absorption. Administration of saline cathartics may be useful. Dermal exposures are mitigated by bathing with glycerol followed by liquid dish soap. Supportive therapy for shock, liver and kidney damage, respiratory failure, and acidosis are important. Use of *N*-acetylcysteine has been recommended. Oral antibiotics, B vitamins, vitamin E, and high-quality-protein diets may aid recovery.

6.8 Pentachlorophenol (PCP) Poisoning

PCP, commonly known as penta, has been used as a fungicide, molluscicide, insecticide, and wood preservative. Commercial lots of technical-grade penta contain small but biologically significant amounts of highly toxic impurities such as chlorinated dioxins and dibenzofurans, tetrachlorophenols, and hydroxychlorodiphenyl ethers; these compounds can exert their own effects such as early fetotoxicity. Penta is now permitted only for industrial purposes; agricultural and domestic uses are prohibited, because it is classified as a highly hazardous pesticide.

Mode of Action Penta can be absorbed through intact skin and lungs and is an intense irritant to the skin and mucous membranes. Penta absorption in skin was greater in water or water-based mixtures than in 100% ethanol. When absorbed, penta increases metabolism by uncoupling cellular phosphorylation.

Toxicity Commercial-grade penta causes hepatic porphyria, increased microsomal monooxygenase activity, and increased liver weight. Pure penta was not teratogenic in rats. Pentachlorophenol is considered to be a carcinogen and a tumor promoter,

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although studies have shown that the pure material does not increase the incidence of tumors in rats and mice. The technical-grade material has also been shown to be immunotoxic in laboratory studies. Cattle and pigs exposed to wood treated with commercial-grade penta had increased mortality, possibly decreased fertility in boars, and reduced productivity (milk, meat, etc.). Penta must be handled very carefully and kept away from animal contact.

Treatment There is no known antidote. Termination of exposure, bathing dermally exposed animals, oral administration of activated charcoal, and supportive therapy may be indicated. Treatment involves cooling the animal and administering fluids, electrolytes, and anticonvulsants. Bathing should be done gently with cold water and detergent so as not to cause vasodilation and increased absorption. Antipyretics, e.g., aspirin and acetaminophen, should not be used.

6.9 Smoke Inhalation

Smoke inhalation caused by fires is a major cause of fatalities in animals. Important agents involved in smoke inhalation include thermal injury, soot, carbon monoxide, cyanide gas, nitrogen, methane, oxides of nitrogen (NO_x), zinc oxide, phosphorus, sulfur trioxide, titanium tetrachloride, oil fog, Teflon® particles, and Teflon® pyrolysis products (polymer fume fever). Nitrogen and methane are not especially toxic; however, they are important in fires because they dilute oxygen in the breathable atmosphere.

Toxicity The most important aspects are duration and the circumstances of exposure (e.g., enclosed versus open spaces), amount of smoke inhaled, severity of injury to other animals, and the sources of the smoke (i.e., what toxicants are likely to have been present in the smoke). Smoke inhalation often occurs in the absence of obvious external physical injury. However, facial burns, oropharyngeal blistering and/or edema, changed voice, stridor, coughing, upper airway mucosal lesions, and carbonaceous discharges may be present. Evidence of lower respiratory tract injury such as tachypnea, dyspnea, cough, decreased breath sounds, wheezing, rales, rhonchi, and retractions may be present. In general, evidence of asphyxiant exposure commonly includes CNS depression, changes in affect, lethargy, generalized muscle weakness, and obtundation. Neurologic injury secondary to hypoxia, often permanent, is common under these circumstances. Coma after smoke inhalation is most commonly caused by severe carbon monoxide poisoning and the ensuing hypoxia. The prognosis is poor.

6.10 Household Hazards

Household chemicals such as products containing alcohols, bleaches, or corrosives found in the home represent a risk of toxicosis if companion animals are exposed to concentrates or undiluted products, but casual exposure to areas in which these

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compounds have been used appropriately rarely causes any serious problems (see also Chap. 4 Rodenticide Poisoning, Chap. 7 Toxicities from Human Drugs, Chap. 8 Poisonous Plants and Chap. 13 Food Hazards).

6.10.1 Chlorine Bleaches

Household bleaches contain sodium hypochlorite, and pool treatments may contain lithium, calcium, or sodium hypochlorites. Pets may be exposed by chewing on containers of undiluted product, drinking from buckets containing product diluted in water, or swimming in recently treated pools.

Toxicity The relative hazard of a particular bleach product depends on the concentration of hypochlorite, pH, and dilution of the product. In general, levels of hypochlorite <10% tend to be mild irritants; however, if the product has a pH >11 or <3.5, alkaline or acid corrosive injury may occur. Ingestion of dilute or moderate pH household bleach products rarely causes more than mild vomiting, hypersalivation, depression, anorexia, and/or diarrhea. Concentrated (>10%) bleach products or products with pH >11 may cause significant GI corrosive injury. Ingestion or inhalation of significant amounts of chlorine bleach occasionally results in hypernatremia, hyperchloremia, and/or metabolic acidosis. Acute inhalation may result in immediate coughing, gagging, sneezing, or retching. In addition to the immediate respiratory signs, animals exposed to concentrated chlorine fumes may develop pulmonary edema 12–24 h after exposure. Ocular exposures may result in epiphora, blepharospasm, eyelid edema, and/or corneal ulceration. Dermal exposure may result in mild dermal irritation and bleaching of the hair coat. Oral, dermal, and ocular irritation or ulceration are possible. Respiratory lesions may include tracheitis, bronchitis, alveolitis, and pulmonary edema.

Treatment For oral exposures, emesis and activated charcoal are contraindicated; instead, dilution with milk or water is recommended. If necessary, fluid therapy along with symptomatic treatment may be given. Bathing with mild shampoo and thorough rinsing is recommended for significant dermal exposures. Ocular exposures should be treated with physiologic saline, followed by fluorescein staining of the cornea to detect corneal injury.

6.10.2 Detergents, Soaps, and Shampoos

Mild detergents, soaps, and shampoos contain anionic and nonionic detergents; products included in this group include human and pet shampoos, liquid hand dishwashing soaps, bar bath soaps (except homemade soaps, which may contain lye), many laundry detergents, and many household all-purpose cleaners.

Toxicity Soaps and shampoos containing anionic and nonionic detergents are mild irritants, and toxicity is limited to ocular, oral, or GI irritation, which is usually mild and self-limiting. Cats exposed to undiluted shampoos or other products containing

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sodium lauryl sulfate may develop significant respiratory compromise after inhalation during grooming, including dyspnea, increased bronchial secretions, and mild pulmonary edema. Although the exact mechanism of this syndrome is not known, it may relate to interference by the detergent with normal pulmonary surfactants. Nausea, vomiting, and diarrhea are the most common signs. Secondary dehydration and electrolyte imbalance may develop in rare instances due to protracted vomiting or diarrhea. Cats grooming after application of sodium lauryl sulfate-containing products may develop moist respiratory sounds, cyanosis, and dyspnea within 1–3 h of exposure.

Treatment Dilution with milk or water may reduce the risk of spontaneous vomiting. Vomiting is usually self-limiting and responds to short periods of food and water restriction. In severe cases, antiemetics may be required. Rarely, parenteral fluid therapy is required to correct electrolyte or hydration abnormalities due to protracted vomiting or diarrhea. For ocular exposures, irrigation of eyes using tepid water or physiologic saline will usually suffice. For cats that have respiratory compromise, supplemental oxygen and general supportive care are recommended; in most cases, signs resolve within 24 h.

6.11 Questions and Answers

6.11.1 Short Questions and Answers

Exercise 1

Q.1. What are solvents?
- Solvents are frequently complex mixtures and may include nitrogen- or sulfur-containing organics—gasoline and other oil-based products. Solvents can be (a) *aliphatic hydrocarbons*, such as hexane; (b) *halogenated aliphatic hydrocarbons*, such as methylene dichloride, chloroform, and carbon tetrachloride; (c) *aliphatic alcohols*, such as methanol and ethanol; (d) *glycols and glycol Ethers*, such as *e*thylene and propylene glycols; and (e) *aromatic hydrocarbons*, such as benzene and toluene.

Q.2. What are common routes of exposure of solvents?
(a) Oral
(b) Inhalation (major)
(c) Skin

Q.3. What are biological properties of solvents?
- From a biological perspective, the most important properties of solvents are:
  (a) Volatility
  (b) High fat solubility (lipophilicity)
  (c) Small molecule size

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Q.4. What is a painter's syndrome?
- The painter's syndrome was first described in Scandinavia in the late 1970s and became a recognized occupational disease in these countries. The cluster of symptoms includes headache, fatigue, sleep disorders, personality changes, and emotional instability, which progress to impaired intellectual function and, ultimately, dementia. Early symptoms are often reversible if exposure is stopped.

Q.5. What are Inhalants?
- Inhalants are a broad range of intoxicative drugs whose gases or volatile vapors are breathed in via the nose or mouth. They are taken by room temperature volatilization or from a pressurized container (e.g., nitrous oxide) and do not include drugs that are sniffed after burning or heating. For example, amyl nitrite and toluene—the solvent used in contact cement and model airplane glue—are considered inhalants, but tobacco, cannabis, and crack are not, even though the latter are also inhaled (as smoke).

Q.6. What is sudden sniffing death syndrome?
- Sudden sniffing death syndrome (SSDS) is the most common killer of inhalant abusers. An especially exciting or frightening hallucination could also trigger SSDS. When the abuser is surprised or startled, he has a sudden surge of the hormone *epinephrine*.

Q.7. List three organic solvents that can cause hazards and risks.
(a) Chloroform
(b) Carbon tetrachloride
(c) Ethanol

Q.8. What are the hazards and risks of chloroform?
(a) Effective fat solvent, easily ingested, attacks the liver and the brain and nervous system, causing loss of control and anesthesia.
(b) Removes natural oils from skin, causing blistering.
(c) Dissolves sealants in plumbing systems.
(d) Vapors are poisonous and affect the nervous system: not flammable.

Q.9. What are hazards and risks of carbon tetrachloride?
(a) Carbon tetrachloride is an effective fat solvent, easily ingested, attacks the liver and the brain and nervous system, causing loss of control and anesthesia.
(b) Removes natural oils from skin, causing blistering.
(c) Dissolves sealants in plumbing systems.
(d) Liver damage may lead to liver cancer.

Q.10. How does ammonia poisoning occur in animals?
- It is caused by abrupt addition of feed-grade urea or ammonium salts to the ruminant diet.
- Mature ruminants are most susceptible, as they convert nonprotein nitrogen to ammonia, which is toxic.
- Toxic symptoms include muscle tremors, weakness, difficulty breathing, and death.

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6.11.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. Which of the following statements regarding solvents is *false*?
- (a) Solvents can be absorbed from the GI tract and through the skin.
- (b) Equilibration of absorbed solvents/vapors occurs most quickly in the lungs.
- (c) Solvents are small molecules that lack charge.
- (d) Volatility of solvents increases with molecular weight.
- (e) Most solvents are refined from petroleum.

Q.2. What is the route in which most solvents enter the environment?
- (a) Chemical spills
- (b) Contamination of drinking water
- (c) Evaporation
- (d) Improper waste disposal
- (e) Wind

Q.3. All of the following statements are true *except*:
- (a) Most solvents can pass freely through membranes by diffusion.
- (b) A solvent's lipophilicity is important in determining its rate of dermal absorption.
- (c) Hydrophilic solvents have a relatively low blood: air partition coefficient.
- (d) Biotransformation of a lipophilic solvent can result in the production of a mutagenic compound.
- (e) Hepatic first-pass metabolism determines the amount of solvent absorbed in the GI tract.

Q.4. Which off the following statements regarding age solvent toxicity is *true*?
- (a) GI absorption is greater in adults than it is in children.
- (b) Polar solvents reach higher blood levels in the elderly than they do in children.
- (c) Children are always more susceptible to solvent toxicity than are adults.
- (d) Increased alveolar ventilation increases uptake of lipid-soluble solvents to a greater extent than water-soluble solvents.
- (e) Increased body at percentage increases clearance of solvent chemicals.

Q.5. Huffing gasoline can result in which of the following serious health problems?
- (a) Renal failure
- (b) Pneumothorax
- (c) Hodgkin's disease
- (d) Encephalopathy
- (e) Thrombocytopenia

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Q.6. Which of the following statements regarding benzene is *false*?
(a) High-level exposure to benzene could result in acute myelogenous leukemia (AML).
(b) Gasoline vapor emissions and auto exhaust are the two main contributors to benzene inhalation.
(c) Benzene is used as an ingredient in unleaded gasoline.
(d) Benzene metabolites covalently bind DNA, RNA, and proteins and interfere with their normal functioning within the cell.
(e) Reactive oxygen species can be derived from benzene.

Q.7. Which of the following is *not* a criterion for fetal alcohol syndrome diagnosis?
(a) Maternal alcohol consumption during gestation
(b) Pre- and postnatal growth retardation
(c) Microcephaly
(d) Ocular toxicity
(e) Mental retardation

Q.8. Which of the following is *not* an important enzyme in ethanol metabolism?
(a) Alcohol dehydrogenase
(b) Formaldehyde dehydrogenase
(c) CYP2E1
(d) Catalase
(e) Acetaldehyde dehydrogenase

Q.9. Which of the following is *not* associated with glycol ether toxicity?
(a) Irreversible spermatotoxicity
(b) Craniofacial malformations
(c) Hematotoxicity
(d) Seminiferous tubule atrophy
(e) Cleft lip

Q.10. Which of the following statements regarding chlorinated hydrocarbons is *false*?
(a) Toxicities of trichloroethylene (TCE) are mediated mostly by reactive metabolites, not the parent compound.
(b) Glutathione conjugation is an important metabolic step of both trichloroethylene (TCE) and perchloroethylene (PERC).
(c) Many chlorinated hydrocarbons are used as degreasing agents.
(d) Chloroform interferes with intracellular calcium homeostasis.
(e) Carbon tetrachloride causes hepatocellular and kidney toxicity.

Q.11. The most serious consequence of crude oil or kerosene ingestion by cattle is
(a) Liver damage
(b) Kidney damage
(c) Aspiration pneumonia
(d) Central nervous system stimulation
(e) Leukemia

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Q.12. In regard to chemically induced adverse effects on the eye,
(a) No chemical has been shown to cause glaucoma.
(b) Nonionic detergents damage the eye more than cationic detergents.
(c) 2,4-Dinitrophenol, corticosteroids, and naphthalene are known to cause cataracts in humans.
(d) Methanol produces blindness by rendering the cornea and lens opaque.
(e) Acids usually produce late-appearing ocular toxicity as contrasted to alkalis which produce immediate damage.

Q.13. Which of the following agents would *not* likely produce reactive airways dysfunction syndrome (RADS)?
(a) Carbon monoxide
(b) Chlorine
(c) Ammonia
(d) Toluene diisocyanate
(e) Acetic acid

Q.14. The most serious consequence of crude oil or kerosene ingestion by cattle is
(a) Liver damage
(b) Kidney damage
(c) Aspiration pneumonia
(d) Central nervous system stimulation
(e) Leukemia

Q.15. Benzene is similar to toluene
(a) In its metabolism to redox active metabolites
(b) Regarding covalent binding of its metabolites to proteins
(c) In its ability to produce CNS depression
(d) In its ability to produce acute myelogenous leukemia
(e) In its ability to be metabolized to benzoquinone

Q.16. Sorbitol and other sugar alcohols have been associated with
(a) Respiratory distress syndrome
(b) Osmotic diarrhea
(c) Hepatotoxicity
(d) Immediate hypersensitivity reaction
(e) CNS depression

Q.17. Chloroform is *not*
(a) Central nervous system depressant
(b) Hepatotoxic
(c) Metabolized to phosgene
(d) Peroxisome proliferator
(e) Contaminant of chlorinated water

Q.18. Each of the following solvents is paired with a correct target organ of toxicity *except*___
(a) Methanol: retina
(b) Ethylene glycol: kidney
(c) Ethylene glycol monomethyl ether: kidney
(d) Dichloromethane: central nervous system
(e) Carbon tetrachloride: liver

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Q.19. Which of the following is *not* associated with spermatotoxicity in rats?
(a) Ethylene glycol monomethyl ether
(b) Ethylene glycol monoethyl ether
(c) Ethoxyacetic acid
(d) Methoxy acetic acid
(e) Propylene glycol monomethyl ether

Q.20. Methyl bromide (CH3Br)
(a) Is a liquid used primarily as a fumigant
(b) Has essentially no warning properties, even at physiologically hazardous concentrations
(c) Is extremely flammable
(d) Is of greater concern from its oral toxicity than from its inhalation toxicity
(e) Would not be expected to be readily absorbed through the lungs

Answers

Exercise 2

1. d	11. c
2. c	12. c
3. c	13. a
4. b	14 c
5. d	15. c
6. b	16. b
7. d	17. d
8. b	18. c
9. a	19. e
10. d	20. b

6.11.3 Match the Statements

Exercise 3

Match the statements in columns A and B

Column A	Column B
Q.1. Ethylene Glycol	(a) Hematopoietic toxicity
Q.2. Benzene	(b) Hepatotoxicity
Q.3. Alkyl benzene	(c) Reproductive toxicity
Q.4. Methanol	(d) Pulmonary toxicity
Q.5. Ethanol	(e) CNS toxicity
Q.6. Chlorinated hydrocarbons	(f) Ocular toxicity

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Answers

Exercise 3

Q.1.	c) Reproductive toxicity
Q.2.	a) Hematopoietic toxicity
Q.3.	e) CNS toxicity
Q.4.	f) Ocular toxicity
Q.5.	b) Hepatotoxicity
Q.6	d) Pulmonary toxicity

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Toxicities from Human Drugs

7

Abstract

This chapter deals with both veterinary and human drugs encompassing a large number of products, many containing multiple active ingredients, which are most often reported to cause acute poisonings or adverse reactions in animals. Drug poisonings in animals occur commonly due to off-label use of medicines, wrong dosage, negligence, accidental ingestion, and deliberate poisonings. Exposures to OTC drugs in pets can be accidental or intentional; however, veterinary drugs may become toxic in therapeutic doses when adverse effects may occur. In dogs, accidental ingestion and deliberate poisonings containing ma huang and guarana can have synergistic effects when ingested together and can lead to severe hyperactivity, tremors, seizures, vomiting, tachycardia, hyperthermia, and death within a few hours of exposure. Pets commonly ingest prescription medications from countertops, pill minders, mail-order packages, or other sources.

Keywords

Drug poisonings · OTC drug toxicity · Accidental ingestion · Accidental poisonings · Deliberate poisoning · Toxicities from human drugs · Question and answer bank · Multiple choice questions

7.1 Introduction

The topic of Toxicities from human drugs is complicated, encompassing a large number of products, many containing multiple active ingredients. These products quite often are causes of poisoning in both small and large animals. Drug poisonings in animals occur commonly due to off-label use of medicines, wrong dosage, negligence, accidental ingestion and deliberate poisonings. Toxicity of veterinary drugs may become evident also in therapeutic doses when adverse effects may occur. This chapter deals with both veterinary and human drugs encompassing a large number of products, many containing multiple active ingredients, which are most often reported

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to cause acute poisonings or adverse reactions in animals. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, and fill in the blanks as relevant to use of drugs. Supplements containing cyanobacteria (blue-green algae) that have been associated with microcystin toxicosis is addressed in Chap. 9.

Key Points

- Drug poisonings in animals occur commonly due to off-label use of medicines, wrong dosage, negligence, accidental ingestion, and deliberate poisonings.
- Toxicity of veterinary drugs may become evident also in therapeutic doses when adverse effects may occur.
- Exposures to OTC drugs in pets can be accidental or intentional.
- In dogs, accidental ingestion of herbal supplements containing ma huang and guarana can have synergistic effects when ingested together and can lead to severe hyperactivity, tremors, seizures, vomiting, tachycardia, hyperthermia, and death within a few hours of exposure.
- Pets commonly ingest prescription medications from countertops, pill minders, mail-order packages, or other sources.

7.2 Toxicities from Over-the-Counter Drugs

The drugs over-the-counter (OTC) may contain multiple active ingredients. Products are available for oral, topical, intraocular, intranasal, and intrarectal administration, although most veterinary exposures are through ingestion. These products that are readily available in many homes without a prescription are known as over-the-counter (OTC) medications. Exposures to OTC drugs in pets can be accidental or intentional.

Medicines used for the relief of cold, flu, and allergies are common and can contain multiple active ingredients, including analgesics, decongestants, antihistamines, antitussives, and expectorants. Decongestants may be sympathomimetic amines such as pseudoephedrine, ephedrine, phenylephrine, and phenylpropanolamine (PPA), and imidazolines such as oxymetazoline, xylometazoline, and tetrahydrozoline. Sympathomimetic amines and imidazolines are used as decongestants because of their vasoconstriction effects. Among these, pseudoephedrine is the most common decongestant associated with toxicosis in small animals, more often dogs than cats. Pseudoephedrine has been commonly used in cold and allergy preparations, but due to its illicit use in the manufacture of methamphetamine, many US states now regulate its sale. Pseudoephedrine is a stereoisomer of the plant alkaloid ephedrine. Ephedrine is found in *Ephedra* spp., an herbal drug used in asthma, allergy, and cold formulations, diet pills, and various supplements. Phenylephrine is

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found in nasal sprays and hemorrhoid creams. Other possible ingredients include ethanol, caffeine, xylitol, and benzocaine. These medications can come in a variety of forms, including oral tablets, extended-release tablets, dissolving granules/tablets, lozenges, and as syrup (liquid). Sympathomimetic amines can interact with digoxin, MAO inhibitors, halothane, and methylxanthines. Certain conditions are known to predispose animals to adverse reactions when given sympathomimetic amines. These include diabetes, hypothyroidism, hyperthyroidism, cardiac disease, hypertension, seizure disorders, renal disease, and glaucoma.

7.2.1 Decongestants

Toxicity Clinical symptoms depend up on the type and amount of the drug ingested by the animal. CNS stimulation is the common presentation for animals with decongestant overdose. Hyperactivity, restlessness, agitation, pacing, and vocalization are reported. Hallucinatory behaviors in dogs include staring into a corner or at unseen objects, perhaps even biting at them. Tremors, seizures, and head-bobbing can be observed. Hyperthermia can be secondary to increased activity, and disseminated intravascular coagulation (DIC) or rhabdomyolysis with associated renal failure are possible outcomes. Cardiovascular changes may include tachycardia, reflex bradycardia, hypertension, myocardial damage, hypertensive retinopathy, retinal detachment, and developed oral mucosal ulcers during hospitalization, which may resolve after recovery.

Treatment Treatment consists of detoxification, symptomatic, and supportive care. Emetics use is contraindicated in dogs with central nervous system signs due to the potential for aspiration. Gastric lavage can be performed in the stabilized, anesthetized, and intubated patient after a large ingestion. Activated charcoal and cathartic have been recommended. Tachycardia is treated with β-blockers. Use of propranolol and drugs α-adrenergic receptor-blocking agents, prazosin or phentolamine, can be given. Severe CNS stimulation sometimes requires treatment with more than one anticonvulsant. Acepromazine can be used to treat pseudoephedrine, ephedrine, or phenylpropanolamine (PPA) toxicosis. Acepromazine or chlorpromazine and, if needed, phenobarbital can be given for refractory seizures. Isoflurane anesthesia has been recommended to control severe clinical signs. Use of benzodiazepines is contraindicated because the dissociative effects of this drug class can exacerbate clinical signs of sympathomimetic amines. Fluid therapy and cautious urinary acidification help promote excretion.

7.2.2 Antihistamines

Antihistamines are often found in combination with other ingredients (e.g., decongestants, analgesics like acetaminophen, or NSAIDs) in many OTC cold, sinus, and allergy medications. A few of the commonly used antihistamines include

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chlorpheniramine, clemastine, dimenhydrinate and diphenhydramine, promethazine hydrochloride, meclizine, loratadine, and cetirizine. Antihistamines act by competitive inhibition of histamine at H_1 receptors. Binding is reversible but can become irreversible or slow to dissociate at high doses, as with terfenadine. H1 receptors are found in a variety of tissues, including the mast cells of the skin, smooth muscle of airways, gastrointestinal tract, urogenital tract, cardiovascular system, endothelial cells and lymphocytes, and mammalian CNS.

Toxicity Clinical signs of antihistamine overdose are usually evident within a few dosing. Signs of CNS depression can occur with therapeutic doses of first-generation antihistamines and include sedation, ataxia, and drowsiness. More severe clinical signs, such as profound depression, coma, respiratory suppression, convulsions, and myocardial depression, can lead to death. A dog with hydroxyzine toxicosis presented with tachycardia and weakness progressing to stupor, coma, loss of gag reflex, and apnea. Higher doses of antihistamines can have a stimulatory effect on the CNS, particularly in children and young animals. These effects are less common in adults. Overdosed young individuals appear to experience hallucinations, lack of coordination, disorientation, irritability, anxiety, aggression, seizures, and pyrexia. Salivation, vomiting, and diarrhea have been associated with first-generation antihistamines. Anticholinergic effects include dry mucous membranes, fixed and dilated pupils, tachycardia, and arrhythmia, and animals can be either hypertensive or hypotensive. Cardiac abnormalities were documented in humans and dogs that ingested terfenadine. Animals can have allergic reactions to topical or oral antihistamines. A list of associated clinical signs includes dermatitis, pyrexia, and photosensitization. Rhabdomyolysis, and associated renal lesions, or disseminated intravascular coagulation (DIC) are possible complications of antihistamine toxicosis.

Treatment Treatment of antihistamine toxicosis is primarily symptomatic and supportive. Emesis should only be considered in asymptomatic patients. Activated charcoal may be useful for recent ingestion. Symptomatic patients should be watched for anticholinergic signs (agitation, mydriasis, tachycardia, decreased intestinal motility) and treated as needed. Propranolol can be helpful to treat consistent tachycardia in normotensive patients. Diazepam can be used to control seizures or seizure-type activity. Physostigmine is recommended to counteract the CNS anticholinergic effects of antihistamine overdoses in people, although the risk of seizures associated with this drug may limit its use. IV fluids should be given as needed.

7.2.3 Gastrointestinal Drugs

H_2-receptor antagonists are structural analogs of histamine, commonly used to treat GI ulcers, erosive gastritis, esophagitis, and gastric reflux. They act at the H_2 receptors of parietal cells to competitively inhibit histamine, reducing gastric acid secretions during basal conditions and when stimulated by food, amino acids, pentagastrin, histamine, or insulin. Cimetidine, famotidine, nizatidine, and ranitidine are

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examples of this group, also commonly referred to as H_2 blockers. Ranitidine is widely distributed throughout the body. H_2 blockers are primarily metabolized in the liver. Nizatidine, famotidine, and ranitidine are excreted in the urine as metabolites and unchanged drug, whereas cimetidine is eliminated in feces. Because cimetidine may inhibit the hepatic microsomal enzyme system, ingestion of an H_2 blocker may result in reduced metabolism of certain drugs, including β-blockers, calcium channel blockers, diazepam, metronidazole, and theophylline.

Toxicity H_2 blockers have a wide margin of safety, with acute oral overdoses typically resulting in minor effects such as vomiting, diarrhea, anorexia, and dry mouth. Serious adverse effects, such as tremors, hypotension, and bradycardia, are more likely to occur with IV H_2-blocker overdoses. Most exposures require only monitoring for development of GI signs and supportive care, although massive overdoses may also warrant decontamination.

7.2.4 Antacids

Antacids are frequently used to treat GI upset. Common antacids include calcium carbonate, aluminum hydroxide, and magnesium hydroxide (milk of magnesia). These agents are poorly absorbed orally. Calcium- and aluminum-containing antacids generally cause constipation, whereas magnesium-containing antacids tend to cause diarrhea. Some products contain both aluminum and magnesium salts in an attempt to balance their constipating and laxative effects. Acute single ingestion of calcium salts may cause transient hypercalcemia but is unlikely to be associated with significant systemic effects. Induction of emesis within 2–3 h of exposure may help prevent severe GI upset.

7.2.5 Analgesics

7.2.5.1 Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used class of human medications in the world. Because of their widespread availability and use, acute accidental ingestion of human NSAIDs in dogs and cats is quite common. Ibuprofen, aspirin, and naproxen are some of the most commonly encountered NSAIDs in pet animals.

NSAIDs inhibit the enzyme cyclooxygenase (COX; also referred to as prostaglandin synthetase), blocking the production of prostaglandins. It is believed that most NSAIDs act through COX inhibition, although they may also have other mechanisms of action.

Toxicity The most common clinical signs of toxicosis were vomiting and diarrhea, CNS depression, and circulatory manifestations. Pets are at risk from NSAID toxicosis through administration by the owners or accidental consumption of improperly stored drugs.

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Treatment Treatment of NSAID toxicosis consists of early decontamination and supportive care. Vomiting should be induced in recent exposures, followed by administration of activated charcoal with a cathartic. Omeprazole, a proton-pump inhibitor used to inhibit gastric acid secretions, can be used instead of an H_2 blocker in dogs. Use of IV fluids and alkalinization of the urine with sodium bicarbonate results in ion trapping, but it should be used judiciously.

7.2.5.2 Acetaminophen

Acetaminophen is a synthetic nonopiate derivative of p-aminophenol widely used for its antipyretic and analgesic properties. Its use has largely replaced salicylates because of the reduced risk of gastric ulceration. Cats are more sensitive to acetaminophen toxicosis, because they are deficient in glucuronyl transferase and therefore have limited capacity to glucuronidate this drug.

Toxicity In cats, acetaminophen is primarily metabolized via sulfation; when this pathway is saturated, toxic metabolites are produced. In dogs, signs of acute toxicity are rare. Methemoglobinemia and hepatotoxicity characterize acetaminophen toxicosis. Renal injury is also possible. Acute keratoconjunctivitis sicca has been reported in some dogs after high doses of acetaminophen ingestion. Cats primarily develop methemoglobinemia within a few hours, followed by Heinz body formation. Methemoglobinemia makes mucous membranes brown or muddy in color and is usually accompanied by tachycardia, hyperpnea, weakness, and lethargy. Other clinical signs of acetaminophen toxicity include depression, weakness, hyperventilation, icterus, vomiting, hypothermia, facial or paw edema, cyanosis, dyspnea, hepatic necrosis, and death. Liver necrosis is more common in dogs than in cats. Liver damage in dogs is usually seen 24–36 h after ingestion. Centrilobular necrosis is the most common form of hepatic necrosis seen with acetaminophen toxicity.

Treatment Treatment consists of decontamination, prevention or treatment of methemoglobinemia and hepatic damage, and provision of supportive care. Induction of emesis is useful when performed early. This should be followed by administration of activated charcoal with a cathartic. Activated charcoal may be repeated, because acetaminophen undergoes some enterohepatic recirculation. Administration of N-acetylcysteine (NAC), a sulfur-containing amino acid, can reduce the extent of liver injury or methemoglobinemia. NAC provides sulfhydryl groups, directly binds with acetaminophen metabolites to enhance their elimination, and serves as a glutathione precursor.

7.2.6 Multivitamins and Iron

The common ingredients in multivitamins include ascorbic acid (vitamin C), cyanocobalamin (vitamin B_{12}), folic acid, thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), biotin, pantothenic acid, pyridoxine (vitamin B_6), calcium, phosphorus, iodine, iron, magnesium, copper, zinc, and vitamins A, D, and

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E. Among these ingredients, iron and vitamins A and D may cause significant systemic signs. Acute ingestion of other listed ingredients in companion animals can result in self-limiting GI upset (e.g., vomiting, diarrhea, anorexia, lethargy). However, toxicity is typically rare in pets.

7.2.7 Topical Preparations

Zinc oxide ointments or creams are commonly used as topical skin protectants, astringents, and bactericidal agents. Most ointments contain zinc oxide. Acute ingestion of zinc oxide–containing products usually results in gastric irritation (vomiting) and diarrhea, without the intravascular hemolysis and liver and renal damage associated with ingestion of elemental zinc. Signs are usually seen within 2–4 h of a significant exposure. Vomiting animals should be managed symptomatically and supportively. Some dogs show hypersensitivity-type reactions manifested by facial and ocular edema. Such cases can be treated with diphenhydramine or other antiallergic medications.

7.2.8 5-Hydroxytryptophan

Several OTC herbal supplements containing 5-hydroxytryptophan (5-HTP) or Griffonia seed extracts claim to treat depression, headaches, insomnia, and obesity. In cases of 5-HTP overdose, excessive concentrations of serotonin at target cells (GI, CNS, cardiovascular, and respiratory systems) can lead to a serotonin-like syndrome in dogs (e.g., seizures, depression, tremors, ataxia, vomiting, diarrhea, hyperthermia, transient blindness, and death). Clinical signs can develop within 4 h after ingestion and last up to 36 h. Treatment consists of early decontamination, control of CNS signs (diazepam, barbiturates, phenothiazines such as acepromazine or chlorpromazine), thermoregulation (cool water bath, fans), fluid therapy, and administration of a serotonin antagonist such as cyproheptadine.

7.2.9 Herbal Supplements (Toxicity)

Several herbal supplements, sold with the claim of providing weight loss and energy, contain guarana (*Paullinia cupana*), a natural source of caffeine, and ma huang (*Ephedra sinica*), a natural source of ephedrine. The amount of ma huang and guarana present in herbal products may vary considerably (labels should be read for amounts).

Toxicity In dogs, accidental ingestion of herbal supplements containing ma huang and guarana can have synergistic effects when ingested together and can lead to severe hyperactivity, tremors, seizures, vomiting, tachycardia, hyperthermia, and death within a few hours of exposure. The use of ephedra-containing supplements has been banned by the FDA.

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Treatment Treatment of pseudoephedrine toxicosis consists of decontamination, controlling the CNS and cardiovascular effects, and supportive care. Vomiting should be induced only in asymptomatic patients, followed by administration of activated charcoal with a cathartic. If the animal's condition contraindicates induction of emesis, a gastric lavage with a cuffed endotracheal tube should be performed. Hyperactivity, nervousness, or seizures can be controlled with acepromazine, chlorpromazine, phenobarbital, or pentobarbital. Diazepam should be avoided, because it can exaggerate hyperactivity. Phenothiazines should be used with caution because they can lower the seizure threshold, lower blood pressure, and cause bizarre behavioral changes. Tachycardia can be controlled with propranolol. Acidifying the urine with ammonium chloride or ascorbic acid may enhance urinary excretion of pseudoephedrine. Acid-base status should be monitored if ammonium chloride or ascorbic acid is given.

7.3 Toxicities from Prescription Drugs

Pets commonly ingest prescription medications from countertops, pill minders, mail-order packages, or other sources. Veterinarians also can prescribe certain human drugs for animals. Safety data for human prescription drugs in certain animal species may not be available.

7.3.1 Cardiovascular Medications

Several Cardiovascular Medications are used therapeutically to treat congestive heart failure in dogs and cats. These medications can significantly contribute to the overall toxicity in pet animals. Thus such medicines deserve attention. A systematic overview of such drugs includes the following group of medicines used therapeutically to treat congestive heart failure in dogs and cats.

7.3.1.1 Angiotensin-Converting Enzyme (ACE) Inhibitors

Several angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, captopril, lisinopril, benazepril) are used therapeutically to treat congestive heart failure in dogs and cats. The primary concern in cases of acute ACE inhibitor overdose is usually marked hypotension. If hypotension is severe, secondary renal damage may result. Onset occurs within a few hours of exposure, depending on the agent (extended-release formulations may have a delayed onset of action). Other clinical signs of overdose may include vomiting, poor mucous membrane color, weakness, and tachycardia or bradycardia. Activated charcoal is effective in binding the drug from the GI tract if administered within 1–2 h of ingestion. Blood pressure should be monitored and IV fluids given at twice the maintenance rate if hypotension develops. Renal function should be monitored if severe or persistent hypotension develops.

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7.3.1.2 Calcium Channel Blockers

Calcium channel blockers (e.g., diltiazem, amlodipine, nifedipine, verapamil) inhibit movement of calcium from extracellular sites through cell membrane–based calcium channels.

Toxicity The most common signs seen with overdoses of calcium channel blockers are hypotension, bradycardia, GI upset, noncardiogenic pulmonary edema, and heart block. Reflex tachycardia may develop in response to the drop in blood pressure.

Treatment Management of an acute overdose includes correcting hypotension and rhythm disturbances. In general, emesis is induced within 2 h of ingestion only if the animal is showing no clinical signs. Induction of emesis in animals with signs can increase vagal tone and worsen the bradycardia. Activated charcoal binds unabsorbed drug in the GI tract and is most useful when administered within the first few hours after ingestion; if a sustained-release product was ingested, repeat doses of activated charcoal. Depending upon the complications, use of IV fluids, calcium gluconate, atropine, isoproterenol, etc. are recommended. Because of the lipophilic nature of calcium channel blockers, using IV lipid emulsion solution may help sequester calcium channel blockers in overdose situations and prevent them from reaching their site of action.

7.3.1.3 β-Adrenergic Blockers

Drugs in this class (e.g., propanolol, metoprolol, atenolol, timolol, esmolol) act by competitively inhibiting catecholamine binding to β-adrenergic receptor sites.

Toxicity The most common signs of overdose are bradycardia and hypotension; respiratory depression, coma, seizures, hyperkalemia, and hypoglycemia may occur. It is also possible to precipitate congestive heart failure.

Treatment Because of rapid absorption, emesis should only be induced in asymptomatic animals within 2 h of ingestion. Administration of activated charcoal, IV fluids, and atropine can be used for bradycardia. Glucagon or isoproterenol can also be used if needed. If hyperkalemia is confirmed, administration of insulin, followed by IV glucose, may drive the excess potassium back into the cells.

7.3.1.4 Phenylpropanolamine

Phenylpropanolamine (PPA) is a sympathomimetic amine used primarily for treating urinary incontinence in dogs and cats. PPA is believed to indirectly stimulate both α- and β-adrenergic receptors, causing the release of norepinephrine. It is rapidly absorbed orally and distributes to various tissues, including the CNS. PPA is mainly excreted through the kidneys as a parent drug.

Toxicity Overdose of PPA can result in CNS effects (restlessness, agitation, nervousness) and cardiovascular signs (hypertension or hypotension, tachycardia or bradycardia, premature ventricular contractions, cardiovascular collapse). Dogs can

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also show piloerection, hyperemia, vomiting, hyperthermia or hypothermia, and mydriasis.

Treatment Treatment consists of early decontamination (emesis in asymptomatic animals within a couple of hours of ingestion, followed by administration of activated charcoal). CNS effects and mild hypertension can be managed with acepromazine. A nitroprusside constant-rate infusion can be tried for hypertension not responsive to acepromazine. Lidocaine can be considered for treating premature ventricular contractions. IV fluids should be given to promote excretion. Other signs should be treated symptomatically.

7.3.1.5 Diuretics

Oral diuretic agents include thiazides (e.g., chlorothiazide, hydrochlorothiazide), loop diuretics such as furosemide, and potassium-sparing agents such as spironolactone (an aldosterone antagonist) and triamterene. Osmotic diuretics, administered by injection, include mannitol and urea. The most common signs of diuretic overdose include vomiting, depression, polyuria and polydipsia, and electrolyte changes. Electrolytes, especially potassium, may shift subsequent to a large ingestion of a diuretic. Management should include monitoring hydration and electrolytes, with correction as needed.

7.3.2 Phenothiazine Tranquilizers/Benzodiazepines

7.3.2.1 Phenothiazine Tranquilizers

Commonly used phenothiazine tranquilizers in veterinary medicine are acepromazine, chlorpromazine, and promazine. In domestic animals, they are used as tranquilizers, preanesthetic agents, antiemetics, and for treatment of CNS agitation after specific drug overdoses (amphetamines, cocaine).

Toxicity The most common signs of overdose are sedation, weakness, ataxia, collapse, behavioral changes, hypothermia, hypotension, tachycardia, and bradycardia.

Treatment Treatment consists of symptomatic and supportive care. Because of the rapid onset of CNS signs, emesis should only be attempted in a recent exposure and should be followed by administration of activated charcoal and a cathartic. Repeated doses of activated charcoal may be helpful, especially for large ingestions. Hypotension should be treated with IV fluids. Dopamine may be used if fluid administration does not correct hypotension. Body temperature, heart rate, and blood pressure should be monitored and treated symptomatically.

7.3.2.2 Benzodiazepines

Benzodiazepines bind γ-aminobutyric acid (inhibitory neurotransmitter) receptors and are used for seizure control and as anxiolytics. Diazepam is probably best

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known in the veterinary field. Other commonly prescribed medications include alprazolam, chlordiazepoxide, clonazepam, lorazepam, oxazepam, clorazepate and triazolam. Metabolism is mostly by glucuronidation, so cats may be more sensitive to adverse effects.

Toxicity Clinical signs of toxicity include CNS depression, respiratory depression, ataxia, weakness, disorientation, nausea, and vomiting. Some animals, especially at high doses, may show CNS excitation instead of depression (paradoxical reaction), which may be followed by CNS depression. Other common signs are hypothermia, hypotension, tachycardia, muscle hypotonia, and meiosis. Some cats develop signs of acute, potentially fatal hepatic failure after repeated oral administration of diazepam for several days.

Treatment Symptomatic treatment such as emesis and use of gastric lavage, followed by administration of activated charcoal and IV fluids, can be performed if the ingested amount is very high. If the affected animal is recumbent and severe respiratory depression has developed, the reversal agent flumazenil can be given at a slow IV, in both cats and dogs. Flumazenil has a short half-life, so it may need to be repeated. Benzodiazepines should not be used to control CNS excitation, because a paradoxical reaction may occur. In such situations, low doses of acepromazine or barbiturates may be useful to control initial CNS excitation.

7.3.3 Antidepressants and Sleep Aids

7.3.3.1 Antidepressants

Antidepressants fall into several classes.

(a) *Barbiturates*: which may be long-acting or short-acting. The long-acting group includes phenobarbital, mephobarbital, and primidone—all commonly used as anticonvulsants or sedatives. The short-acting (butabarbital, pentobarbital, secobarbital) and ultrashort-acting (thiamylal and thiopental) barbiturates are used mainly for induction of anesthesia and seizure control. All are readily absorbed from the gut and have extensive liver metabolism; metabolites are primarily excreted via the kidneys. The onset of clinical signs varies from 15 min to several hours, and duration can be up to several days for the long-acting class. The most common signs are sedation, ataxia, respiratory depression, coma, loss of reflexes, hypotension, and hypothermia.
(b) *Selective Serotonin Reuptake Inhibitors*: Selective serotonin reuptake inhibitors (SSRIs) include sertraline, fluoxetine, paroxetine, and fluvoxamine. They block the activity of serotonin receptors at presynaptic membranes and have little effect on other neurotransmitters. In veterinary medicine, these SSRIs are sometimes used to control aggression, obsessive-compulsive disorder, separation anxiety, pruritus, and inappropriate elimination in dogs and cats.

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(c) *Tricyclic Antidepressants*: Tricyclic antidepressants such as amitriptyline, clomipramine, nortriptyline, etc. are commonly used as psychoactive agents. They are structurally similar to the phenothiazines, with similar anticholinergic, adrenergic, and α-blocking properties. These compounds may exert their major toxicity via a nonspecific membrane-stabilizing effect, similar to chlorpromazine and the β-blockers. They also have central and peripheral anticholinergic activity, along with antihistaminic effects. Clinical signs of toxicosis include CNS stimulation (agitation, confusion, pyrexia), cardiac arrhythmias, hypertension, myoclonus, nystagmus, seizures, metabolic acidosis, urinary retention, dry mouth, mydriasis, and constipation. This may be followed by CNS depression (lethargy), ataxia, hypothermia, respiratory depression, cyanosis, hypotension, and coma.
(d) *Monoamine Oxidase Inhibitors*: Monoamine oxidase inhibitors are antidepressants used mainly to treat atypical depression in people. In dogs, selegiline, a monoamine oxidase-B inhibitor, is used to treat Cushing disease and cognitive dysfunction (canine dementia).
(e) *Miscellaneous (Atypical) Antidepressants*: These antidepressants have nonselective receptor-blocking effects and are used when SSRIs or tricyclic antidepressants have not been effective. Examples include bupropion, trazodone, and mirtazapine.

Toxicity In general, an overdose of almost any of them can result in development of serotonin syndrome. This group of clinical signs usually includes three of the following features: altered mental status, agitation, nervousness, myoclonus, hyperreflexia, tremors, diarrhea, incoordination, cardiovascular changes (heart rate and blood pressure), and fever. It often occurs because of repeated use or overdose or ingestion of substances that result in increased free levels of serotonin.

Treatment Emesis should be induced in cases of recent exposure if the animal is asymptomatic. This can be followed by activated charcoal (even several hours after ingestion) plus a cathartic such as sorbitol or sodium sulfate (magnesium sulfate is contraindicated, because it can add to CNS depression). Diazepam can be given to control seizures. Serotonin syndrome signs should be managed as needed. Heart rate and rhythm should be monitored, and cardiac arrhythmias treated. Atropine should not be used to control bradycardia, because it can aggravate anticholinergic effects of tricyclic antidepressants.

7.3.3.2 Sleep Aids

Drugs such as zolpidem, zaleplon, and eszopiclone are used as sleep aids and have a mechanism of action similar to that of the benzodiazepines. These agents have a very rapid onset (usually <30 min) and a similarly short half-life. While the expected result from ingestion would be marked sedation, paradoxical excitement also occurs. Dosages as low as 0.22 mg/kg have resulted in sedation and ataxia, and dogs have developed tremors, vocalizing, and pacing at dosages as low as 0.6 mg/kg. Treatment includes GI decontamination; if paradoxical excitement develops, symptomatic

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treatment should be given. Hyperexcitation may be controlled with low doses of acepromazine or other phenothiazines. Use of diazepam may aggravate signs of CNS depression. Flumazenil can be used if clinical signs of toxicosis are severe.

7.3.4 Muscle Relaxants (Toxicity)

The most commonly encountered centrally acting muscle relaxants include baclofen, carisoprodol, methocarbamol, tizanidine, and cyclobenzaprine. Baclofen is rapidly absorbed orally.

Toxicity The onset of clinical signs of toxicosis may be <30 min to 2 h after ingestion. The most common signs of toxicosis are vocalization, salivation, vomiting, ataxia, weakness, tremors, shaking, coma, seizures, bradycardia, hypothermia, and blood pressure abnormalities. Cyclobenzaprine, often used in management of acute muscle spasms, is almost completely absorbed after an oral dose, with peak plasma levels in 3–8 h. It has extensive liver metabolism and undergoes enterohepatic recirculation. The most common signs seen in dogs and cats include depression and ataxia.

Treatment Treatment of muscle relaxant overdose consists of symptomatic and supportive care. Vomiting should be induced if the exposure is recent and no clinical signs are present, followed by administration of activated charcoal. Respiratory support (i.e., ventilator) should be provided if needed. Recumbent or comatose animals should be monitored for hypothermia and aspiration. Seizures can be controlled with diazepam. Cyproheptadine seems to work well for vocalization in dogs. IV fluids should be given as needed. Treatment with IV lipid emulsion solution may be beneficial.

7.3.5 Topical Agents (Toxicity)

Pets ingest many topical preparations, often resulting in only mild gastroenteritis. For example, ingestion of most corticosteroid-containing creams or ointments usually results in only mild to moderate stomach upset, polydipsia, and polyphagia. However, ingestion of certain topical agents in pet animals, such as 5-fluorouracil and calcipotriene, can be fatal even at low doses.

7.3.6 Toxicities from Nonsteroidal Prescription Drugs

(a) *Etodolac*: Etodolac is an indole acetic acid–derivative NSAID labeled for use in dogs to treat pain and inflammation associated with osteoarthritis. It is rapidly absorbed orally, with peak serum concentrations seen 2 h after dosing. Etodolac appears to be well tolerated by dogs when used at the labeled dosage

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(10–15 mg/kg/day, PO) for 1 year. With multiple doses, clinical signs of toxicity such as GI ulcers, vomiting, diarrhea, and weight loss can be seen at 40 mg/kg. Six of eight dogs died or became moribund because of GI ulceration at 80 mg/kg.

(b) *Meloxicam*: Meloxicam is an enolic acid–derivative NSAID approved for use in dogs and cats for controlling pain and inflammation. Some dogs if meloxicam is given for longer period have shown clinical signs consistent with NSAID toxicity (vomiting, diarrhea, renal effects). In cats, the margin of safety appears to be narrow as compared to dogs and may have adverse effects even after a few doses.

(c) *Deracoxib*: Deracoxib is a coxib COX-2 inhibitor (in vitro) used to treat osteoarthritis in dogs. It is not approved for use in cats. Dogs that have received a higher dose (25 mg/kg/day, 50 mg/kg/day, or 100 mg/kg/day for 10–11 days) showed vomiting and melena; no hepatic or renal lesions were seen in these dogs. Dogs ingesting >100 mg/kg should be aggressively decontaminated and treated with IV fluids to prevent renal damage.

(d) *Piroxicam*: Piroxicam is an oxicam derivative. It is not approved in dogs and cats. Adverse GI effects were seen in 18% of dogs given piroxicam at 0.3 mg/kg/day, PO, for several months.

(e) *Indomethacin*: Indomethacin is an indole acetic acid derivative available as the base and as the sodium trihydrate salt. The drug is structurally and pharmacologically related to another NSAID, sulindac. Administration of indomethacin to dogs at 2 mg/kg for 30 days resulted in GI ulcers in 60% of dogs and perforation in 20%.

(f) *Nabumetone*: Nabumetone differs from other NSAIDs in that it is neutral as opposed to acidic. The risk of GI ulcers from nabumetone is considered less than that of other NSAIDs. At higher dosage (>300 mg/kg), the lower GI tract and the kidneys were affected in rats, mice, rabbits, and rhesus monkeys.

Treatment Treatment for a drug toxicity will depend on the level of toxicity. Removing the toxin if the drug was only an hour or two prior, the veterinarian may induce vomiting (or your dog may already be doing this as a result of the toxin) and use activated charcoal to bind the stomach contents for easier removal. Intravenous fluids will help to improve kidney function, antiemetics for nausea and vomiting, vitamin K to help the liver, antiseizure medication, and antibiotics. In some critical cases, canines will need blood transfusions for anemia. Some pets will need respiratory support. Dogs who have had gastrointestinal perforations may need surgery to repair the tears.

7.3.7 Toxicities from Illicit and Abused Drugs

Potential for exposure to illegal or abused drugs exists for many companion animals, horses, and even other livestock on occasion. Exposures to these drugs can be accidental, intentional, or malicious. Among companion animals, dogs are the most

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susceptible to poisoning with illicit substances, though toxicoses occasionally arise in cats, ferrets, birds, or other household pets. Police dogs are at particular risk for ingestion of illegal drugs. Generally, dogs can contact large quantities of the high-purity chemicals in the line of duty. They sometimes ingest whole bags of drugs. Illicit drugs are often adulterated with other pharmacologically active substances, making the diagnosis even more difficult. Treatment is symptomatic, supportive, and care.

7.3.7.1 Amphetamines and Related Drugs

Amphetamines and their derivatives are CNS and cardiovascular system stimulants commonly used in people for suppression of appetite, narcolepsy, attention deficit disorder, parkinsonism, and some behavior disorders. Some commonly encountered amphetamines or related drugs are benzphetamine, dextroamphetamine, lisdexamfetamine, pemoline, methylphenidate, phentermine, diethylpropion, phendimetrazine, methamphetamine, methylenedioxymethamphetamine (MDMA, "Ecstasy"), and phenmetrazine. Amphetamines sold on the street have common names such as speed, bennies, or uppers. Commonly used adulterants are caffeine, ephedrine, or phenylpropanolamine.

Mode of Action Amphetamine stimulates the release of norepinephrine, affecting both α- and β-adrenergic receptor sites. Amphetamine also stimulates catecholamine release centrally in the cerebral cortex, medullary respiratory center, and reticular activating system. It increases the amount of catecholamine at nerve endings by increasing release and inhibiting reuptake and metabolism. The neurotransmitters affected in the CNS are norepinephrine, dopamine, and serotonin.

Toxicity Clinical signs of amphetamine and cocaine toxicosis are similar and difficult to differentiate clinically. The comparison indicates that monkeys are more susceptible to MDMA toxicity than rats. The most commonly reported signs are hyperactivity, aggression, hyperthermia, tremors, ataxia, tachycardia, hypertension, mydriasis, circling, head bobbing, and death.

Treatment Treatment is symptomatic and care. Phenothiazines are preferred to control CNS signs in amphetamine toxicosis. Other anticonvulsants, such as diazepam, barbiturates, or isoflurane, may be used if needed. Acidifying the urine with ammonium chloride or ascorbic acid may enhance amphetamine elimination in the urine. Cyproheptadine may also be given for serotonin syndrome (disorientation, muscle stiffness, agitation). Heart rate and rhythm, body temperature, and electrolytes should be monitored and treated as needed.

7.3.7.2 Cocaine

Cocaine (benzoylmethylecgonine) alkaloid is obtained from the leaves of the coca plant, *Erythroxylon coca*, and *E. monogynum*. Some common street names for cocaine are coke, gold dust, stardust, snow, C, white girl, white lady, baseball, and speedball (cocaine and heroin). Cocaine alkaloid from coca leaves is processed into

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cocaine hydrochloride salt, then reprocessed to form cocaine alkaloid or free base (a process called free-basing or base balling), which is colorless, odorless, transparent, and more heat stable. Free-base cocaine is also called crack, rock, or flake. Cocaine is cut (diluted) several times before it reaches the user. Xanthine alkaloids, local anesthetics, and decongestants are some of the most common adulterants.

Cocaine is a schedule II drug approved for human use. Its medical uses are restricted to topical administration as a local anesthetic on mucous membranes of the oral, laryngeal, and nasal cavities. However, it is mostly used as a recreational drug.

Toxicity Cocaine is absorbed from most routes. Orally, it is better absorbed in an alkaline medium (i.e., intestine). Cocaine acts on the sympathetic division of the autonomic nervous system. It blocks the reuptake of dopamine and norepinephrine in the CNS, leading to feelings of euphoria, restlessness, and increased motor activity. Cocaine can also decrease concentrations of serotonin or its metabolites. Topical use of cocaine causes vasoconstriction of small vessels. Hyperthermia in cocaine toxicosis may develop either due to increased heat production from muscular activity or due to decreased heat loss from vasoconstriction. Toxicity leads to CNS excitation, hyperactivity, shaking, ataxia, panting, agitation, mydriasis, nervousness, seizures, tachycardia, hypertension, acidosis, or hyperthermia that characterize cocaine toxicosis. CNS depression and coma may follow CNS excitation. Death may be due to hyperthermia, cardiac arrest, or respiratory arrest. Some nonspecific chemistry changes may include hyperglycemia and increased CK and liver-specific enzymes.

Treatment The objectives of treatment are GI decontamination, stabilization of CNS and cardiovascular effects, thermoregulation, and supportive care. After CNS and cardiovascular effects have been stabilized, IV fluids should be administered, and electrolyte changes and acid-base status monitored and corrected as needed. Treatment and monitoring should continue until all clinical signs have resolved.

7.3.7.3 Marijuana

Marijuana refers to a mixture of cut, dried, and ground flowers, leaves, and stems of the leafy green hemp plant *Cannabis sativa*. Several cannabinoids are present in the plant resin, but delta-9-tetrahydrocannabinol (THC) is considered the most active and main psychoactive agent. The concentration of THC in marijuana varies between 1% and 8%. Hashish is the resin extracted from the top of the flowering plant and is higher in THC concentration than marijuana. Street names for marijuana include pot, Mary Jane, hashish, weed, grass, THC, ganja, bhang, and charas. Pure THC is available by prescription under the generic name dronabinol. A synthetic cannabinoid, nabilone, is also available. Marijuana or hashish sold on the streets may be contaminated with phencyclidine, LSD, or other drugs.

Toxicity The most common route of exposure is oral. In dogs, clinical signs begin within 30–90 min and can last up to 72 h. Clinical signs of toxicosis from ingestion of synthetic marijuana in dogs can be more severe and last longer than those of THC. The most common signs of marijuana toxicosis are depression, ataxia,

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bradycardia, hypothermia, vocalization, hypersalivation, vomiting, diarrhea, urinary incontinence, seizures, and coma. Marijuana toxicosis can be confused with ethylene glycol (antifreeze, see Ethylene Glycol Toxicity) or ivermectin toxicosis; hypoglycemia; benzodiazepine, barbiturate, or opioid overdose; intervertebral disc problems; or head trauma.

Treatment Treatment consists of supportive care. If the exposure is recent and there are no contraindications, emesis should be induced and activated charcoal administered. Comatose animals should be monitored for aspiration pneumonia, given IV fluids, treated for hypothermia, and rotated frequently to prevent dependent edema or decubital ulceration. Diazepam can be given for sedation or to control seizures. For cases of synthetic marijuana toxicosis, in addition to the preceding treatment options, use of IV lipid emulsion solution may be considered.

7.3.7.4 Opiates

The term opiate initially referred to all naturally occurring alkaloids obtained from the sap of the opium poppy (*Papaver somniferum*). Opium sap contains morphine, codeine, and several other alkaloids. Currently, opioid refers to all drugs, natural or synthetic, that have morphine-like actions or actions mediated through opioid receptors. Some of the widely used opioids in veterinary medicine include tramadol, buprenorphine, fentanyl, loperamide (antidiarrheal), and hydromorphone. The use of meperidine is no longer common.

Opioids are used primarily for analgesia. In addition, they are used as cough suppressants and to treat diarrhea. Occasionally, opioids are used for sedation before surgery and as a supplement to anesthesia.

Toxicity Opioids are generally well absorbed after oral, rectal, or parenteral administration. Because cats are deficient in glucuronidase, the half-life of some opioids in cats may be prolonged. Toxicity of opioids in animals is highly variable. The effects of opioids are due to their interaction with opiate receptors (μ, κ, δ, σ, and ε) found in the limbic system, spinal cord, thalamus, hypothalamus, striatum, and midbrain. The primary effects of opioids are on the CNS, respiratory, cardiovascular, and GI systems. Commonly reported clinical signs of toxicosis include CNS depression, drowsiness, ataxia, vomiting, seizures, miosis, coma, respiratory depression, hypotension, constipation/defecation, and death. Some animals—especially cats, horses, cattle, and swine—can show CNS excitation instead of CNS depression.

Treatment Clinical signs can be reversed with the opiate antagonist naloxone. Administration of naloxone should be repeated as needed (hourly), because its duration of action may be shorter than that of the opioid toxicity being treated. Animals should be closely monitored for respiratory depression and ventilatory support provided if needed. Other signs should be treated symptomatically. Dysphoric reactions (vocalization, agitation, restlessness, and excitation) can be treated with diazepam or other benzodiazepines. For serotonin-like syndrome (disorientation, muscle rigidity, agitation) induced by some opioids, cyproheptadine once or twice can be tried.

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7.4 Questions and Answers

7.4.1 Short Questions and Answers

Exercise 1

Q.1. How opium is collected from the plant?
The opium is usually collected after all the flower petals have fallen off from the capsule, by making slits along its circumference, allowing the milky latex to ooze out and harden. After the plastic gummy opium is removed, it can be refined into heroin, morphine, and codeine.

Q.2. Is there a difference between opium and opiates?
Opium is the "raw material" that you get from the opium poppy (*P. somniferum*). Opiates are group of drugs you can create from opium, such as morphine or codeine

Q.3. What is drug abuse?
Drug abuse is using any drug for something other than its intended purpose or using it improperly. This can include using too much prescription medication, or using it too often, other than the prescribed way as directed by the doctor. It is using alcohol to the point where you get intoxicated. Drug abuse is a conscious choice.

Q.4. Whether datura is toxic to animals?
Although only slightly toxic in small quantities, **a** large consumption **of** this plant by horse, dog, or cat can produce colic (in horses) and possible kidney failure.

Q.5. What are the long-term effects of alcohol on the body?
Alcohol is extremely toxic. In long term it will cause liver, kidney, and heart disease, hypertension, and respiratory distress and contribute significantly to the deterioration of the alcoholic's overall state of health and well-beings.

Q.6. What is the botanical name of datura?
The botanical name of datura is *Datura stramonium*.

Q.7. What are the uses of opium?
Opium is used extensively as a sedative and painkiller.

Q.8. What is the source of heroin?
Heroin is an opiate and is obtained from the opium plant.

Q.9. Why certain medicines are more toxic to cats than dogs?
Because cats have an altered ability to metabolize drugs or poisons through their liver, they are often more sensitive to certain products or chemicals as compared to dogs or humans. While very safe in dogs, pyrethrins or pyrethroids are highly toxic to cats.

Q.10. What are the effects of morphine?
Morphine is a very effective sedative and painkiller and is very useful in patients who have undergone surgery but is harmful if used as an opioid. It is a depressant, slows down the body functions, and affects the CNS and GI tract.

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7.4.2 Multiple Choice Questions

(Choose the best statement; it can be one, two, or all or none.)

Exercise 2

Q.1. Toxicity associated with any chemical substance is referred to as
(a) Poisoning
(b) Intoxication
(c) Overdose
(d) Toxicology

Q.2. Clinical toxicity which is secondary to accidental exposure is
(a) Toxicology
(b) Intoxication
(c) Poisoning
(d) Overdose

Q.3. Chest pain is related to
(a) Neurological examination
(b) Cardiopulmonary examination
(c) GI examination
(d) Both cardiopulmonary examination and GI examination

Q.4. Technique in which anticoagulated blood is passed through a column containing activated charcoal or resin particles is referred to as
(a) Whole bowel irrigation
(b) Forced dieresis
(c) Hemodialysis
(d) Hemoperfusion

Q.5. Which of the following substances is not easily adsorbed by activated charcoal?
(a) Iron
(b) Ethanol
(c) Methanol
(d) All of the above

Q.6. The effect of syrup ipecac starts within 30 minutes of administration and lasts for approximately
(a) 30 minutes
(b) 1 hour
(c) 1 hour and 30 minutes
(d) 2 hours

Q.7. Which of the following procedure(s) is/are contraindicated for patients who have ingested strong acids?
(a) Emesis
(b) Gastric lavage
(c) Whole bowel irrigation
(d) Both emesis and gastric lavage

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Q.8. Which of the following technique is helpful in removing ethanol from the body?
(a) Dialysis
(b) Activated charcoal
(c) Diuresis
(d) Hemoperfusion

Q.9. The most effective treatment in GI decontamination with acetaminophen is --
(a) Emesis
(b) Gastric lavage
(c) Activated charcoal
(d) Dialysis

Q.10. Drug X is available as a 2.5% solution for intravenous administration. The desired dosage of this drug is 5 mg/kg. What volume of drug should be injected if the animal weighs 50 kg?
(a) 0.2 mL
(b) 1.0 mL
(c) 2.0 mL
(d) 10 mL
(e) 20 mL

Answers

Exercise 2

1. b	6. d
2. c	7. a and b
3. b	8. a
4. d	9. c
5. d	10. d

7.4.3 Fill in the Blanks

Exercise 3

Q.1. A target organ of toxicity is _____.
Q.2. What type of allergic contact dermatitis is _____.
Q.3. Duration of ultrashort-acting barbiturate is _____.
Q.4. Specific chemical used for cyanide poisoning is _____.
Q.5. _____ is contraindicated to treat theophylline seizures.

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Answers

Exercise 3

1. Kidney
2. Delayed type IV hypersensitivity reaction
3. 15–20 minutes
4. Sodium nitrite
5. Phenytoin

Further Reading

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Poisonous and Venomous Organisms

8

Abstract

This chapter deals with poisonous and venomous animals such as venomous arthropods, snakes, toads, and lizards. The animal kingdom is populated by a vast variety of creatures. Many animals have developed chemical means of defense and/or food procurement. Every phylum within the animal kingdom contains species that produce poisons or venoms. The most well-known venomous animals are probably snakes. Venom is produced by a specialized gland and is delivered either injected into a wound or through biting or stinging (generally venom will not hurt if delivered other than this mode, even if you swallow it), e.g., snake venom. Most venoms and poisons are not composed of a single chemical substance but, rather, are mixtures of a variety of chemical compounds that often act synergistically to produce their toxic effects. Typical constituents include peptides, amines, serotonin, quinones, polypeptides, and enzymes. These compounds are collectively termed toxins. The pharmacological and toxicological properties of most venoms are incompletely understood because of their complexity, difficulties of obtaining sufficient venom, and extracting individual components. Anaphylaxis and other allergic reactions to venom components are possible.

Keywords

Snakes · Venomous arthropods · Fish poisoning · Marine bites · Biotoxins · Venomous organisms · Tick paralysis · Question and answer bank · Multiple choice questions

8.1 Introduction

Many animals are poisonous or venomous. It can be a defense mechanism to prevent predation or it can be a way to subduing prey. Many, though not all animals, that are poisonous are also very brightly colored. This chapter deals with poisonous and venomous animals such as venomous arthropods, snakes, toads, and lizards. This chapter also highlights the key points about the subject matter followed by

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sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements as related to toxic effects of poisonous and venomous organisms on the animals.

Key Points

- The animal kingdom is populated by a vast variety of creatures.
- The science of the study of toxins is termed toxinology, and toxins produced by members of the animal kingdom are collectively termed zootoxins.
- Many animals have developed chemical means of defense and/or food procurement.
- Every phylum within the animal kingdom contains species that produce poisons or venoms.
- The most well-known venomous animals are probably snakes. Venom is produced by a specialized gland and is delivered either injected into a wound or through biting or stinging (generally venom will not hurt if delivered other than this mode, even if you swallow it), e.g., snake venom.
- Most venoms and poisons are not composed of a single chemical substance but, rather, are mixtures of a variety of chemical compounds that often act synergistically to produce their toxic effects. Typical constituents include peptides, amines, serotonin, quinones, polypeptides, and enzymes. These compounds are collectively termed toxins.
- The pharmacological and toxicological properties of most venoms are incompletely understood because of their complexity, difficulties of obtaining sufficient venom, and extracting individual components.
- Anaphylaxis and other allergic reactions to venom components are possible.
- Different ticks from nine different genera have been associated with tick paralysis.
- Blister beetles produce toxins that are highly toxic to sheep and cattle, but primarily to horses.

8.2 Classification of Venomous Arthropods

There are more than a million species of arthropods, generally divided into 25 orders, of which at least 12 are of importance to humans and animal species. These include:

1. Arachnids (spiders, scorpions, whip scorpions, solpugids, mites, and ticks)
2. Myriapods (centipedes and millipedes)

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3. Insects—Hymenoptera (ants, bees, wasps, and hornets), Formicidae (ants), Apidae (bees), Vespidae (wasps), Lepidoptera (caterpillars, moths, and butterflies), Heteroptera (true bugs, water bugs, assassin bugs, and wheel bugs).
4. Beetles (blister beetles).

8.3 Arachnids (Spiders, Scorpions, Whip Scorpions, Solpugids, Mites, and Ticks)

8.3.1 Spiders

At least 30,000 species of spiders are distributed throughout the world. Spiders have eight segmented legs and bisegmented bodies composed of head/thorax (prosoma or cephalothorax) and abdomen (opisthosoma). Venom is stored in two glands located in the cephalothorax and empties through fangs (chelicerae) located at the rostral end of the prosoma. With the exception of spiders in the family Ulobiridae (found in Australia), all spiders are capable of inflicting an envenomating bite via fangs. Most spider envenomations, however, are likely to cause few signs other than local swelling and pain. Anaphylaxis and other allergic reactions to venom components are possible. It appears that fewer than 100 spider species can inflict a bite of medical significance.

The spiders in the USA that are capable of causing clinical envenomation belong to two groups: black widow spiders (*Latrodectus* spp.) and brown spiders (mostly *Loxosceles* spp.).

8.3.1.1 Black Widow Spiders (*Latrodectus* spp.)

Out of several species, the most common species is the black widow spider, *Latrodectus mactans*, characterized by a red hourglass shape on its ventral abdomen. Venom from the spiders is one of the most potent biologic toxins. The most important of its five or six components is a neurotoxin that causes release of the neurotransmitters norepinephrine and acetylcholine at synaptic junctions, which continues until neurotransmitters are depleted.

Toxicity Clinical signs include rapid, shallow, irregular respiration; shock; abdominal rigidity or tenderness; and painful muscle rigidity, sometimes accompanied by intermittent relaxation (which may progress to clonus and eventually to respiratory paralysis). Partial paresis also has been described.

Treatment An antivenin (equine origin) is commercially available. Symptomatic treatment is usually sufficient but may require a combination of therapeutic agents such as calcium gluconate, meperidine hydrochloride, or morphine. Muscle relaxants and diazepam are also beneficial. Tetanus antitoxin also should be administered. Recovery may be prolonged; weakness and even partial paralysis may persist for several days.

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8.3.1.2 Brown Spiders (Mostly *Loxosceles* spp.)

Brown recluse spider, *L. reclusa*, is the most common, and envenomation by it is typical for the genus. Brown recluse spider venom has vasoconstrictive, thrombotic, hemolytic, and necrotizing properties. It contains several enzymes, including a phospholipase (sphingomyelinase D) that attacks cell membranes. Pathogenetic mechanisms of the characteristic dermal necrosis are poorly understood, but activation of complement, chemotaxis, and accumulations of neutrophils affect (or amplify) the process.

Toxicity After bite a discrete, erythematous, intensely pruritic skin lesion that may have irregular ecchymoses may appear at the bite wound, and sometimes a blanched zone surrounds the erythematous area, producing a "bull's-eye" appearance to the lesion. The central area sometimes appears pale or cyanotic. The vesicle may degenerate to an ulcer that, unless treated in a timely manner, may enlarge and extend to underlying tissues, including muscle. Sometimes, a pustule follows the vesicle and, on its breakdown, a black eschar remains. However, medical authorities claim that not all brown recluse spider bites result in severe, localized dermal necrosis.

Systemic signs sometimes such as hemolysis, thrombocytopenia, and disseminated intravascular coagulation are more likely to occur in cases with severe dermal necrosis. Fever, vomiting, edema, hemoglobinuria, hemolytic anemia, renal failure, and shock may result from systemic loxoscelism.

Treatment Immediate application of cold packs is beneficial, and if administered early, corticosteroids protect against cutaneous necrosis by stabilizing cell membranes and suppressing chemotaxis. Dapsone, an inhibitor of leukocyte function, which is frequently used in the treatment of leprosy, is currently considered the drug of choice for brown recluse spider bites. Broad-spectrum antibiotics are useful in preventing secondary infection, and tetanus immunoprophylaxis should be considered.

8.3.2 Scorpions

Most of the scorpions possess posterior abdominal stingers that connect to venom glands. The stinger and its associated venom can be used both as mechanisms of self-defense and of predation. For the most part, the stings of these scorpions are considered to be innocuous in most domesticated mammalian species, because the amount of venom is too minute or the venom has very little pharmacologic potency. The sting of these arthropods is analogous to an insect sting/bite, with pain and swelling at the site of the injury.

Relative to pharmacologically potent scorpion stings in domesticated animals, there are two geographic scenarios of veterinary clinical importance. The first involves *Centruroides sculpturatus*, commonly known as the Arizona bark scorpion. This venomous arthropod can be found in all counties, and at least two components, a hemolytic and a neurotoxic fraction, have been identified: α-scorpion toxin found in *Androctonus*, *Leiurus*, and *Buthus* spp. and β-scorpion toxin found in

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Centruroides spp. Both toxins can be found in the venom of *Tityus* spp. These venoms block voltage-sensitive sodium and potassium channels in nerves.

It has been reported to produce envenomation in dogs; however, its sting is similar to that of the venomous hymenopterans, producing local pain and swelling with the possibility of associated hypertension. Most animals recover without a problem, but more severe reactions are possible.

Treatment In most cases, the treatment of scorpion stings consists of analgesics and local wound care. Systemic signs are treated symptomatically with control of hypertension, heart rate changes, and neurologic signs. Some antivenoms are produced, but their use in veterinary patients is considered controversial.

8.3.3 Ticks Paralysis

Ticks are well known as being vectors for many human and animal diseases (Fig. 8.1). Worldwide, 43 species of ticks from nine different genera have been associated with tick paralysis: *Amblyomma*, *Argas*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, *Ornithodoros*, *Otobius*, and *Rhipicephalus*. Tick paralysis has been reported in North America, Europe, Africa, Australia, and the former Soviet Union. Almost all ticks belong to one of two major families, the Ixodidae or hard ticks, which are difficult to crush, and the Argasidae or soft ticks. Adults have ovoid or pear-shaped bodies, which become engorged with blood when they feed, and have eight legs. As well as having a hard shield on their dorsal surfaces, hard ticks have a beak-like structure at the front containing the mouthparts, whereas soft ticks have their mouthparts on the underside of the body. Both families locate a potential host by odor or from changes in the environment.

Mechanism of Action The exact mechanism(s) of action of tick toxins is not well known, but in most tick species, it is suspected that the toxin interferes with the synthesis and/or release of acetylcholine at the neuromuscular junctions, resulting in lower motor neuron paresis and paralysis very similar to that produced by



Fig. 8.1 Tropical bont ticks, *Amblyomma variegatum* Fabricius, feeding on the calf ear. Note the large "nutmeg" size of the females. (Reproduced from https://commons.wikimedia.org/wiki/File:Rhipicephalus-appendiculatus-calf-ear.jpg)

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botulinum toxin. The Australian tick, *Ixodes holocyclus*, toxin may differ because it appears to have more of an effect on central nerve centers rather than on peripheral.

Toxicity Tick paralysis has been reported in a large variety of animal species, including dogs, cats, cattle, sheep, goats, llamas, poultry, wild antelope, bison, foxes, wolves, mice, ground hogs, black-tailed deer, and several species of wild birds. In North America, most cases of tick paralysis in livestock occur in the Pacific Northwest due to *Dermacentor andersoni*, whereas most cases in dogs are due to *Dermacentor variabilis*. *Dermacentor occidentalis* occasionally causes tick paralysis in cattle, ponies, and deer but not dogs. Tick paralysis has occurred following the bite of a single tick, and heavily infested animals may succumb quickly. Clinical signs include an ascending ataxia that progresses to paresis and flaccid paralysis. Early in the intoxication, animals remain bright, alert, and able to eat and drink if properly supported. Eventually, paralysis of the respiratory muscles leads to respiratory failure and death. Paralysis produced by *I. holocyclus*, the Australian tick, generally occurs more rapidly and tends to persist following removal of the tick.

Treatment The main goal of treatment is to remove the ticks and provide supportive care (especially respiratory support) until recovery occurs. Recovery can occur quite rapidly following complete removal of the ticks, or it may take a few days. The use of topical insecticides may aid in the removal of ticks and can be especially helpful in cases in which numerous ticks are embedded.

8.4 Myriapoda: Centipedes and Millipedes

Centipedes and millipedes are distantly related to lobsters, crayfish, and shrimp. These arthropods are widely distributed throughout the world, and they are characterized by a long, flat, multisegmented body with one (centipede) or two (millipede) legs emerging from each body segment. All centipedes have a pair of modified front legs (forcipules) that serve as fangs and that are connected to venomous glands directly under the head. Centipedes belong to Arthropods and are organic animal irritants. They have a long segmented dark to brownish black-colored body with a pair of legs in each segment (Fig. 8.2). Larger centipedes can inflict painful bites resulting in local swelling, erythema, and lymphangitis. In addition, the legs of *Scolopendra* spp. are tipped with sharp claws that are capable of penetrating skin, and toxin produced at the attachment point of each leg may drop into these wounds, causing inflammation and irritation due to mast cell degranulation.

Centipede venom has been poorly studied, but components identified in various centipedes include a phospholipase A2, metalloproteases, and hyaluronidase, serotonin, a β-pore-forming compound, a hemolysin (γ-glutamyl transpeptidase), and histamine. In most cases, systemic toxicosis is not expected, although local necrosis may occur.

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Fig. 8.2 Poisonous insect: centipede in peat marshland. (Available at Wikimedia Commons. https://en.wikipedia.org/wiki/Centipede)

Millipedes do not bite but can emit irritating and foul-smelling secretions from repugnatorial glands; some species can spray these fluids over distances of several inches. These secretions are irritating to mucosal surfaces, particularly the eyes, and corticosteroids have been recommended to decrease the inflammatory response

8.5 Insects: Heteroptera (True Bugs) and Hymenoptera (Ants, Bees, Wasps, and Hornets),

8.5.1 Ants, Bees, Wasps, and Hornets

Insect and insect-related problems are common in domestic and wild animals. Insects such as lice, fleas, deerflies, horseflies, sand flies, mosquitoes, blackflies, and biting midges may cause severe annoyance to animals because of biting behavior.

Members of several groups of insects (ants, bees, wasps, and hornets) can inject venom when they bite or sting, most notably bees, wasps, and ants. Bites or stings from insects such as bees, ants (Fig. 8.3), wasps, and chiggers may cause direct effects from venoms or may result in allergic host reactions resulting from overresponsive host immune systems. The stinger in honeybees is barbed which gets struck in the victim's skin along with venom sac (Fig. 8.4). Hence, stinger apparatus is lost and results in death of the insect. Wasps can withdraw the stinger as it is not barbed and can sting multiple times (Fig. 8.5). Contact allergies may occur when certain beetles or caterpillars touch the skin. Stings related to these hymenopterans involve the injection of venom, which is almost always acutely painful. Chemical composition of insects is hugely complex mixture of all sorts of compounds—proteins, peptides, enzymes, and other molecules including phospholipase A, the enzyme hyaluronidase, and histamine.

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Fig. 8.3 Fire ant (Solenopsis). (http://l7.alamy.com/zooms/0ee1cd49640d458088d931783f8add2d/fire-ants-solenopsis-invicta-adult-closeup-sting-and-bite-causing-d1kpfj.jpg)



Fig. 8.4 Honeybee (**a**) and stinger of honeybee (barbed) (**b**). ((**a**) Reproduced from Shutterstock https://thumb1.shutterstock.com/display_pic_with_logo/278821/524883124/stock-photo-detail-of-bee-or-honeybee-in-latin-apis-mellifera-european-or-western-honey-bee-isolated-on-the-524883124.jpg. (**b**) Reproduced from American Association for the Advancement of Science. http://www.sciencemag.org/sites/default/files/styles/article_main_large/public/images/snticks.jpg?itok=sqYE42-k)

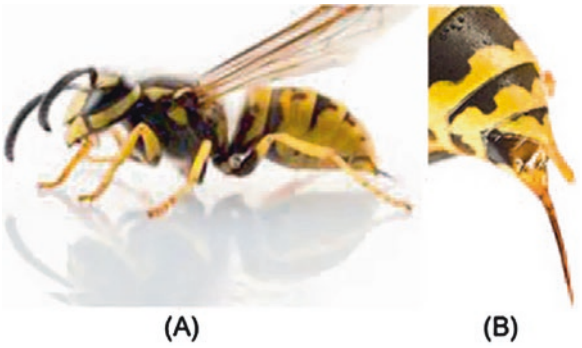


Fig. 8.5 Insect wasp (**a**) and stinger of wasp (unbarbed) (**b**). ((**a**) Reproduced from Irabia Plagas https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSACSKPU7ZWc-jd6H-vZFmqnyJ6klUt4TcibUvtaafoV3Oq0ViTe. (**b**) Reproduced from Shutterstock https://www.shutterstock.com/image-photo/thorn-flesh-81929605?src=AZ3pYVsWXl7S6HsaPOyisA-1-13)

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Mechanism of Action The mechanism of action of various toxic venoms may involve interference with enzyme systems responsible for active transport across mitochondrial membranes, resulting in membrane disruption and permeability changes, and contribute toward pain-inducing agents.

Toxicity Clinical signs vary with the dose ingested. Massive doses may cause shock and death within 4 h. Smaller doses may cause gastroenteritis, nephrosis, cystitis, and/or urethritis; thus, signs may include anorexia, soft feces, mucoid to bloody feces, intestinal atony, colic, dysuria (frequent, painful urination, or oliguria to anuria), and hematuria. The body temperature may elevate. Other signs observed include depression, weakness, muscle rigidity, collapse, prostration, dehydration, and sweating. Animals frequently become dyspneic, and rales may be detected on auscultation due to pulmonary edema. Myocarditis may initiate cardiovascular signs including tachycardia, congested mucous membranes, and decreased capillary refill time. Synchronous diaphragmatic flutter and muscle fasciculations have been reported in horses and are thought to be the results of hypocalcemia. Ulceration of the oral mucosa membranes may be observed, and animals may be seen dipping their muzzles into water without drinking. Diarrhea may be observed in animals that live for a few days. The course of the disease may be as short or may lead to lethal poisoning. In horses, the mortality rate is approximately 50%, with horses surviving more than 1 week having a favorable prognosis.

Treatment There is no specific treatment. The administration of either activated charcoal or mineral oil. General supportive therapy should include correction of fluid loss and electrolyte imbalances, particularly hypocalcemia and hypomagnesemia. Broad-spectrum antimicrobial therapy may be necessary to counter secondary bacterial invasion. Avoiding aminoglycosides and other medications that are potentially nephrotoxic or excreted via the kidney.

8.6 Blister Beetle Poisoning (Cantharidin Poisoning)

Beetles belonging to the Meloidae family. More than 200 species of beetles have been described, representing 30–40% of all known insects. Blister beetles (Fig. 8.6) produce toxins that can cause adverse reactions when they are touched or ingested. These beetles are highly toxic to sheep and cattle, but primarily to horses. Members of the genus *Epicauta* are most frequently associated with toxicosis in horses. The striped blister beetles (*E. occidentalis*, *E.* temexia, and *E. vittata*) are particularly troublesome in the southwestern USA. The black blister beetle, *E. pennsylvanica*, has caused toxicosis in horses in Illinois. The toxic principle in meloid beetles, cantharidin, is a bicyclic terpenoid, but its concentration in beetles varies widely.

Blister beetles usually feed on various weeds and occasionally move into alfalfa fields in large swarms. These insects are gregarious and may be found in hay in large numbers when it is baled. One flake of alfalfa may contain several hundred beetles, but a flake from the other end of the same bale may have none. Animals are usually exposed by eating alfalfa hay or alfalfa products that have been contaminated with

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Fig. 8.6 Blister beetle on a wild plant, black and yellow color, hairy body. (https://image.shutterstock.com/image-photo/blister-beetle-on-wild-plant-450w-499578124.jpg)

blister beetles. The tissues most often affected by cantharidin are gastrointestinal mucosa (including the mouth), renal or bladder, and the heart muscle.

There is no antidote for cantharidin. The only treatment is supportive. Intravenous fluids with or without calcium are indicated to combat dehydration. Activated charcoal and mineral oil may be administered through a nasogastric tube. Gastric protectants may decrease gastrointestinal discomfort and colic. Antibiotics are mainly prophylactic (preventive).

8.7 Toad Poisoning

Poisonous frogs belong to the Dendrobatidae family. Toads have been associated with toxicosis in domestic animals. They have nearly 500 different bioactive alkaloids in their skin secretions. Toads are found throughout the world, and all are considered to produce zootoxins capable of causing clinical effects in animals. However, only the larger toads, specifically *Bufo blombergi*, *Bufo alvarius*, *Bufo regularis*, and *Rhinella marinus* (formerly *Bufo marinus*), are generally considered to produce sufficient poison to cause serious toxicosis. Toad secretions contain a variety of compounds, including bufogenins, bufotoxins, and bufotenines.

Mechanism of Action Bufogenins inhibit sodium-potassium ATPase activity in a manner similar to cardiac glycosides such as digitalis, ultimately causing increased intracellular calcium in myocardial cells that results in cardiac arrhythmia. Bufotoxins have a similar mechanism of action as bufogenins. Bufotenines are indolalkylamines such as serotonin and 5-hydroxytryptophan and in combination with catecholamines may be responsible for many of the neurologic and gastrointestinal effects of toad toxins.

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Toxicity The relative potency of toad toxins varies with species of toad, geographic location, and size of the toad. Clinical effects of toad poisoning include hypersalivation, anxiety, and vomiting, which can occur almost immediately following exposure; also, death may occur. Other signs, including hyperemic mucous membranes, recumbency, collapse, and tachypnea, may also be present. Neurologic effects and cardiac arrhythmias are common. Pulmonary edema, hyperthermia, and hyperkalemia have also been reported.

Treatment Treatment is symptomatic and supportive such as emesis and endoscopic or surgical removal of the toad from the stomach, and multiple doses of activated charcoal with a cathartic may be used when entire toads are ingested. Seizures may be managed with diazepam or a barbiturate. Intravenous fluid therapy is essential to aid in cardiovascular support. Control arrhythmias should be managed as they develop. Bradycardia may be treated using atropine, whereas propranolol or esmolol may be used to treat tachycardia. Correction of potassium imbalances should be performed as needed.

8.8 Snake Poisoning

There are nearly 3000 species of snake in the world. Only around 375 snake species are venomous, and only a small proportion of these are potentially harmful to humans. Most snake species have only one functional lung. Venomous snakes are usually defined as those which possess venom glands, and specialized venom-conducting fangs inflict serious bites upon their victims. In general, there are five families of venomous snakes recognized:

1. The Colubridae, possess small rear fangs
2. The Elapidae and Hydrophidae, possess small front fangs
3. The viper group, consists of the Viperidae and Crotalidae

Venomous snakes are widely distributed throughout the world.

8.8.1 Crotalids

The crotalids are also known as pit vipers, so named for the indented, heat-sensing pits located between the nostrils and eyes. Other features of this family include elliptical pupils, triangular-shaped heads, retractable and hollow front fangs, and a single row of subcaudal scales distal to the anal plate. Rattlesnakes have special keratin "rattles" on the ends of their tails and are members of the genera *Crotalus* and *Sistrurus* (Fig. 8.7). At least 29 subspecies of rattlesnakes are found throughout the USA; however, they do not occur in several islands such as New Zealand, Ireland, Iceland, and the Azores and Canaries. Pit vipers inject their venom by rotating their retractable fangs downward and forward in a stabbing motion. Contraction

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Fig. 8.7 Hemotoxic venomous snake *Crotalus horridus*. (Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Crotalus_horridus_(1).jpg)

of muscles in the venom glands then forces the venom through the hollow fangs and into the tissues of the victim. Snakes can control the amount of venom delivered to the victim by regulating the muscular contraction of the venom glands.

Mechanism of Action Crotalid venoms are complex combinations of enzymes, cytotoxins, neurotoxins, cardiotoxins, hemolysins, coagulants, anticoagulants, lipids, nucleosides, nucleotides, organic acids, and cations such as zinc. Most venoms contain a minimum of ten of these different components. Hyaluronidase ("spreading factor") and other enzymes break down collagen and other connective tissues, allowing for rapid penetration of venom components throughout the victim's tissues. Low-molecular-weight myotoxins open sodium channels in the muscle cell membrane, leading to myocyte necrosis. Phospholipase A stimulates hypercontraction of myocyte membranes, resulting in myofibril rupture. Alteration of blood coagulation may lead to either hyper- or hypocoagulation through either direct effects on clotting factors or induction of hyperfibrinolysis, resulting in dissolution of clots as they are forming. Some diamondback rattlesnake venoms contain cardiotoxic agents (myocardial depressant factors) that cause profound hypotension unresponsive to fluid therapy. Neurotoxic components bind the presynaptic nerve membrane, inhibiting neurotransmitter release and causing paralysis.

Toxicity Dogs are the domestic species most commonly bitten by pit vipers. Most bites involved young dogs and were located on the head. Horses are most commonly bitten on the muzzle, and cattle are more commonly bitten on the tongue or muzzle. The toxicity of any given crotalid bite will depend on both victim and snake factors. In most cases of snakebite, the initial signs are usually local pain and swelling, followed by petechiation, ecchymosis, and discoloration of the skin in the region of the bite. Swelling and/or the hair coat of the victim may mask bite wounds. Bites from snake species that possess only neurotoxic venom may show little local swelling. Neurotoxic effects, largely attributed to Mojave toxins, reported in dogs and cats following rattlesnake envenomation include ataxia, postural deficits, fasciculation,

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paresis, paralysis, and seizures. Horses bitten on the muzzle may succumb to asphyxiation due to occlusion of the nares due to tissue swelling. Horses develop pitting edema that frequently progresses to involve the entire head and neck or limb, but tissue necrosis is uncommon. Hemolysis, rhabdomyolysis, thrombocytopenia, and coagulopathy may occur.

Treatment Management of snakebites includes suction, electric shock, ice packs, and tourniquets to avoid the spread of venom and attempting to keep the bitten area below heart level. Besides symptomatic and supportive treatment, tracheostomy may be required in cases in which severe swelling in the head or neck region results in respiratory compromise or in cases of obligate nasal breathers (e.g., horses and llamas) that are bitten on the muzzle. Horses should receive tetanus antitoxin or toxoid. The use of intravenous antivenin in crotalid snakebites can result in the reversal of potentially life-threatening problems such as coagulopathy, thrombocytopenia, and paralysis. Administration of antivenin should begin as early as possible.

8.8.2 Elapids

There are two North American species of venomous elapid snakes (Fig. 8.8). Sonoran coral snake *(Micruroides euryxanthus*) and several subspecies of *Micrurus fulvius*, including the Texas coral snake (*M. fulvius tenere*), the eastern coral snake (*M. fulvius fulvius*), and the South Florida coral snake (*M. fulvius barbouri*), are brightly colored, with alternating bands of black, red, and yellow, and they have small heads and round pupils. The venom delivery apparatus of coral snakes includes short, fixed (nonhinged) front fangs that are partially covered by a membrane. During the bite,

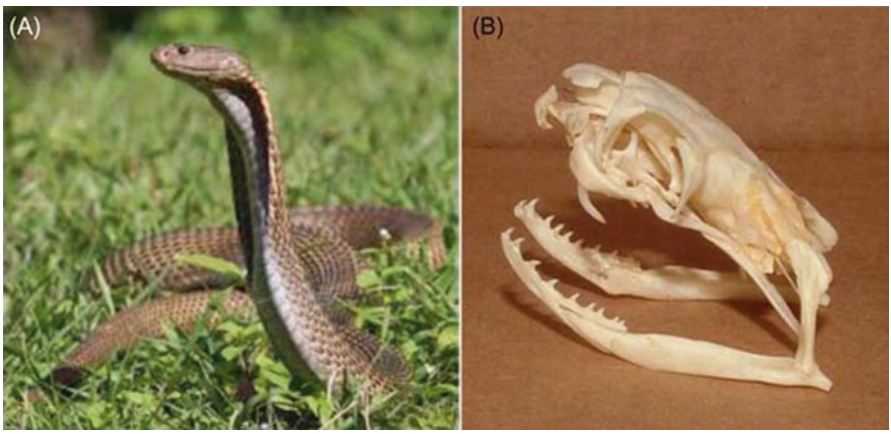


Fig. 8.8 Elapid snake (King Cobra, *Naja philippinensis*) in defensive posture (**a**) and skull (**b**). ((**a**) Available at Wikimedia Commons. https://en.wikipedia.org/wiki/Philippine_cobra. (**b**) Available at Wikimedia commons: https://upload.wikimedia.org/wikipedia/commons/8/87/Ophiophagus_hannah_skull.jpg)

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the membrane is pushed away, coral snakes hold onto the victim and chew, delivering additional venom to the wound. Like crotalid venom, coral snake venom is composed of a variety of compounds, mostly small polypeptides and enzymes.

Mechanism of Action Elapidae and Hydrophidae venoms are rich in neurotoxic polypeptides. These venoms are typically fast acting on nerve tissue and neurotransmitters, often degrading neurotransmitters or depolarizing the axonal membrane for long periods of time, thereby preventing nervous impulses from being conducted. Neurotoxic polypeptides in coral snake venom cause a nondepolarizing postsynaptic neuromuscular blockade similar to the effects of curare. Binding of neurotoxins to postsynaptic receptors appears to be irreversible. Enzymes within the venom can cause local tissue necrosis, myoglobinemia in cats, and hemolysis in dogs.

Toxicity As with crotalid envenomations, the severity of the bite is related to the size of the victim and the amount of venom delivered. The amount of venom injected is related to the duration of the bite, intensity of chewing, and reason for the bite (offensive versus defensive). Clinical signs vary with the species of the victim. Cats develop primarily neurologic signs, including progressive ascending flaccid paralysis, decreased nociperception, CNS depression, and diminished spinal reflexes. Hypotension, respiratory depression, anisocoria, myoglobinemia, and hypothermia have also been described in cats. In dogs, depression of the CNS, decreased spinal reflexes, muscle weakness, and respiratory depression may occur. Vomiting, hypersalivation, hypotension, dyspnea, dysphagia, muscle fasciculation, tachycardia, and hemolysis have also been reported in dogs. Potential complications include dysphagia leading to aspiration pneumonia. Death is due to respiratory paralysis.

Treatment Besides symptomatic and supportive treatment, administration of specific Micrurus antivenin should be considered if neurologic signs begin to develop; early administration is recommended because the antivenin is poorly effective at displacing venom components bound to receptor sites. As with crotalid antivenin, anaphylaxis is a potential complication of Micrurus antivenin administration. Broad-spectrum antibiotics and symptomatic wound care may be indicated.

8.9 Lizards

Venomous lizards found in North and Central America are members of the genus *Heloderma*. *Heloderma suspectum* and *Heloderma cinctum* are commonly referred to as Gila monsters, whereas *Heloderma horridum* is known as the Mexican beaded lizard. Venomous lizards are large and heavily bodied, with blunt, rounded tails, powerful jaws, and short legs with clawed, hand-like feet. *Heloderma* spp. possess venom glands in the lower jaw at the base of the teeth, and venom is delivered through grooves in the teeth via capillary action as the lizard masticates. The venom is considered a defensive weapon rather than one for procuring food.

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Mechanism of Action *Heloderma* venom is composed of a complex mixture of proteins and enzymes, many of which are similar to those found in snake venoms, including hyaluronidase, phospholipase A2, serotonin, and a variety of enzymes. Hyaluronidase ("spreading factor") catalyzes the cleavage of internal glycoside bonds of acid mucoglycosides, resulting in decreased viscosity of hyaluronic acid, which in turn increases tissue permeability and allows deeper penetration of venom into tissue. Phospholipase A2 uncouples oxidative phosphorylation, which inhibits cellular respiration, causes cell membrane destruction, and inhibits platelet aggregation. Various proteolytic enzymes result in local tissue damage as well as aid in the spread of venom through the tissue. Gilatoxin is considered to be the major lethal factor in *Heloderma* venom.

Toxicity The toxicity of *Heloderma* venoms is dependent on the amount of venom delivered to tissues, which in turn is dependent on the duration and severity of the bite. Due to their inquisitive nature and tendency to harass wildlife that they encounter, dogs are the species most likely to have a significant encounter with *Heloderma* spp. The clinical effects of Heloderma envenomation include intense local pain, edema, and hemorrhage at the site of the wound (which may contain fractured teeth). Regional lymphangitis and local ecchymoses may occur, although tissue necrosis is not common. Hypotension, tachycardia, and respiratory distress have been reported in dogs and cats injected with boluses of Heloderma venom, although reports of these conditions in natural exposures are lacking.

Treatment Treatment is symptomatic and supportive. Such as disengaging a lizard, if that is still attached to the victim. The bite site should be irrigated with 2% lidocaine and the wound probed with a 25-gauge needle to detect any embedded tooth fragments. Use of benzodiazepines, analgesics, and intravenous fluid therapy is indicated. Broad-spectrum antibiotics should be administered to prevent infection.

8.10 Questions and Answers

8.10.1 Short Questions and Answers

Exercise 1

Q.1. Define venomous animal.
- A venomous animal can produce venom in specialized glands or cells and deliver it either by biting or stinging or in some cases by acquiring or spitting.

Q.2. Define poisonous animal.
- A poisonous animal possesses a toxin(s) within its tissue that can have deleterious effects when ingested.

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Q.3. How one can differentiate toxin, poison, and venom?
- Toxins are proteins that lead to immune reaction.
  Poisons are chemical substances (not injected by biological vector), i.e., if poison is injected by snake, it becomes venom.
  Venoms are biological poisons.

Q.4. Define hemotoxicity.
- Hemotoxicity is related to blood toxicity. It includes coagulopathies, cardiotoxicity, and hemolysis.

Q.5. What are the local actions of neurotoxic snakebite?
- Local manifestations of neurotoxic venoms are severe burning at bite site, rapid edema, and inflammatory changes, and oozing of serum may be observed.

Q.6. Define nature of toxins produced by scorpions.
- Many scorpion venoms contain low-molecular-weight proteins, peptides, amino acids, nucleotides, and salts, among other components. Venom (toxalbumin) having two components, a hemolytic and a neurotoxic fraction.

Q.7. Why the stinger is lost due to stinging and results in death of honeybee?
- The stinger in honeybees is barbed which gets struck in the victim's skin along with venom sac. Hence, stinger apparatus is lost and results in death of the insect.

Q.8. Why wasps can sting multiple times?
- Wasps can withdraw the stinger as it is not barbed and can sting multiple times.

Q.9. What is tick paralysis?
- Tick paralysis (Dermacenter sps. and Riphicephalus sps) is the only tick-borne disease that is not caused by an infectious organism. The illness is caused by a neurotoxin produced in the tick's salivary gland.

Q.10. Define in brief nature of toxins of ants.
- Fire ant is the common name for several species of ants in the genus *Solenopsis*. Ant venom is any of, or a mixture of, irritants and toxins inflicted by ants. Most ants spray or inject a venom, the main constituent of which is formic acid only in the case of subfamily Formicinae. The ants get a grip and then sting (from the abdomen) and inject a toxic alkaloid venom called Solenopsin, a compound from the class of piperidines.

Q.11. What are the signs and symptoms of toxicity by fire ants?
- In human being signs of toxicity include sterile pustules on the body.

Q.12. Why alcohol is contraindicated in cleaning the area of snakebite?
- Alcohol causes vasodilation promoting the spread of the venom in the body.

Q.13. What are local actions of myotoxic venomous snakes?
- Myotoxic venomous snakes produce minimal swelling and pain.

Q.14. What are systemic actions of myotoxic venomous snakes?
- Myotoxic symptoms are common with Hydrophidae or sea snakes. The venom produces generalized muscular pain, myalgia, muscular stiffness, myoglobinuria, renal tubular necrosis, and death which usually occurs due to respiratory failure.

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Q.15. Why snakebite in human beings and dogs is fatal compared to large animals?
- Human beings and dogs are relatively smaller in size compared to other large animals like horses and cattle. Hence, the bite is fatal in smaller subjects than the larger ones.

8.10.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. Which of the following statements regarding animal toxins is *false*?
(a) Animal venoms are strictly metabolized by the liver.
(b) The kidneys are responsible for the excretion of metabolized venom.
(c) Venoms can be absorbed by facilitated diffusion.
(d) Most venom fractions distribute unequally throughout the body.
(e) Venom receptor sites exhibit highly variable degrees of sensitivity.

Q.2. Scorpion venoms do *not*:
(a) Affect potassium channels
(b) Affect sodium channels
(c) Affect chloride channels
(d) Affect calcium channels
(e) Affect initial depolarization of the action potential

Q.3. Which of the following statements regarding widow spiders is *true*?
(a) Widow spiders are exclusively found in tropical regions.
(b) Both male and female widow spiders bite and envenomate humans.
(c) The widow spider toxin decreases calcium concentration in the synaptic terminal.
(d) Alpha-latrotoxin stimulates increased exocytosis from nerve terminals.
(e) A severe alpha-latrotoxin envenomation can result in life-threatening hypotension.

Q.4. Which of the following diseases is not commonly caused by tick envenomation?
(a) Rocky Mountain spotted fever
(b) Lyme disease
(c) Q ever
(d) Ehrlichiosis
(e) Cat scratch fever

Q.5. Which of the following is *not* characteristic Lepidoptera envenomation?
(a) Increased prothrombin time
(b) Decreased fibrinogen levels
(c) Decreased partial thromboplastin time
(d) Increased risk of hemorrhaging
(e) Decreased plasminogen levels

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Q.6. Which of the following animals has a venom containing histamine and mast cell–degranulating peptide that is known for causing hypersensitivity reactions?
(a) Bees
(b) Ants
(c) Snakes
(d) Spiders
(e) Reduviidae

Q.7. Which of the following enzymes is *not* typically found in snake venoms?
(a) Hyaluronidase
(b) Lactate dehydrogenase
(c) Collagenase
(d) Phosphodiesterase
(e) Histaminase

Q.8. Which of the following statements regarding snakes is *false*?
(a) Inorganic anions are often found in snake venoms.
(b) About 20% of snake species are venomous.
(c) Snake venoms often interfere with blood coagulation mechanisms.
(d) Proteolytic enzymes are common constituents of snake venoms.
(e) Snakebite treatment is often specific for each type of envenomation.

Q.9. Which of the following is false regarding botulism toxin? Please choose only one answer:
(a) Ach release is blocked in the presynaptic neuron resulting in flaccid paralysis.
(b) Botulism occurs via ingestion or wound contamination of spores or preformed toxin.
(c) Preformed toxin sources are decaying carcasses.
(d) For prevention, vaccination against *C. botulism* with toxoid can prevent clinical disease.
(e) Clinical signs include "sawhorse stance," muscle rigidity, erect ears, and a reluctance to eat due to "locked jaw."

Q.10. Cyanobacteria can cause hepatoxicity via ingestion of _____ and neurotoxicity via ingestion of _____.
(a) Microcystin/nodularin, anatoxin
(b) Anatoxin, microcystin/nodularin

Q.11. Blister beetles cause cathardin toxicosis which occurs when livestock eat _____
(a) Grain
(b) Alfalfa hay
(c) Dead chicken carcasses
(d) Locoweed
(e) Cardenolide

Q.12. Which of the following is false regarding Bufo toad toxicity?
(a) Onset of clinical signs can be rapid and death can occur within 15 minutes.

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(b) The cardiac glycosides bind and inhibit Na/K ATPase resulting in a depressed electrical conduction. Mucous membranes appear pale and tacky.
(c) Prognosis is good with most animals with early decontamination and appropriate symptomatic therapy. Majority of animals present with neurologic abnormalities including convulsions, ataxia, nystagmus, stupor, and coma.

Q.13. Which is false regarding pit vipers?
(a) Most bites are by copperheads.
(b) Venom is delivered by the retractable fangs downward and stabbing forward.
(c) Echinocytes greatly increase the likelihood that victim has been envenomed.
(d) Initial clinical sign is usually marked tissue swelling.
(e) Antivenin treatment (CroFabTM) substantially increases the likelihood of survival.

Q.14. How would you identify a female black widow spider?
(a) Red, yellow, or orange hourglass on ventral abdomen.
(b) The bite causes a "bull's-eye "lesion and systemic deletion of clotting factors (VII, IX, and XII).
(c) Within 30 min of bite, expanding area of wound will reach up to 15 cm and rupture with serious discharge.
(d) Female black widow spiders only build nests in barns housed by talking pigs named Wilbur.
(e) The nests will be built on ground level since black widows are poor climbers.

Q.15. Poisoning from these animals is referred to as tegenarism and can generate a wound that takes years to properly heal.
(a) Black widow
(b) Hobo spider
(c) Brown recluse
(d) Tarantula
(e) Scorpion

Answers

Exercise 2

1. a	9. e
2. d	10. a
3. d	11. b
4. e	12. c
5. c	13. e
6. a	14. a
7. e	15. b
8. a	

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8.10.3 Fill in Blanks

Exercise 3

Q.1. The order under the class Insecta, which includes greatest number of poisonous insect species, is _____.
Q.2. The antigenic component of honeybee venom, which can cause allergies or anaphylactic shock, is _____.
Q.3. The drug of choice for treatment of systemic reactions produced by stinging from bees or wasps is _____.
Q.4. The potent cytotoxin present in ant venom is _____.
Q.5. The piperidine alkaloid component of fire ant venom is _____.
Q.6. Focal necrotic ulcers of the cornea and conjunctiva in calves are caused by the bite of _____ insect.
Q.7. The most potent neurotoxin present in the venom of black widow spider (*Latrodectus mactans*) is _____.
Q.8. The most dangerous species of scorpion is _____.
Q.9. The most common tick species, which are responsible for development of tick paralysis, are _____.
Q.10. Tick paralysis is caused by the injection of _____ which is neurotoxic.

Answers

Exercise 3

1. Hymenoptera
2. Mellitin
3. Epinephrine (adrenaline)
4. Formic acid
5. Solenopsin
6. Fire ants
7. α-Latrotoxin
8. *Leiurus quinquestriatus*
9. *Riphicephalus* and *Dermacentor*
10. Saliva

8.10.4 True or False Statements

Exercise 4

Q.1. Cantharidin toxicosis from blister beetles can cause irritation in the terminal ends of the esophagus, stomach, and intestines leading to ulcerative lesions.
Q.2. Coral snakes have short fixed, non-hinged front fangs that are partially membrane covered, but 60% of bites do not result in venom delivery.

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Q.3. Coral snake venom is rapidly cleared from the body.
Q.4. 99% of all the snakebites to animals in North America are by coral snakes.
Q.5. Tarantula species native to the USA are not capable of delivering serious envenomation and thus are effectively innocuous.
Q.6. Do not remove tick; just provide respiratory support for treatment of tick toxin.

Answers

Exercise 4

1. T	4. F
2. T	5. T
3. F	6. F

Further Reading

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Bacterial and Cyanobacterial (Blue-Green Algae)

9

Abstract

This chapter deals with the toxic effects of botulinum toxins, enterotoxemias (*Clostridium perfringens* infections), and blue-green algae (cyanobacterial toxins). Bacteria generate toxins which may be exotoxins (generated and actively secreted) or endotoxins (remain part of the bacteria). An endotoxin is part of the bacterial outer membrane, and it is not released until the bacterium is killed by the immune system. Blue-green algae produce toxins from cyanobacteria. There are >30 species of cyanobacteria that can be associated with toxic water blooms responsible for most cases of toxicity in animals. Classical mode of action of botulinum toxins is to presynaptically bind to high-affinity recognition sites on the cholinergic nerve terminals, decrease the release of acetylcholine, and produce presynaptic neuromuscular blockade. Enterotoxemia is induced by toxins produced by *Clostridium perfringens*. There are several strains of *C. perfringens* (Type B, Type C, and Type D) that may lead to toxemias. Toxins produced from blue-green algae are specifically toxic to the liver; microcystins cause severe hepatomegaly macroscopically and progressive centrolobular hepatocyte rounding, dissociation, and necrosis; and breakdown of the sinusoidal endothelium and intrahepatic hemorrhage ultimately result in death in animals.

Keywords

Botulinum toxins · Enterotoxemias · Clostridium perfringens · Blue green algae · Cyanobacterial toxins · Question and answer bank · Multiple choice question

9.1 Introduction

This chapter deals with the toxic effects of botulinum toxins, enterotoxemias (*Clostridium perfringens* infections), and blue-green algae (cyanobacterial toxins). The chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements as relevant to various toxic effects of poisonous and venomous organisms on the animals.

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Key Points

- Bacteria generate toxins which may be exotoxins (generated and actively secreted) or endotoxins (remain part of the bacteria).
- An endotoxin is part of the bacterial outer membrane, and it is not released until the bacterium is killed by the immune system.
- Botulinum toxin is obtained from *Clostridium botulinum* and are the most potent natural toxins known. The body's response to an endotoxin can involve severe inflammation.
- Microbial toxins promote infection and disease by directly damaging host tissues and by disabling the immune system.
- Enterotoxemia is induced by toxins produced by *Clostridium perfringens*. There are several strains of *C. perfringens* (Type B, Type C, and Type D) that may lead to toxemias.
- Blue-green algae produce toxins from cyanobacteria. There are >30 species of cyanobacteria that can be associated with toxic water blooms responsible for most cases of toxicity in animals.

9.2 Botulinum Toxins (Botulism)

Botulinum toxins are a family of structurally similar, but antigenically and serologically distinct, exotoxins produced by *Clostridium botulinum*, a Gram-positive anaerobic rod-shaped bacterium, and related *Clostridia* including *C. butyricum*, *C. baratii*, and *C. argentinense*. These neurotoxins that consist of two basic components:

(a) Neurotoxic component (light chain)
(b) Accessory component (heavy chain)

There are now eight antigenically distinct toxin serotypes (A, B, C1, C2, D, E, F, G, H). Human botulism is mostly caused by serotypes A, B, E and F.

Toxicity

Serotypes A, B, C1, and D have been associated with outbreaks of botulism in domestic animals, livestock, poultry, and wildlife. Botulism is relatively low in cattle and horses, probably more frequent in chickens, and high in wild waterfowl. Dogs, cats, and pigs are comparatively resistant to all types of botulinum toxin when challenged orally; however, there are recent individual case reports mentioning botulism in dogs. Most botulism in cattle occurs where a combination of extensive agriculture and phosphorus deficiency in soil creates conditions ideal for the disease in animals. Botulism in sheep has been encountered in Australia, associated not with phosphorus deficiency as in cattle, but with protein and carbohydrate

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deficiency, which results in sheep eating carcasses of rabbits and other small animals found on the range. Botulism in horses often results from forage contaminated with type C or D toxin.

Toxicoinfectious botulism is the name given to the disease in which *C. botulinum* grows in tissues of a living animal and produces toxins there. The toxins are liberated from the lesions and cause typical botulism. This has been suggested as a means of producing the shaker foal syndrome. Gastric ulcers, foci of necrosis in the liver, abscesses in the navel and lungs, wounds of the skin and muscle, and necrotic lesions of the GI tract are predisposing sites for development of toxicoinfectious botulism. This disease of foals and adult horses appears to resemble "wound botulism" in people. Type B toxin is often implicated in botulism in horses and foals in the eastern USA. Toxicoinfection is also suggested as a cause of equine grass sickness, a fatal dysautonomia of unknown etiology. This disease causes marked reduction of GI motility due to widespread degeneration within the autonomic nervous system. It is seen throughout northern Europe, and a few cases have been diagnosed in the USA in the same geographic area (Midwest) that has a high prevalence of canine dysautonomia.

Botulism in mink usually is caused by type C strains that have produced toxin in chopped raw meat or fish. Type A and E strains are occasionally involved. Botulism has not been reported in cats but occurs sporadically in dogs. Type C toxin is usually responsible, but there have been reports in which type D was incriminated.

Mechanism of Action The overall classical mode of action of toxin is to presynaptically bind to high-affinity recognition sites on the cholinergic nerve terminals, decrease the release of acetylcholine, and produce presynaptic neuromuscular blockade. Denervation muscular atrophy accompanies the neuromuscular blockade. Although effected neuromuscular junctions may eventually recover, most of the recovery from botulinum toxin neuromuscular blockade results from proximal axonal sprouting and muscle reinnervation through the synthesis of new neuromuscular junctions.

Toxicity The signs of botulism are caused by flaccid muscle paralysis and include progressive motor paralysis, disturbed vision, difficulty in chewing and swallowing, and generalized progressive paresis. Death is usually due to respiratory or cardiac paralysis. The toxin prevents release of acetylcholine at motor endplates (neuromuscular junction). Passage of impulses down the motor nerves and contractility of muscles are not hindered. No characteristic gross and histologic lesions develop, and pathologic changes may be ascribed to the general paralytic action of toxin, particularly in the muscles of the respiratory system, rather than to the specific effect of toxin on any particular organ.

Epidemics have occurred in dairy herds in which up to 65% of adult cows developed clinical botulism and died 6–72 h after the onset of recumbency. Major clinical findings included drooling, decreased tongue tone, dysphagia, inability to urinate, and sternal recumbency that progressed to lateral recumbency just before death. Skin sensation is usually normal, and withdrawal reflexes of the limbs are weak.

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Initially, clinical signs resemble second-stage parturient paresis (see Parturient Paresis in Cows), but the cows do not respond to parenteral calcium therapy.

Clinical signs in horses are very similar, with progressive muscle paresis, recumbency, dysphagia, and decreased muscle tone (tail, tongue, jaw), respiratory distress, and death. In the shaker foal syndrome, foals are usually <4 weeks old. They may be found dead without premonitory signs; most often, they exhibit signs of progressive symmetric motor paralysis. Stilted gait, muscular tremors, and the inability to stand for >4–5 min are salient features. Other clinical signs include dysphagia, constipation, mydriasis, and frequent urination. As the disease progresses, dyspnea with extension of the head and neck, tachycardia, and respiratory arrest occur. Death ensues most often 24–72 h after the onset of clinical signs due to respiratory failure. The most consistent necropsy findings are pulmonary edema and congestion and excessive pericardial fluid, which contains free-floating strands of fibrin.

Treatment and Control Any dietary deficiencies in range animals should be corrected and carcasses disposed of, if possible. Decaying grass or spoiled silage should be removed from the diet. Immunization of cattle with types C and D toxoid has proved successful in South Africa and Australia. Toxoid is also effective in immunizing mink and has been used in pheasants.

Botulinum antitoxin has been used for treatment with varying degrees of success, depending on the type of toxin involved and the species of host. Treatment of ducks and mink with type C antitoxin is often successful; however, such treatment is rarely used in cattle. Early administration of antitoxin (type B) specific or polyvalent to foals before recumbency is reported to be successful. Supportive care in valuable animals is essential; prognosis is poor in recumbent animals. In endemic areas, vaccination with type B toxoid appears to be effective.

9.3 Enterotoxemias (*Clostridium perfringens* Infections)

Enterotoxemia, also known as overeating or pulpy kidney disease. Enterotoxemia is induced by the absorption of large volumes of toxins produced by *Clostridium perfringens* from the intestines. There are five strain types of *C. perfringens*, which are denoted by an A–E classification. The classification is dependent upon the type of major lethal toxin the strain is able to produce. Type A bacteria produce alpha toxin; type B bacteria produce alpha, beta, and epsilon toxins; type C bacteria produce alpha and beta toxins; type D bacteria produce alpha and epsilon toxins; and type E bacteria proteins produce alpha and iota toxins. Each strain is also capable of producing secondary toxins, which include, but are not limited to, enterotoxin and beta-2 toxin. The alpha toxin, found in type A strains of *C. perfringens* causes gas gangrene and also hemolysis in infected individuals. These bacteria are normally found in the soil and as part of the normal microflora in the gastrointestinal tract of healthy sheep and goats.

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9.3.1 Type A Enterotoxemia (Necrotic Enteritis)

Type A strains of *C. perfringens* are commonly found as part of the normal intestinal microflora of animals and lack some of the powerful toxins produced by strains of other types.

Mechanism of Action The alpha toxin of *C. perfringens* requires zinc for activation, after which the toxin binds to the surface of the host cell, whereby a series of pathways result in increased permeability in blood vessels. As such, the alpha toxin promotes infection by reducing blood supply to tissues.

Toxicity *C. perfringens* produces a necrotizing toxin associated with necrotic enteritis in poultry and dogs, colitis in horses, and diarrhea in pigs. *C. perfringens* type A is implicated in a rarely occurring hemorrhagic diarrhea in dogs and has been associated with nosocomial and acquired acute and chronic diarrhea in dogs. The acute form is characterized by a necrotic enteritis in which there is massive destruction of the villi and coagulation necrosis of the small intestine. *C. perfringens* isolated from pigs with diarrhea are typically nonenterotoxigenic but produce the cytotoxic β2 toxin, which possibly plays a role in disease.

In poultry the clinical illness is usually very short, and often the only signs are a severe depression followed quickly by a sudden increase in flock mortality. The disease primarily affects broiler chickens raised on litter but can also affect commercial layer pullets raised in cages.

Treatment and Prevention Addition of antibiotics in the feed such as virginiamycin, bacitracin, and lincomycin, as well as ionophore-class anticoccidial, may be useful. The move to antibiotic-free feeds has also been associated with markedly increased use of coccidiosis vaccines, resulting in early circulation of mixed *Eimeria* infections that are associated with the resurgence in incidence of necrotic enteritis. Avoiding drastic changes in feed and minimizing the level of fishmeal, wheat, barley, or rye in the diet can also help prevent necrotic enteritis.

9.3.2 Type B and C Enterotoxemia (Lamb Dysentery)

Infection with *C. perfringens* types B and C causes severe enteritis, dysentery, toxemia, and high mortality in young lambs, calves, pigs, and foals. Types B and C both produce the highly necrotizing and lethal beta toxin responsible for severe intestinal damage. This toxin is sensitive to proteolytic enzymes, and disease is associated with inhibition of proteolysis in the intestine. Sow colostrum, which contains a trypsin inhibitor, has been suggested as a factor increasing the susceptibility of young piglets. Type C also causes enterotoxemia in adult cattle, sheep, and goats.

Toxicity Lamb dysentery is an acute disease of lambs <3 weeks old. A fetid, blood-tinged diarrhea is common, and death usually occurs within a few days. In calves,

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there is acute diarrhea, dysentery, abdominal pain, convulsions, and opisthotonos. Death may occur in a few hours, but less severe cases survive for a few days, and recovery is possible. Pigs become acutely ill within a few days of birth, and there are diarrhea, dysentery, reddening of the anus, and a high fatality rate; most affected piglets die within 12 h. In foals, there is acute dysentery, toxemia, and rapid death. Struck in adult sheep is characterized by death without premonitory signs. Hemorrhagic enteritis with ulceration of the mucosa is the major lesion in all species.

Treatment and Prevention Treatment is usually supportive. Give specific hyperimmune sera and oral antibiotics. The disease is best controlled by vaccination of the pregnant dam during the last third of pregnancy. When outbreaks occur in newborn animals from unvaccinated dams, antiserum should be administered immediately after birth.

9.3.3 Type D Enterotoxemia (Pulpy Kidney Disease, Overeating Disease)

This classic enterotoxemia of sheep is seen less frequently in goats and rarely in cattle. The causative agent is *C. perfringens* type D. Predisposing factors are essential, the most common being the ingestion of excessive amounts of feed or milk in the very young and of grain in feedlot lambs. As starch intake increases, it provides a suitable medium for overgrowth of *C. perfringens*, producing epsilon toxin. The toxin causes vascular damage, particularly in capillaries of the brain. Many adult sheep carry strains of *C. perfringens* type D as part of their normal intestinal microflora, which is the source of organisms that infect the newborn. Most such carriers have nonvaccinal antitoxin serum titers.

Toxicity Usually, sudden deaths in the best-conditioned lambs are the first indication of enterotoxemia. In some cases, excitement, incoordination, and convulsions occur before death. Opisthotonos, circling, and pushing the head against fixed objects are common neurologic signs; frequently, hyperglycemia or glycosuria is present. Diarrhea may or may not develop. Occasionally, adult sheep are affected too, showing weakness, incoordination, convulsions, and death within 24 h. In goats, the course of disease ranges from peracute to chronic, with signs that vary from watery diarrhea with or without blood to sudden death. Affected calves not found dead show mania, convulsions, blindness, and death within a few hours. Subacutely affected calves are stuporous for a few days and may recover. In goats, diarrhea and nervous signs are seen, and death may occur over several weeks. Type D enterotoxemia occasionally is seen in young horses that have overeaten. Necropsy may reveal only a few hyperemic areas on the intestine and a fluid-filled pericardial sac. In older animals, hemorrhagic areas on the myocardium may be found as well as petechiae and ecchymoses of the abdominal muscles and serosa of the intestine. Bilateral pulmonary edema and congestion frequently occur but usually not in

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young lambs. Rapid postmortem autolysis of the kidneys has led to the popular name of pulpy kidney disease; however, pulpy kidneys are by no means always found in affected young lambs and are seldom found in affected goats or cattle. Hemorrhagic or necrotic enterocolitis may be seen in goats.

Treatment and Control If the disease is seen consistently in young lambs, ewe immunization probably is the most satisfactory method of control. Breeding ewes should be given type D toxoid. Enterotoxemia in feedlot lambs can be controlled by reducing the amount of concentrate in the diet.

9.4 Blue-Green Algae Poisoning (Cyanobacterial Toxins)

Algal poisoning is an acute, often fatal condition caused by high concentrations of toxic blue-green algae (more commonly known as cyanobacteria—literally blue-green bacteria) in drinking water as well as in water used for agriculture, recreation, and aquaculture. Fatalities and severe illness of livestock, pets, wildlife, birds, and fish from heavy growths of cyanobacteria water blooms occur in almost all countries of the world. Acute lethal poisonings have also been documented in people. Poisoning usually occurs during warm seasons when the water blooms are more intense and of longer duration. Most poisonings occur among animals drinking cyanobacteria-infested freshwater, but aquatic animals, especially maricultured fish and shrimp, are also affected. The toxins of cyanobacteria comprise six distinct chemical classes collectively called cyanotoxins. Several strains and species of *Anabaena*, *Aphanizomenon*, *Cylindrospermopsis*, *Microcystis*, *Nodularia*, *Nostoc*, *Oscillatoria*, and *Planktothrix* are responsible for most cases of toxicity; there are >30 species of cyanobacteria that can be associated with toxic water blooms (Fig. 9.1).

Toxins Several neurotoxic alkaloids (called anatoxins) can be produced by *Anabaena*, *Aphanizomenon*, and *Planktothrix*, while saxitoxins (also called paralytic shellfish toxins) can be produced by *Anabaena*, *Aphanizomenon*, and *Lyngbya*. Hepatotoxic heptapeptides called microcystins can be produced by *Anabaena*, *Microcystis*, *Nostoc*, and *Planktothrix*. The brackish water genus *Nodularia* produces a hepatotoxic pentapeptide related, in both structure and function, to microcystins. *Cylindrospermopsis*, *Anabaena*, *Aphanizomenon*, *Raphidiopsis*, and *Umezakia* can produce a potent hepatotoxic alkaloid called cylindrospermopsin. Some genera, especially *Anabaena*, can produce both neuro- and hepatotoxins. Other noncyclic peptides and amino acids produced by cyanobacteria can also have biological activity. One recent amino acid with neurologic degenerative activity is BMAA (ß-methylamino alanine). BMAA has been implicated as the causative agent of amyotrophic lateral sclerosis or parkinsonism dementia.

Mechanism of Action Specifically toxic to liver, microcystins cause severe hepatomegaly macroscopically and progressive centrolobular hepatocyte rounding, dissociation, and necrosis microscopically. Breakdown of the sinusoidal endothelium

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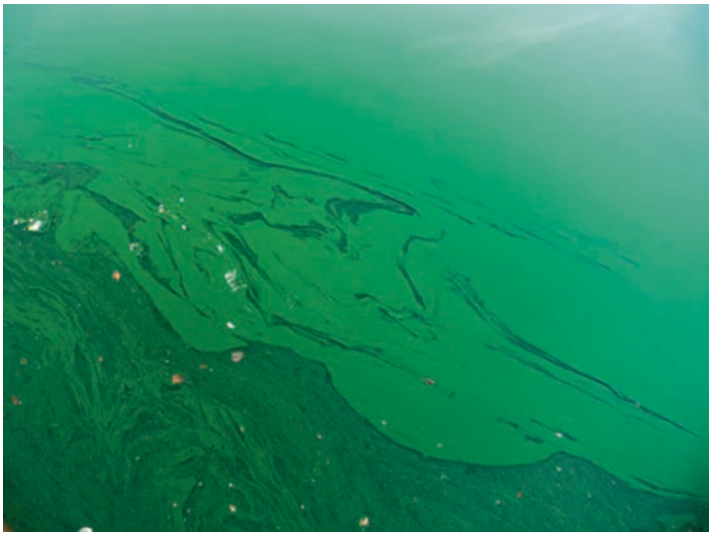


Fig. 9.1 Toxic blue-green algae. (Reproduced from https://commons.wikimedia.org/wiki/File:CyanobacteriaLamiot2009_07_26_290.jpg)

and intrahepatic hemorrhage ultimately result in death. Unable to permeate cell membranes, microcystins enter hepatocytes via the bile acid transporter mechanism. Once inside the hepatocytes, microcystins are potent inhibitors of protein phosphatases 1 and 2A. The disruption of the cytoskeletal components and the associated rearrangement of filamentous actin within hepatocytes account for the morphological changes, although other mechanisms play a role in the development of liver lesions. Microcystins induce apoptosis of hepatocytes via induction of free radical formation and mitochondrial alterations. In addition, microcystins are classified as tumor-promoting compounds. Investigations have indicated the role of protooncogenes in this tumorigenesis, hypothesized to be a sequelae of dysregulation of phosphorylation. Microcystins can also induce DNA damage in liver cells.

Species and strains of *Anabaena*, *Aphanizomenon*, *Oscillatoria*, and *Planktothrix* can produce a potent, postsynaptic cholinergic (nicotinic) agonist called anatoxin-a that causes a depolarizing neuromuscular blockade. Strains of *Anabaena* can produce an irreversible organophosphate anticholinesterase called anatoxin-a(s). *Anabaena*, *Aphanizomenon*, *Cylindrospermopsis*, and *Lyngbya* can produce the potent, presynaptic sodium channel blockers called saxitoxins.

Toxicity Various factors such as size and species of livestock influence the degree of intoxication. Monogastric animals are less sensitive than ruminants and birds. Depending on water bloom densities and toxin content, animals may need to ingest only a few ounces to be affected. However, if the water bloom is less dense or cyanotoxin content is low, as much as several gallons may be needed to cause acute or lethal toxicity. Among domestic animals, dogs are most susceptible to a toxic water

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bloom. This is due to their preference for swimming and drinking in dense water blooms and a greater species sensitivity to the cyanotoxins, especially the neurotoxins.

Sheep poisoned with *Nodularia spumigena* suffer difficulty in breathing and muscular weakness and may show paralysis or nervous twitching. They may lapse into a coma before dying quietly.

Most commonly, they are simply found dead near affected water. Sometimes the algal scum can be found on the forelimbs, lips and muzzle. Death from hepatotoxicosis induced by cyclic peptides is generally accepted as being the result of intrahepatic hemorrhage and hypovolemic shock. Death occurring in minutes to a few hours from respiratory arrest, may result from ingestion of the cyanobacteria that produce neurotoxic alkaloids.

Treatment and Control After removal from the contaminated water supply, affected animals should be placed in a protected area out of direct sunlight. Ample quantities of water and good quality feed should be made available. Because the toxins have a steep dose-response curve, surviving animals have a good chance for recovery. Although therapies for cyanobacterial poisonings have not been investigated in detail, activated charcoal slurry is likely to be of benefit. In laboratory studies, an ion-exchange resin such as cholestyramine has proved useful to absorb the toxins from the GI tract, and certain bile acid transport blockers such as cyclosporin A, rifampin, and silymarin injected before dosing of microcystin have effectively prevented hepatotoxicity. No therapeutic antagonist has been found effective against anatoxin-a, cylindrospermopsin, or the saxitoxins, but atropine and activated charcoal reduce the muscarinic effects of the anticholinesterase anatoxin-a(s).

9.5 Questions and Answers

9.5.1 Short Questions and Answers

Exercise 1

Q.1. Name at least four toxins and bacteria involved in toxicity in animals and human beings.

Name of Toxin	Bacteria Involved
Botulinum toxin	*Clostridium botulinum*
Tetanus toxin	*Clostridium tetani*
Diphtheria toxin (Dtx)	*Corynebacterium diphtheria*
Exotoxin A	*Pseudomonas aeruginosa*

Q.2. Define algal toxins.

Algal toxins are broadly defined to represent the chemicals derived from many species of cyanobacteria (blue-green bacteria), dinoflagellates, and diatoms. The toxins produced by these freshwater and marine organisms

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often accumulate in fish and shellfish inhabiting the surrounding waters, causing both human and animal poisonings, as well as overt fish kills. Unlike many of the microbial toxins, algal toxins are generally heat stable and, therefore, not altered by cooking methods, which increases the likelihood of human exposures and toxicity.

Q.3. What are cyanobacterial (blue-green bacteria) toxins?

Cyanobacterial (blue-green bacteria) toxins are produced (biotoxins and cytotoxins) by several species of cyanobacteria.

Q.4. What are Ambush predator toxins?

Ambush predator (*Pfiesteria piscicida* and toxic *Pfiesteria* complex) toxins are produced by several dinoflagellate species.

Q.5. What is algal poisoning?

Algal poisoning is an acute, often fatal condition caused by high concentration of toxic blue algae (more commonly known as cyanobacteria—literally blue-green bacteria) in drinking water as well as basin water used in agriculture, recreation, and agriculture.

Q.6. How do animals get poisoned by algae?

Severe illness and fatalities of livestock, pets, wildlife, birds, and fish occur in almost all countries of the world. Most poisonings occur due to consumption of water contaminated with cyanobacteria that contain harmful toxins.

Q.7. Define bacterial toxins.

Bacteria generate toxins which can be classified as either exotoxins or endotoxins.

1. Exotoxins are generated and actively secreted.
2. Endotoxins remain part of the bacteria. Usually, an endotoxin is part of the bacterial outer membrane, and it is not released until the bacterium is killed by the immune system. The body's response to an endotoxin can involve severe inflammation. In general, the inflammation process is usually considered beneficial to the infected host, but if the reaction is severe enough, it can lead to sepsis.

Q.8. What is toxinosis?

Toxinosis is a pathogenesis caused by the bacterial toxin alone, not necessarily involving bacterial infection (e.g., when the bacteria have died but have already produced toxins, which are ingested). It can be caused by *Staphylococcus aureus* toxins.

Q.9. What is botulism type of food poisoning?

In botulism type, the food poisoning results from the ingestion of preformed botulinum toxin in the preserved food. The toxin is produced by *C. botulinum*.

Q.10. Define harmful algal bloom (HAB).

Harmful algal blooms or HABs are algal blooms composed of phytoplankton known to naturally produce biotoxins; they can occur when certain types of microscopic algae grow quickly in water, forming visible patches that may harm the health of the environment, plants, or animals.

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9.5.2 Multiple Choice Questions

(Choose the correct answer. It may be one, two of all, or none.)

Exercise 2

Q.1. Exotoxins produced by *Clostridium botulinum* are _____.
(a) Hemotoxin
(b) Botulinum toxins
(c) Fish meal
(d) Neurotoxins

Q.2. *Clostridium perfringens* types B and C both produce the highly necrotizing and lethal _____ responsible for severe intestinal damage.
(a) Histamine
(b) Tetrodotoxin
(c) *Gambierdiscus Toxicus*
(d) Beta toxin

Q.3. Serotypes _____ have been associated with outbreaks of botulism in domestic animals.
(a) Melittin and *Salmonella*
(b) A, B, C1, and D
(c) *Salmonella* and *E. coli*
(d) Solenopsin and melittin

Q.4. Beta toxin produced by *C. perfringens* is sensitive to _____
(a) Proteolytic enzymes
(b) Heat
(c) Cold
(d) None

Q.5. Algal poisoning is an acute, often fatal condition caused by _____ bacteria.
(a) *Salmonella*
(b) *Latrodectus Mactans*
(c) *Leiurus quinquestriatus*
(d) *Cyanobacteria*

Q.6. The most susceptible species of animal for tetanus is _____.
(a) Horse
(b) Cattle dog
(c) Hen
(d) Elephant

Q.7. The overall classical mode of action of botulinum toxin is to presynaptically bind to high-affinity recognition sites on _____.
(a) Axons
(b) Cholinergic nerve terminals
(c) Postganglionic neurons
(d) None

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Q.8. The specific treatment for tetanus is administration of _____.
(a) Beta toxin
(b) Alpha toxin
(c) Botulinum toxins
(d) Tetanus antitoxin

Q.9. Botulism has not been reported in _____.
(a) Cats
(b) Horse
(c) Cattle
(d) Hen

Q.10. The practice of using chicken manure as cattle feed or fertilizer can cause _____
(a) Early Growth
(b) Stunted Growth
(c) Increased Egg Production
(d) Botulinum Toxicosis

Answers

Exercise 2

1. b	6 a
2. d	7. b
3. b	8 d
4. a	9. a
5 d	10. d

9.5.3 Fill in the Blanks

Exercise 3

Q.1. Exotoxins produced by *Clostridium botulinum* is _____.
Q.2. Serotypes _____ have been associated with outbreaks of botulism in domestic animals.
Q.3. Botulism is relatively _____ in cattle and horses, probably more _____in chickens.
Q.4. Type B toxin of *C. botulinum* is often implicated in botulism in _____.
Q.5. Botulism has not been reported in _____ but occurs sporadically in dogs.
Q.6. The overall classical mode of action of botulinum toxin is to presynaptically bind to high-affinity recognition sites on _____.
Q.7. Enterotoxemia, also known as overeating or _____ disease.

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Q.8. *C. perfringens* types B and C both produce the highly necrotizing and lethal _____ responsible for severe intestinal damage.
Q.9. Beta toxin produced by *C. perfringens* is sensitive to _____.
Q.10. Algal poisoning is an acute, often fatal condition caused by _____ bacteria.
Q.11. The practice of using chicken manure as cattle feed or fertilizer can cause _____ toxicosis.
Q.12. Botulinum acts as a neurotoxin by inhibiting the release of _____ neurotransmitter.
Q.13. The specific treatment for botulism is _____.
Q.14. Tetanus toxin (also called tetanospasmin) is produced by _____.
Q.15. The most susceptible species of animal for tetanus is _____.
Q.16. "Sawhorse" or "wooden horse" condition in horses is caused by _____.
Q.17. Spinal stimulation in botulism is caused mainly due to inhibition of _____ neurotransmitter.
Q.18. The specific treatment for tetanus is administration of _____.

Answers

Exercise 3

1. Botulinum toxins	10. Cyanobacteria
2. A, B, C1, and D	11. Botulinum
3. Low. Frequent	12. Acetylcholine
4. Horses and foals	13. Polyvalent botulinum antitoxin
5. Cats	14. *Clostridium tetani*
6. Cholinergic nerve terminals	15. Horse
7. Pulpy kidney	16. Tetanus
8. Beta toxin	17. Glycine
9. Proteolytic enzymes	18. Tetanus antitoxin

9.5.4 True or False Statements

Exercise 4

Q.1. Botulinum toxins are produced by *Clostridium botulinum*, a Gram-negative anaerobic bacteria.
Q.2. *Clostridium botulinum* 28 antigenically distinct toxin serotypes.
Q.3. *Clostridium botulinum* grows in tissues of a living animal and produces toxins.
Q.4. Botulism in mink usually is caused by type A and D strains.

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Q.5. Mode of action of botulism toxin is to presynaptically bind cholinergic nerve terminals.
Q.6. Enterotoxemia, also known as overeating or pulpy kidney disease.
Q.7. Type A strains of *C. perfringens* are the most potent toxicants.
Q.8. Infection with *C. perfringens* types B and C causes hepatitis and nervous symptoms in animals.
Q.9. Type D enterotoxemia (pulpy kidney disease, overeating disease) is more common in cats than other animals
Q.10. Algal poisoning is an acute disease caused by *E. Coli* bacteria.

Answers

Exercise 4

1. F	6. T
2. F	7. F
3. T	8. F
4. F	9. F
5. T	10. F

9.5.5 Match the Statements

Match the statements in columns A and B

Exercise 5

	Column A		Column B
Q.1	*Botulinum toxin*	*a*	*hepatomegaly*
Q.2	*Tetanus toxin*	*b*	*Anatoxins*
Q.3	*diphtheria toxin (Dtx)*	*c*	*A, B, C1, and D*
Q.4	*Exotoxin A*	*d*	*necrotic enteritis in poultry*
Q.5	*Botulinum Serotypes*	*e*	*Corynebacterium diphtheria*
Q.6	*Enterotoxemia,*	*f*	*pulpy kidney disease*
Q.7	*C perfringens*	*g*	*Pseudomonas aeruginosa*
Q.8	*Algal poisoning*	*h*	*cyanobacteria*
Q.9	*Neurotoxic alkaloids*	*i*	*Clostridium tetani*
Q.10	*Microcystins*	*J*	*Clostridium botulinum*

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Answers

Exercise 5

Q.1	Botulinum toxin	j	*Clostridium botulinum*
Q.2	Tetanus toxin	i	*Clostridium tetani*
Q.3	diphtheria toxin (Dtx)	e	*Corynebacterium diphtheria*
Q.4	Exotoxin A	g	*Pseudomonas aeruginosa*
Q.5	Botulinum Serotypes	c	A, B, C1, and D
Q.6	Enterotoxemia,	f	pulpy kidney disease
Q.7	C perfringens	d	necrotic enteritis in poultry
Q.8	Algal poisoning	h	*Cyanobacteria*
Q.9	Neurotoxic alkaloids	b	anatoxins
Q.10	Microcystins	a	Hepatomegaly

Further Reading

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Mycotoxicoses

10

Abstract

This chapter deals with acute or chronic toxicoses that can result from exposure to feed or bedding contaminated with toxins produced during growth of various saprophytic or phytopathogenic fungi or molds on cereals, hay, straw, pastures, or any other fodder. These fungi are known to produce various toxins and lead to various problems in animals. A few of commonly observed toxicoses observed in animals include aflatoxicosis, ochratoxin A (OTA) poisoning, ergot poisoning (also known ergotism), estrogenism, vulvovaginitis, facial eczema, fescue lameness (fescue foot), fumonisin toxicosis, mycotoxic lupinosis, trichothecene toxicosis, ryegrass staggers, paspalum staggers, slaframine toxicosis, Degnala disease, tremorgenic mycotoxicosis, etc. Some toxins are not consistently produced by specific molds and are known as secondary (not essential) metabolites that are formed under conditions of stress to the fungus or its plant host.

Keywords

Mycotoxicoses · Aflatoxicosis · Ochratoxin A (OTA) poisoning · Ergot poisoning · Tremorgenic mycotoxicosis · Ryegrass staggers · Paspalum staggers · Slaframine toxicosis · Question and answer bank · Multiple choice questions

10.1 Introduction

This chapter deals with acute or chronic toxicoses that can result from exposure to feed or bedding contaminated with toxins produced during growth of various saprophytic or phytopathogenic fungi or molds on cereals, hay, straw, pastures, or any other fodder. These toxins are not consistently produced by specific molds and are known as secondary (not essential) metabolites that are formed under conditions of stress to the fungus or its plant host. A few of commonly observed toxicoses observed in animals include aflatoxicosis, ochratoxin toxicity, ergotism, facial eczema, mycotoxic lupinosis, trichothecene toxicosis, tremorgenic mycotoxins, and ryegrass staggers. This chapter also highlights the key points about the subject

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matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, true/false, and match the statements as relevant to mycotoxic diseases in animals.

Key Points

- The cause of mycotoxic diseases may not be immediately identified.
- Mycotoxic diseases are not transmissible from one animal to another.
- Outbreaks are often seasonal, because particular climatic sequences may favor fungal growth and toxin production.
- Mycotoxic diseases may have specific association with a particular feed.
- Large numbers of fungi or their spores found on examination of feedstuffs do not necessarily indicate that toxin production has occurred. However, absence of molds does not exclude mycotoxicosis, because feed storage or preparation conditions, e.g., acid treatment or high pelleting, can destroy molds while the heat-tolerant mycotoxin persists.
- Aflatoxicosis occurs in many parts of the world and affects growing poultry (especially ducklings and turkey poults), young pigs, pregnant sows, calves, and dogs.
- Adult cattle, sheep, and goats are relatively resistant to the acute form of the disease but are susceptible if toxic diets are fed over long periods.
- Treatment with drugs or antibiotics has little effect on the course of the disease.

10.2 Aflatoxicosis

Aflatoxicosis is caused by aflatoxins that are toxic metabolites produced primarily by some strains of *Aspergillus flavus* and by most, if not all, strains of *A. parasiticus*, plus related species (Figs. 10.1, 10.2, and 10.3). Growth of *A. nomius* and *A. niger* in/on foods and feeds such as peanuts, soybeans, corn (maize), and other cereals either in the field or during storage when moisture content and temperatures are sufficiently high for mold growth is quite common. They are probably the best known and most intensively researched mycotoxins in the world. There are four major aflatoxins, B1, B2, G1, and G2, plus two additional metabolic products—M1 and M2—which are of significance as direct contaminants of foods and feeds.

Toxicity Aflatoxicosis occurs in many parts of the world and affects growing poultry (especially ducklings and turkey poults), young pigs, pregnant sows, calves, and dogs. Adult cattle, sheep, and goats are relatively resistant to the acute form of the disease but are susceptible if toxic diets are fed over long periods. The toxic response and disease in mammals and poultry vary in relation to species, sex, age, nutritional

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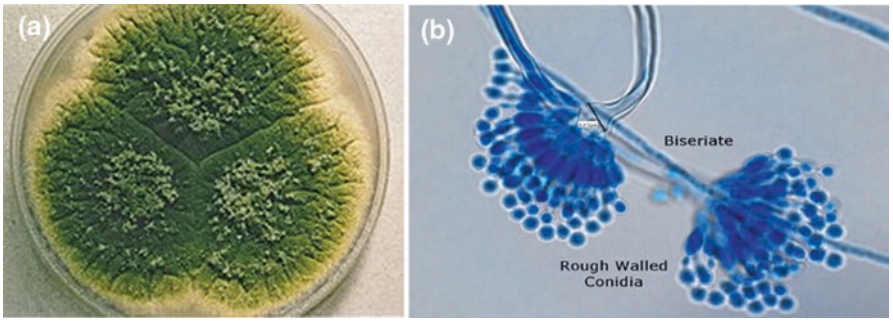


Fig. 10.1 *Aspergillus parasiticus* (**a**) (https://upload.wikimedia.org/wikipedia/commons/thumb/6/68/Aspergillus_parasiticus_UAMH3108.jpg/330px-Aspergillus_parasiticus_UAMH3108.jpg). *Aspergillus flavus* (**b**). (http://2.bp.blogspot.com/-C8V1raxuKnI/UIHZ_6N9U_I/AAAAAAAAIA0/qHzwjfDhsW0/s1600/13-+Aspergillus+calidoustus+%281000+10x%29.jpg)



Fig. 10.2 *Aspergillus flavus* on maize—source of aflatoxins. (https://www.ars.usda.gov/ARSUserFiles/60662500/images/photoCarousel/Weaver%20BCPRU%20Web%20image%203.jpg)

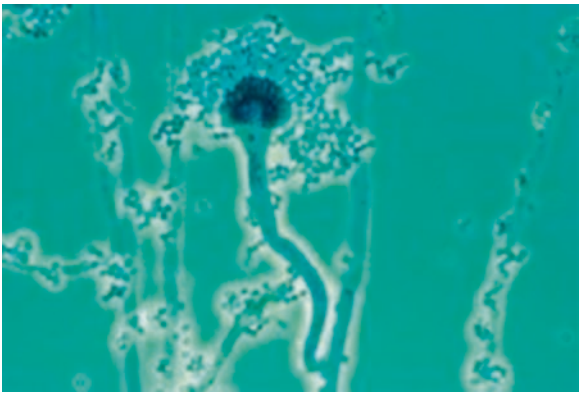


Fig. 10.3 *A. fumigatus*. (http://upload.wikimedia.org/wikipedia/commons/4/4f/Aspergillus.jpg)

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status, and the duration of intake and level of aflatoxins in the ration. Earlier recognized disease outbreaks called "moldy corn toxicosis," "poultry hemorrhagic syndrome," and "*Aspergillus* toxicosis" may have been caused by aflatoxins. The liver is the principal organ affected. High dosages of aflatoxins result in hepatocellular necrosis; prolonged low dosages result in reduced growth rate, immune suppression, and liver enlargement. These toxins result in embryo toxicity in animals that consume low dietary concentrations. The young ones are most susceptible; all ages are affected but in different degrees for different species. Other signs of aflatoxicosis in animals include gastrointestinal dysfunction, reduced reproductivity, reduced feed utilization and efficiency, anemia, and jaundice. Nursing animals may be affected as a result of the conversion of aflatoxin B1 to the metabolite aflatoxin M1 excreted in milk of dairy cattle. Aflatoxin B1, aflatoxin M1, and aflatoxin G1 have been shown to cause various types of cancer in different animal species. However, only aflatoxin B1 has been identified as a carcinogen.

Mode of Action Aflatoxins are metabolized in the liver to an epoxide that binds to macromolecules, especially nucleic acids and nucleoproteins. Their toxic effects include mutagenesis due to alkylation of nuclear DNA, carcinogenesis, teratogenesis, reduced protein synthesis, and immunosuppression. Reduced protein synthesis results in reduced production of essential metabolic enzymes and structural proteins for growth.

Treatment and Control Young, newly weaned, pregnant, and lactating animals require special protection from suspected toxic feeds. Dilution with noncontaminated feedstuffs is one possibility, but this may not be acceptable on a regulatory basis. Numerous products are marketed as anticaking agents to sequester or "bind" aflatoxins and reduce absorption from the GI tract. One effective binder for aflatoxins is hydrated sodium calcium aluminosilicates (HSCAS), which reduce the effects of aflatoxin when fed to pigs or poultry. Other adsorbents (sodium bentonites, polymeric glucomannans) have shown variable but partial efficacy in reducing low-level aflatoxin residues in poultry and dairy cattle.

10.3 Ochratoxin A Toxicity

Ochratoxin A (OTA) is an ubiquitous mycotoxin produced by fungi of improperly stored food products. OTA is nephrotoxic and is suspected of being the main etiological agent responsible for human Balkan endemic nephropathy (BEN) and associated urinary tract tumors. Striking similarities between OTA-induced porcine nephropathy in pigs and BEN in humans are observed. International Agency for Research on Cancer (IARC) has classified OTA as a possible human carcinogen (group 2B). Currently, the mode of carcinogenic action by OTA is unknown. OTA is genotoxic following oxidative metabolism. This activity is thought to play a central role in OTA-mediated carcinogenesis and may be divided into direct (covalent DNA adduction) and indirect (oxidative DNA damage) mechanisms of action.

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Evidence for a direct mode of genotoxicity has been derived from the sensitive 32P-postlabeling assay. OTA facilitates guanine-specific DNA adducts in vitro and in rat and pig kidney orally dosed, one adduct comigrates with a synthetic carbon (C)-bonded C8-dG OTA adduct standard. The available evidence suggests that OTA is a genotoxic carcinogen by induction of oxidative DNA lesions coupled with direct DNA adducts via quinone formation.

10.4 Ergotism

Poisoning produced by eating food (grazing seed heads or from infected grains in concentrate rations) affected by ergot is known as ergotism. Ergotism is a worldwide disease of farm animals that results from ingestion of sclerotia of the parasitic fungus *Claviceps purpurea*, which replaces the grain or seed of rye and other small grains or forage plants, such as the bromes, bluegrasses, fescues, and ryegrasses. The hard, black, elongated sclerotia may contain varying quantities of ergot alkaloids, of which ergotamine and ergonovine (ergometrine) are pharmacologically most important (Fig. 10.4). Cattle, pigs, sheep, and poultry are involved in sporadic outbreaks, and most other species are susceptible.

Mode of Action Ergot causes vasoconstriction by direct action on the muscles of the arterioles, and repeated doses injure the vascular endothelium. These actions initially reduce blood flow and eventually lead to complete stasis with terminal necrosis of the extremities due to thrombosis. A cold environment predisposes the extremities to gangrene. In addition, ergot also causes stimulation of the CNS, followed by depression. Ergot alkaloids inhibit pituitary release of prolactin in many



Fig. 10.4 Fungus *C. purpurea* on rye. (https://media4.picsearch.com/is?l8VTp7WpHlz326esVHyJorSwavwiJWIqIZ0Uj-JnoA4&height=281)

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mammalian species, with failure of both mammary developments in late gestation and delayed initiation of milk secretion, resulting in agalactia at parturition. Ergot alkaloids have also been associated with heat intolerance, dyspnea, and reduced milk production in dairy cattle, similar to the "summer syndrome" described for fescue toxicosis.

Toxicity Cattle may be affected by eating ergotized hay or grain or occasionally by grazing seeded pastures infested with ergot. Lameness, the first sign, may appear 2–6 weeks or more after initial ingestion, depending on the concentration of alkaloids in the ergot and the quantity of ergot in the feed. Hind limbs are affected before forelimbs. Body temperature and pulse and respiration rates are increased. Epidemic hyperthermia and hypersalivation may also occur in cattle poisoned with *C. purpurea* (also see fescue lameness). Ergot alkaloids may interfere with embryonic development in pregnant females.

Associated with the lameness are swelling and tenderness of the fetlock joint and pastern. Eventually, one or both claws or any part of the limbs up to the hock or knee may be sloughed (dry gangrene). In a similar way, the tip of the tail or ears may become necrotic and slough. Exposed skin areas, such as teats and udder, appear unusually pale or anemic (Fig. 10.5). Abortion is not seen. Subcutaneous hemorrhage and some edema occur proximal to the necrotic area.

In pigs, ingestion of ergot-infested grains may result in reduced feed intake and reduced weight gain. Occasionally, swine may show necrosis of the tips of ears or tail. If fed to pregnant sows, ergotized grains result in lack of udder development with agalactia at parturition, and the piglets born may be smaller than normal. Most of the litter die within a few days because of starvation. No other clinical signs or lesions are seen.



Fig. 10.5 Severe cases of ergot poisoning may no longer be able to walk and must be euthanized on site. (http://static.agcanada.com/wp-content/uploads/sites/5/2014/07/ergot-poisoning_Univer_RGB-300x300.jpg)

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Clinical signs in sheep are similar to those in cattle. Additionally, the mouth may be ulcerated, and marked intestinal inflammation may be seen at necropsy. A convulsive syndrome has been associated with ergotism in sheep.

Treatment and Control In horses, parenteral use of the dopamine D2 antagonist domperidone is effective in prevention of agalactia from ergot alkaloids in fescue. Ergotism can be controlled by an immediate change to an ergot-free diet. In pregnant sows, however, removal of ergot in late gestation (<1 week before parturition) may not correct the agalactia syndrome, and animals with clinical peripheral gangrene will not likely recover. Under pasture feeding conditions, frequent grazing or topping of pastures prone to ergot infestation during the summer months reduces flower-head production and helps control the disease. Grain that contains even small amounts of ergot should not be fed to pregnant or lactating sows.

10.5 Estrogenism and Vulvovaginitis (*Fusarium* Estrogenism)

Estrogenism and vulvovaginitis commonly known as atrophic vaginitis is the chronic and progressive inflammation of the vagina (and the lower urinary tract) due to the thinning and shrinking of the vaginal tissues and is often accompanied by vulvar and urinary pathologies. These symptoms are due to a lack of the reproductive hormone estrogen. The disease is caused by *Fusarium* spp. molds that are extremely common and often contaminate growing plants and stored feeds. Corn (maize), wheat, and barley are commonly contaminated (Fig. 10.6). In moderate climates under humid weather conditions, *F. graminearum* may produce



Fig. 10.6 Fusarium roseum—source of zearalenone toxins. (http://www7.inra.fr/hyp3/images/6032317.jpg)

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zearalenone, one of the resorcylic acid lactones (RALs), which is a potent nonsteroidal estrogen and is the only known mycotoxin with primarily estrogenic effects.

Toxins Zearalenone (ZEN), also known as RAL/F-2 mycotoxin, is a potent estrogenic metabolite produced by some *Fusarium* and *Gibberella* species, *F. verticillioides*, and *F. incarnatum*. These species produce toxic substances of considerable concern to livestock and poultry producers, namely, deoxynivalenol, T-2 toxin, HT-2 toxin, diacetoxyscirpenol, and zearalenone.

Mechanism of Action Zearalenone is a weak estrogen with potency 2–4 times less than estradiol. Zearalenone binds to receptors for 17β-estradiol, and this complex binds to estradiol sites on DNA. In sexually mature sows, reproductive toxicosis is caused by inhibiting secretion and release of follicle-stimulating hormone (FSH), resulting in arrest of preovulatory ovarian follicle maturation. Some specific changes in RNA synthesis leads to signs of estrogenism.

Toxicity In pigs, the major metabolite of zearalenone is α-zearalenol, which has greater affinity for estrogen receptors than β-zearalenol, which is formed in cattle. Therefore, pigs are more susceptible than cattle. Estrogenism due to zearalenone was first clinically recognized as vulvovaginitis in prepubertal gilts fed moldy corn (maize), but zearalenone is occasionally reported as a suspected disease-causing agent for sporadic outbreaks in dairy cattle, sheep, chickens, and turkeys. High dietary concentrations (>20–30 ppm) are required to produce infertility in cattle and sheep, and extremely high dosages are required to affect poultry.

In pigs, zearalenone primarily affects weaned and prepubertal gilts, causing hyperemia and enlargement of the vulva (known as vulvovaginitis). There is hypertrophy of the mammary glands and uterus, and abdominal straining results in prolapse of the uterus in severe cases. Zearalenone fed at ≥30 ppm in early gestation may prevent implantation and cause early embryonic death. Zearalenone metabolites can be excreted in milk of exposed sows, resulting in hyperestrogenic effects in their nursing piglets.

In cattle, dietary concentrations >10 ppm may cause reproductive dysfunction in dairy heifers, although mature cows may tolerate up to 20 ppm.

Young males, both swine and cattle, may become infertile, with atrophy of the testes. However, mature boars appear unaffected by as much as 200 ppm dietary zearalenone.

Ewes may show reduced reproductive performance (reduced ovulation rates and numbers of fertilized ova, and markedly increased duration of estrus) and abortion or premature live births.

Treatment and Control Management of swine with hyperestrogenism include changing the grain immediately. Animals should be treated symptomatically for vaginal or rectal prolapse and physical damage to external genitalia. For sexually mature sows with anestrus, one 10-mg dose of prostaglandin F2α, or two 5-mg

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doses on successive days, has corrected anestrus caused by retained corpora. Feeding activated charcoal, cholestyramine, or alfalfa meal may reduce zearalenone absorption and retention, but the high concentrations needed generally render this impractical.

10.6 Facial Eczema

Facial eczema is a type of sunburn (photosensitization) affecting exposed areas of pale skin of sheep (Fig. 10.7) and cattle due to liver damage. It is caused by a poisonous substance called "sporidesmin," which is produced on pasture plants by the fungus *Pithomyces chartarum*, which lives in dead vegetative material in pastures, especially perennial ryegrass. Facial eczema is an example of "secondary photosensitization," in which the skin lesions are really the secondary result of liver damage rather than the direct result of a plant toxin.

Toxicity The clinical symptoms of facial eczema are distressing: restlessness, frequent urination, shaking, persistent rubbing of the head against objects (e.g., fences and trees), drooping and reddened ears, swollen eyes, and avoidance of sunlight by seeking shade. Exposed areas of skin develop weeping dermatitis and scabs that can become infected and attractive to blow fly causing myiasis.

Control To minimize intake of pasture litter and toxic spores, short grazing should be avoided. The application of benzimidazole fungicides to pastures considerably restricts the buildup of *P. chartarum* spores and reduces pasture toxicity. Sheep and cattle can be protected from the effects of sporidesmin if given adequate amounts of zinc. Zinc may be administered by drenching with zinc oxide slurry, by spraying pastures with zinc oxide, or by adding zinc sulfate to drinking water. Sheep may be selectively bred for natural resistance to the toxic effects of sporidesmin.



Fig. 10.7 A sheep showing clinical symptoms of facial eczema. (https://upload.wikimedia.org/wikipedia/commons/8/8b/A_sheep_with_facial_eczema.jpg)

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10.7 Fescue Lameness (Fescue Foot)

Fescue lameness is produced by the endophyte fungus *Neotyphodium coenophialum* in tall fescue grass (*Lolium arundinaceum*, formerly *Festuca arundinacea*). The causative toxic substance, ergovaline, has actions similar to those produced by sclerotia of *Claviceps purpurea*. However, ergot poisoning (see ergotism) is not the cause of fescue lameness.

Mode of Action Ergovaline is an agonist for dopamine D2 receptors, which initiate several physiologic abnormalities. First, inhibition of prolactin secretion causes agalactia in horses and swine and reduced lactation in cattle. The dopaminergic effect also causes imbalances of progesterone and estrogen, associated with early parturition for cattle and prolonged gestation with oversized fetuses in mares. Finally, inadequate prolactin disturbs the hypothalamic thermoregulatory center, leading to temperature intolerance when environmental temperature exceeds 31 °C (88 °F). If sensitive cattle eat enough of the toxin-bearing fescue (α2-adrenergic agonist), it results in constriction of blood vessels to the extremities of the animal's body, such as rear feet and the tail, resulting in swelling of the pastern-hock area. A line of demarcation that resembles a wire being wrapped around the leg appears along with a dry gangrene that may result in sloughing of the lower limb.

Toxicity The severity of the condition varies from field to field and year to year. The endophyte produces toxins that cause a number of problems for grazing animals, although sheep appear to be less affected than cattle and horses (Fig. 10.8). However, sheep are prone to "fescue foot," hyperthermia, poor wool production, and reproductive problems, as well as lowered feed intake and the resulting poor weight gains. Stockpiled fescue is less toxic. Erythema and swelling of the coronary



Fig. 10.8 Fescue toxicosis in horse. (https://encrypted-tbn1.gstatic.com/images?q5tbn:ANd9GcQyK0-Q6f41E2NhvO7JmwWR4Ru_daPxnapvOjdTIG4ey7KMN0D6)

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region occur, and cattle are alert but lose weight and may be seen "paddling" or weight-shifting. The back is slightly arched, and knuckling of a hind pastern may be an initial sign. There are progressive lameness, anorexia, depression, and later, dry gangrene of the distal limbs (hind limbs first). Signs usually develop within 10–21 days after turnout into a fescue-contaminated pasture in fall. A period of frost tends to increase the incidence. Agalactia has been reported for both horses and cattle. Thickened placentas, delayed parturition, and birth of weak foals have been reported in horses. The severity increases when environmental temperatures are >75–80 °F (24–27 °C) and if high nitrogen fertilizer has been applied to the grass.

Treatment and Control All infected forage should be removed. Medical treatment for equine agalactia/reproductive syndrome is domperidone. Removing pregnant horses or cattle 1 month before parturition will usually prevent parturition- and lactation-related problems. Specific feed additives may provide some protection against contaminated hay. Yeast cell derivatives known as glucomannans are reported to improve performance by preventing toxin absorption in cattle; a seaweed product is reported to lessen the immunosuppressive effects of toxic tall fescue.

10.8 Fumonisin Toxicosis

Fumonisins are responsible for two well-described diseases of livestock, equine leukoencephalomalacia and porcine pulmonary edema (PPE). Equine leukoencephalomalacia is a mycotoxic disease of the CNS that affects horses, mules, and donkeys. It occurs sporadically in North and South America, South Africa, Europe, and China. It is associated with the feeding of moldy corn (maize), usually over a period of several weeks. Fumonisins are produced worldwide primarily by *Fusarium verticillioides* (previously *F. moniliforme* Sheldon) and *F. proliferatum*. Conditions favoring fumonisin production appear to include a period of drought during the growing season with subsequent cool, moist conditions during pollination and kernel formation.

Toxins Three toxins produced by the fungi have been classified as fumonisin B1 (FB1), B2 (FB2), and B3 (FB3). Current evidence suggests that FB1 and FB2 are of similar toxicity, whereas FB3 is relatively nontoxic.

Toxicity Signs in Equidae include apathy, drowsiness, pharyngeal paralysis, blindness, circling, staggering, and recumbency. The clinical course is usually 1–2 days but may be as short as several hours or as long as several weeks. It may be present when the liver is involved. The characteristic signs include icterus and liquefactive necrosis of the white matter of the cerebrum—the necrosis is usually unilateral but may be asymmetrically bilateral. Some horses may have hepatic necrosis similar to that seen in aflatoxicosis. Horses may develop leukoencephalomalacia from prolonged exposure to as little as 8–10 ppm fumonisins in the diet, and onset of neurologic signs almost invariably leads to death.

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Fumonisins have also been reported to cause acute epidemics of disease in weanling or adult pigs, characterized by pulmonary edema and hydrothorax. Porcine pulmonary edema is usually an acute, fatal disease and appears to be caused by pulmonary hypertension with transudation of fluids in the thorax, resulting in interstitial pulmonary edema and hydrothorax. Signs of acute PPE include acute onset of dyspnea, cyanosis of mucous membranes, weakness, recumbency, and death, often within 24 h after the first clinical signs. Affected sows in late gestation that survive acute PPE may abort within 2–3 days, presumably as a result of fetal anoxia. Prolonged exposure of pigs to sublethal concentrations of fumonisins results in hepatotoxicosis characterized by reduced growth, icterus, and fatalities which result from disturbances in cardiopulmonary dynamics leading to acute pulmonary edema. Cattle, sheep, and poultry are considerably less susceptible to fumonisins than are horses or swine.

Treatment No effective treatment is available. Avoidance of moldy corn is the only prevention.

10.9 Mycotoxic Lupinosis

Lupinosis is associated with potentially two different types of toxin exposure associated with bitter lupines and sweat lupines. This chapter will discuss only mycotoxic lupinosis (sweat lupines). Alkaloid poisoning caused as a result of consumption of bitter lupine plant that leads to nervous syndrome has been discussed elsewhere (for details, see Chap. 11)

Mycotoxic lupinosis is a mycotoxic condition caused by the ingestion of lupines contaminated with a fungus—*Phomopsis leptostromiformis*. This condition is largely associated with the use of sweet lupines as fodder. Lupinosis is widespread in Australia and South Africa and also has been reported from New Zealand and Europe. There is increasing use of sweet lupines, either as forage crops or through feeding of their residues after grain harvest, as strategic feed for sheep in Mediterranean climate zones. Sheep, and occasionally cattle and horses, are affected, and pigs are also susceptible. This is a mycotoxic disease characterized by liver injury and jaundice, which results mainly from the feeding of sweet lupines. The causal fungus causes *Phomopsis* stem blight, especially in white and yellow lupines; blue varieties are resistant. It produces sunken, linear stem lesions that contain black, stromatic masses, and it also affects the pods and seeds. The fungus is also a saprophyte and grows well on dead lupine material (e.g., haulm, pods, stubble) under favorable conditions. It produces phomopsins as secondary metabolites on infected lupine material, especially after rain.

Toxicity Clinical changes are mainly attributable to toxic hepatocyte injury, which causes mitotic arrest in metaphase, isolated cell necrosis, and hepatic enzyme leakage, with loss of metabolic and excretory function. Early signs in sheep and cattle are inappetence and listlessness. Complete anorexia and jaundice follow, and

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ketosis is common. Cattle may show lacrimation and salivation. Ketosis is a common sequela in pregnant cattle or recently calved cows. Survivors may develop hepatic cirrhosis. Sheep may become photosensitive, and a skeletal muscle myopathy can develop. As disease progresses, liver failure may cause hepatic encephalopathy characterized by stumbling, disorientation, and recumbency before death. In acute outbreaks, deaths occur in 2–14 days.

In acute disease, icterus is marked. Livers are enlarged, orange-yellow, and fatty. More chronic cases show bronze- or tan-colored livers that are firm, contracted in size, and fibrotic. Copious amounts of transudates may be found in the abdominal and thoracic cavities and in the pericardial sac. Some animals may have spongiform lesions in the brain.

Treatment and Control Frequent surveillance of sheep and of lupine fodder material for characteristic black spot fungal infestation, especially after rains, is advised. The utilization of lupine cultivars, bred and developed for resistance to *P. leptostromiformis*, is advocated. Oral doses of zinc may be useful in sheep against liver injury induced by phomopsins.

10.10 Trichothecene Toxicosis

The trichothecene mycotoxins are a group of closely related secondary metabolic products of several families of imperfect or plant pathogenic fungi such as species of *Fusarium* but also from genera of *Trichothecium*, *Myrothecium*, *Cephalosporium*, *Stachybotrys*, *Trichodesma*, *Cylindrocarpon*, and *Verticimonosporium*.

Toxins Trichothecenes are classified as nonmacrocyclic (e.g., deoxynivalenol [DON] or vomitoxin, T-2 toxin, diacetoxyscirpenol [DAS], and others) or macrocyclic (e.g., satratoxin, roridin, verrucarin). For livestock, the most important trichothecene mycotoxin is DON, which is commonly a contaminant of corn, wheat, and other commodity grains.

Mode of Action The trichothecene mycotoxins are highly toxic at the subcellular, cellular, and organic system level. Trichothecenes inhibit protein synthesis by affecting ribosomes to interfere with protein synthesis and covalently bond to sulfhydryl groups.

Toxicity Toxicity of T-2 toxin and DAS is based on direct cytotoxicity and is often referred to as a radiomimetic effect (e.g., bone marrow hypoplasia, gastroenteritis, diarrhea, hemorrhages). Direct contact with skin and oral cavity causes irritation and ulceration. Stomatitis, hyperkeratosis with ulceration of the esophageal portion of the gastric mucosa, and necrosis of the GI tract have been seen after ingestion of trichothecenes. Systemic effects of T-2 and DAS are often self-limiting because of oral irritation and feed refusal. Given in sublethal toxic doses via any route, the trichothecenes are immunosuppressive in mammals; however, long-term feeding of

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high levels of T-2 toxin does not seem to activate latent viral or bacterial infections. The toxins may affect function of helper T cells, B cells, or macrophages or the interaction among these cells.

Hemorrhagic diathesis can occur, and the radiomimetic injury (damage to dividing cells) is expressed as lymphopenia or pancytopenia. Eventually, hypotension may lead to death. Because of the immunosuppressive action of trichothecenes, secondary bacterial, viral, or parasitic infections may mask the primary injury. The lymphatic organs are smaller than normal and may be difficult to find on necropsy. In the past, the ability to cause vomiting had been ascribed to DON only (hence the common name vomitoxin). However, other members of the trichothecene family also can induce vomiting.

Feed refusal response to DON varies widely among species. In swine, reduced feed intake may occur. Poultry may tolerate as much as 100 ppm. Horses may accept as much as 35–45 ppm dietary DON without feed refusal or adverse clinical effects. Dogs also will refuse foods containing DON, usually at concentrations >5 ppm. Related effects of weight loss, hypoproteinemia, and weakness may follow prolonged feed refusal. There is little evidence that DON causes reproductive dysfunction in domestic animals. Experimental studies suggest that DON may cause variable effects of immunosuppression or immunostimulation, but research is continuing to define whether DON has a practical role in disease susceptibility in field conditions. Neurochemical changes may be related to changes in serotonin, dopamine, and 5-hydroxyindoleacetic acid levels in brain.

Macrocyclic trichothecene-related diseases have received a number of specific names. The best known is stachybotryotoxicosis found in horses, cattle, sheep, pigs, and poultry, first diagnosed in the former USSR but occurring also in Europe and South Africa. Cutaneous and mucocutaneous lesions, panleukopenia, nervous signs, and abortions have been seen. Death may occur in 2–12 days.

Myrotheciotoxicosis and dendrodochiotoxicosis have been reported from the former USSR and New Zealand. The signs resemble those of stachybotryotoxicosis, but death may occur in 1–5 days.

Treatment and Control Symptomatic treatment and feeding of uncontaminated feed are recommended. Steroidal antishock and anti-inflammatory agents, such as methylprednisolone, prednisolone, and dexamethasone, have been used successfully in experimental trials. Poultry and cattle are more tolerant of trichothecenes than are pigs. Pigs exposed to DON often recover appetite promptly when uncontaminated feed is offered. DON-contaminated feed treated with various adsorbents, including calcium aluminosilicates, bentonite, sodium bisulfite, and yeast-based glucomannans, has not been helpful to correct feed refusal in swine. Addition of 0.2% glucomannan mycotoxin adsorbent to DON-contaminated diet for pregnant sows increased percentage of pigs born live but did not correct reduced feed intake. Physical seed treatment (abrasive pearling procedure) has removed two-thirds of DON from barley. In general, cleaning and removal of damaged grain (screenings) improve feed quality and acceptance of mycotoxin-contaminated grains.

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10.11 Ryegrass Staggers

Ryegrass staggers is a nervous disease caused by endophyte (fungi that live inside the plant) that produces the mycotoxin lolitrem B. Ryegrass staggers should not be confused with "grass staggers"—a nervous disease caused by a deficiency of magnesium. This disease can be a serious problem in livestock grazing perennial ryegrass pasture during the summer and autumn months. It is most commonly seen in sheep and cattle, but horses, deer, and alpaca are also susceptible. While ryegrass staggers have not been recorded in goats, they may also be susceptible but may not develop symptoms due to their different grazing/browsing habits. Affected animals develop muscle tremors and incoordination, which worsen with stress and external stimuli (Fig. 10.9). They may have a stiff gait, which can progress eventually to paralysis.

10.12 Paspalum Staggers

Paspalum staggers is a neurological disease in horses which occurs from ingestion of dallis grass (*Paspalum dilatatum*) containing the sclerotium (ergot) of *Claviceps paspali*. This condition very closely resembles ryegrass staggers, which is caused by ingestion of perennial ryegrass (*Lolium perenne*). It is a somewhat rare condition in horses, with only a handful of cases occurring in Australia. Paspalum staggers mainly affects cattle. In the cases that occur in horses, the common characteristics were that their pastures were dominated by paspalum plants that had seed heads that were heavily infected with toxic sclerotia of *C. paspali*.



Fig. 10.9 Mycotoxins produced by the endophytes living within ryegrass cells could affect livestock, causing them to tremble and lose coordination. (Reproduced from https://pixabay.com/en/sheep-flock-of-sheep-flock-pasture-1763376/)

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Toxic Principles The major toxins produced by *C. paspali* are tremorgenic indole diterpenes.

Toxicity A sufficiently large single dose causes continuous trembling of the large muscle groups; movements are jerky and uncoordinated. If they attempt to run, they fall over in awkward positions. Appetite remains good, and animals will eat if feed is provided. Affected animals may be belligerent and dangerous to approach or handle. After prolonged exposure, condition deteriorates and complete paralysis can occur. The time of onset of signs depends on the degree of the infestation of seed heads and the grazing habits of the animals. Experimentally, early signs appear in cattle after sclerotia at ~100 g/day has been administered for >2 days. Although the mature ergots are toxic, they are most dangerous just when they are maturing to the hard, black (sclerotic) stage.

Treatment and Control Treatment is symptomatic. Recovery follows removal of the animals to feed not contaminated with sclerotia of *C. paspali*. Animals are less affected if left alone and provided with readily available nutritious forages. Care should be taken to prevent accidental access to ponds or rough terrain where accidental trauma or drowning could occur. Topping of the pasture to remove affected seed heads has been effective in control.

10.13 Slaframine Toxicosis

Slaframine is an alkaloidal mycotoxin produced by the fungus *Rhizoctonia leguminicola* that causes profuse salivation ("slobbers") in animals. *R. leguminicola* is a common fungal pathogen of red clover (*Trifolium pratense*) and causes a syndrome known as black patch disease in the plant. Ingestion of clover hay containing slaframine toxin causes salivary episodes that last from several hours to over 3 days in ruminants and horses.

There is no specific antidote to slaframine toxicosis, although atropine may control at least some of the prominent salivary and GI signs. Removal of animals from the contaminated hay is essential. Prevention of *Rhizoctonia* infection of clovers has been difficult. Some clover varieties may be relatively resistant to black patch disease. Reduced usage of red clover for forages or dilution with other feeds is helpful.

10.14 Degnala Disease

Raising buffaloes and cattle in Pakistan, Nepal, and India is one way of augmenting the financial resources of village people. These animals are mainly raised on rice and wheat straw, which are of poor nutritional quality. Rice and wheat plants, when

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infested by fungus *Fusarium* and in association with other fungi species, are responsible for Degnala disease in Pakistan, Nepal, and India. This disease not only causes severe health problems, but it also can cause significant economic losses as a result of decreased production exacerbated by reduced growth rate, mortality, and poor animal performance. It causes necrosis and gangrene (Fig. 10.10) of the dependent parts in cows and buffaloes (*Bubalus bubalis L.*).

Mode of Action Degnala disease (which is believed to be a mycotoxicosis) has clinical syndrome similar to chronic ergotism and is characterized by the development of edema, necrosis, and gangrene of the legs, tail, ears, etc. As a result, in the dependent parts of the ear, tail, and foot, blood supply is obstructed, and ultimately tissues die of anoxia.

Toxicity The diseased animals were invariably weak; ulcerative wounds and gangrene developed on the limbs and other dependent parts of the body. Almost all cases showed gangrene of the tail, which was shriveled and cold to the touch. Invariably, one or both ears showed signs of dry gangrene (Fig. 10.10). In some cases, the muzzle and even the tip of the tongue became gangrenous and were shed. One or more hooves showed lesions in varying stages of development, legs were swollen up to the knees; hair was denuded and inflammatory changes set in. Later, wounds appeared on the coronet, fetlock, pastern, and knee and in the hock region. In very advanced cases, the lower regions of the feet became gangrenous, hooves were shed, and bones were exposed. The gangrenous portions of the tail, tips of the ears, tongue, and other affected parts of the body dropped off, although wounds healed in the course of time.

Treatment Treatment is symptomatic. Treatment with anti-Degnala liquor 5 mL s/c followed by 2 mL daily for the next 10 days may be useful.



Fig. 10.10 Degnala disease in buffaloes. (http://images.engormix.com/e_articles/2185_78,201.jpg)

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10.15 Tremorgenic Mycotoxins

Over 20 mycotoxins containing a tryptophan-derived indole moiety have demonstrated tremorgenic potential in animals and humans. Tremorgen-producing fungi grow on a wide variety of foodstuffs, including dairy or grain-containing products intended for human consumption, stored grains and nuts, and a number of forages consumed by livestock species, as well as food- or beverage-manufacturing byproducts, garbage, and compost piles. These tremorgenic mycotoxins can elicit either intermittent or sustained tremors in vertebrate species, dog in particular because of their indiscriminate appetite and roaming behavior. Mycotoxin-associated stagger syndromes have been described in livestock. There is no specific treatment or antitoxin available for these toxins.

10.16 Questions and Answers

10.16.1 Short Questions and Answers

Exercise 1

Q.1. Define mycotoxins.
Mycotoxins are toxic by-products (secondary metabolites) produced by fungi. There are 400 mycotoxins produced by 350 species of fungi.

Q.2. Which animals are susceptible to mycotoxins?
It is a worldwide problem caused by ingestion of moldy feed, corn, or certain varieties of mold-infected pasture grass and forage (e.g., fescue grass, rye, and sweet clover). All species of livestock, horses, and poultry are susceptible. Ingestion of these toxins can lead to lameness, paralysis, listlessness, jaundice, and internal bleeding.

Q.3. Which mycotoxins are considered the most serious threat to animals?
Mycotoxins such as aflatoxins, ochratoxin A, fumonisins, certain trichothecenes, zearalenone, and fusarium are considered the most serious threat to human health, animals, and birds due to their potential of carcinogenic, hepatogenic, teratogenic, mutagenic, and other serious effects leading to economic losses.

Q.4. What are aflatoxins?
Aflatoxins are toxic metabolites produced by certain fungi in/on foods and feeds. They are probably the best known and most intensively researched mycotoxins in the world.

Q.5. What are major aflatoxins responsible for toxicity in animals?
There are four major aflatoxins, B1, B2, G1, and G2, plus two additional metabolic products—M1 and M2—which are of significance as direct contaminants of foods and feeds.

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Q.6. Describe in brief three main *Aspergillus* sp. that are potentially toxic.

Mycotoxins are fungal secondary metabolites that are potentially harmful to animals or humans. The word "aflatoxin" came from "*Aspergillus flavus* toxin." Three predominant species responsible for aflatoxin poisoning are:

1. *Aspergillus flavus*
2. *Aspergillus parasiticus*
3. *Aspergillus fumigatus*

Q.7. What are common mycotoxins that cause poisoning?

They include:

1. The ergot alkaloids produced by *Claviceps* sp.
2. Aflatoxins and related compounds produced by *Aspergillus* sp.
3. The tricothecenes produced by several genera of fungi imperfecti, primarily *Fusarium* sp.

Q.8. What is ergotism?

Poisoning produced by eating food (grazing seed heads or from infected grains in concentrate rations) affected by ergot is known as ergotism. Ergotism is a worldwide disease of farm animals that results from ingestion of sclerotia of the parasitic fungus *Claviceps purpurea*, which replaces the grain or seed of rye and other small grains or forage plants, such as the bromes, bluegrasses, fescues, and ryegrasses.

Q.9. What are the toxic principles of ergot?

The active toxic principles are ergotamine, ergotoxin, and ergometrine. They are known to contract arterioles which can lead to gangrene of the part supplied.

Q.10. How are tricothecenes produced?

Tricothecenes are produced particularly by members of the genera *Fusarium* and *Tricoderma*.

10.16.2 Multiple Choice Questions

(Choose the correct answer; it may be one, two, more, or none.)

Exercise 2

Q.1. The maximum permitted level of zearalenone in feed is _____.

(a) 200 ppb
(b) 100 ppb
(c) 10 ppb
(d) 5 ppb

Q.2. The histological picture of the uterus and vagina in zearalenone toxicosis is _____.

(a) Hepatitis
(b) Vaginitis
(c) Nodule formation
(d) Metaplasia

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Q.3. Alimentary toxic aleukia (ATA) in human beings is caused by _____ mycotoxins.
(a) DAS
(b) T-2 toxin
(c) DON
(d) All

Q.4. The mycotoxins that were used as biological warfare agents are _____.
(a) Aflatoxins
(b) Algal toxins
(c) Trichothecenes
(d) Fumonisins

Q.5. The species of animal which is more susceptible to trichothecenes is _____.
(a) Tiger
(b) Elephant
(c) Horse
(d) Cat

Q.6. An example for neurotoxic mycotoxin is _____.
(a) Aflatoxins
(b) Trichothecenes
(c) Tremorgens
(d) None

Q.7. The most potent among the tremorgens is _____.
(a) Ergotoxin
(b) Penitrem A
(c) Mycotoxin
(d) Slafamine

Q.8. The most susceptible species for tremorgen mycotoxins are _____ and _____
(a) Cat and dog
(b) Cattle and sheep
(c) Poultry birds
(d) Horse

Q.9. Ergotoxins are produced by the mold _____.
(a) *Claviceps purpurea*
(b) Ryegrass
(c) Trichothecenes
(d) None

Q.10. Molds generally grow in stored feedstuffs containing a moisture content more than _____.
(a) 25%
(b) 15%
(c) 50%
(d) 40%

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Answers

Exercise 2

1. c	6. c
2. d	7. b
3. d	8. a
4. c	9. a
5. d	10. b

10.16.3 Fill in the Blanks

Exercise 3

Q.1. The aflatoxin content in cattle feeds should not exceed _____.
Q.2. The carcinogenic metabolite formed in the body from aflatoxins is _____.
Q.3. Aflatoxins cause defective protein synthesis by binding with _____ residue of DNA causing mispairing of nucleotides.
Q.4. Aflatoxin epoxide causes carcinogenic and mutagenic effect by causing _____ of the strands of DNA (alkylation forms cross-bridges between DNA strands).
Q.5. Hemorrhage in aflatoxicosis is due to the decrease in _____ and _____.
Q.6. The type of carcinoma caused by aflatoxins is _____.
Q.7. Aflatoxins can be detected by _____ method.
Q.8. Hemorrhagic syndrome in poultry is caused by _____ mycotoxins.
Q.9. Rubratoxins are produced by _____ and _____.
Q.10. The most toxic metabolite of rubratoxins is _____.

Answers

Exercise 3

1. 20 ppb
2. Aflatoxin 8, 9-epoxide
3. N7-guanine
4. Alkylation
5. Prothrombin and vitamin K
6. Hepatocellular carcinoma
7. Thin-layer chromatography
8. Rubratoxins
9. *Penicillium rubrum* and *Penicillium purpurogenum*
10. Rubratoxin B

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10.16.4 True or False Statements

Exercise 4

Q.1. Ruminant's facial eczema is caused by ochratoxin mycotoxicosis.
Q.2. The most potent nephrotoxic mycotoxins which cause mold nephrosis or mycotoxic nephropathy are sporidesmin.
Q.3. Ochratoxins are produced by *Aspergillus ochraceus* and *Penicillium viridicatum.*
Q.4. The most toxic among the ochratoxins is ochratoxin A.
Q.5. The most susceptible species for ochratoxicosis are horse and goat.
Q.6. The level of ochratoxin in feed should not exceed 50 ppb.
Q.7. An example for estrogenic mycotoxin which can cause reproductive disorders is zearalenone (f-2).
Q.8. Zearalenone (f-2) toxins are produced by *Fusarium roseum* mold.
Q.9. The most susceptible species for zearalenone toxicosis is elephant.
Q.10. Vulvovaginitis of hyperestrogenic syndrome in pigs is caused by zearalenone mycotoxin.

Answers

Exercise 4

1. False	6 False
2 False	7 True
3 True	8 True
4 True	9 False
5 False	10 True

10.16.5 Match the Statements

(Match the following statements in Columns A and B.)

Exercise 5

	Column A		Column B
Q,1	Ergotism in cattle	a	Tetanus
Q,2	Ergot alkaloids are partial agonist	b	Alpha receptors
Q,3	Tetanus toxin	c	Horse
Q,4	"Sawhorse" or "wooden horse	d	Rye (c. Purpurea)
Q,5	Form of ergotism commonly found in cattle	e	Gangrenous
Q,6	Most susceptible species of animal for tetanus	f	*Clostridium tetani*
Q,7	Tetanus	g	Chicken
Q,8	Botulinum action	h	Acetylcholine
Q,9	Oxytocic effect on uterus	I	Ergometrine or ergonovine
Q,10	Botulism is most common	J	Tetanus antitoxin

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Answers

Exercise 5

	Column A		Column B
Q,1	Ergotism in cattle	d	Rye (c. Purpurea)
Q,2	Ergot alkaloids are partial agonist	b	Alpha receptors
Q,3	Tetanus toxin	f	*Clostridium tetani*
Q,4	Saw horse" or "wooden horse	a	Tetanus
Q,5	Form of ergotism commonly found in cattle	e	Gangrenous
Q,6	Most susceptible species of animal for tetanus	c	Horse
Q,7	Tetanus	j	Tetanus antitoxin
Q,8	Botulinum action	h	Acetylcholine
Q,9	Oxytocic effect on uterus	i	Ergometrine or ergonovine
Q,10	Botulism is most common	g	Chicken

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Poisonous Plants

11

Abstract

This chapter deals with the toxic effects of some of the common poisonous plants containing various toxic principles such as alkaloids, cyanogenic glycosides, nitrate- and nitrite-accumulating plants, strychnine poisoning, and various mushroom toxins in animals. Problems can also occur with animals in ornamental gardens, natural environments, and homes. Poisoning in humans and companion animals from toxic plants also continues to be a significant risk, especially to pets and children. Plant poisoning in small animals is usually accidental. Lack of understanding and increased grazing pressure on these small acreages often contribute to the consumption of toxic plants by animals. It is recommended (1) not to throw grass, shrub, or tree clippings into paddocks where animals reside (yew clippings are a common cause of poisoning in many animals); (2) provide free access to freshwater and minerals/salt and do not overstock the range or pastures; (3) avoid bedding, lambing/calving, watering, salting, or unloading hungry animals near poisonous plant populations; and (4) avoid excess stress to those animals showing clinical signs of poisoning, and if necessary, contact the veterinarian. If economically feasible, control poisonous plants through hand grubbing, mechanical clipping, or herbicide treatment.

Keywords

Poisonous plants · Pyrrolizidine alkaloid-containing plants · Photosensitizing plants · Cyanogenic glycosides · Nitrate and nitrates · Strychnine poisoning · Question and answer bank · Multiple choice questions

11.1 Introduction

This chapter deals with the toxic effects of some of the common poisonous plants containing various toxic principles such as alkaloids, cyanogenic glycosides, nitrate- and nitrite-accumulating plants, strychnine poisoning, and various mushroom toxins in animals. It is well established that most of the experimental data are available

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on laboratory animals and reported in veterinary literature. Attempts have been made to summarize information as relevant to animals exposed to different poisonous plants. The chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements relevant to toxic plants and their toxic principles in animals.

Key Points

- Poisonous plants and the secondary compounds they produce cause major economic losses to the livestock industries throughout the world.
- Accidents can be prevented by understanding the conditions under which poisoning may be expected to occur and then taking positive steps to prevent its occurrence.
- Problems can occur with animals in ornamental, garden, and natural environments and homes.
- Poisoning in humans and companion animals from toxic plants also continues to be a significant risk, especially to pets and children. Plant poisoning in small animals is usually accidental.
- Lack of understanding and increased grazing pressure on these small acreages often contribute to the consumption of toxic plants by animals.
- It is recommended not to throw grass, shrub, or tree clippings into paddocks where animals reside (yew clippings are a common cause of poisoning in many animals).
- Provide free access to freshwater and minerals/salt, and do not overstock the range or pastures.
- Avoid bedding, lambing/calving, watering, salting, or unloading hungry animals near poisonous plant populations.
- Avoid excess stress to those animals showing clinical signs of poisoning, and if necessary, contact the veterinarian.
- If economically feasible, control poisonous plants through hand grubbing, mechanical clipping, or herbicide treatment.

11.2 *Astragalus* and *Oxytropis* Species

(Locoweeds, Nitro spp., and Selenium spp.)

11.2.1 Locoweeds

The *Astragalus* and *Oxytropis* genera cause the most losses to the livestock industry. *Astragalus* is a very large and complex genus, with more than 350 species and 200 varieties. *Oxytropis* is much smaller, with 22 species and 35 varieties. The

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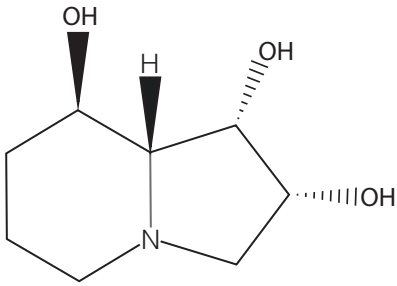


Fig. 11.1 Structure formula of Swainsonine toxin

locoweeds are those species of the *Astragalus* and *Oxytropis* genera that contain the "loco" toxin (swainsonine) and induce the classic neurological and pathological signs of "locoism." Swainsonine is also present in other *Astragalus* species not usually considered locoweeds, such as some selenium and nitro-containing *Astragalus*.

Toxic Principle The toxin in locoweeds is the indolizidine alkaloid swainsonine. The structure is shown in Fig. 11.1.

Toxicity There are numerous adverse effects of locoweed on animals, but the classic syndrome from which the term "locoism" is derived is one of neurological dysfunction. The disease is a chronic one developing after weeks of ingesting locoweeds and beginning with depression, dull-appearing eyes, and incoordination progressing to aberrant behavior including aggression, staggering, solitary behavior, and emaciation and ending in death if continued consumption is allowed. Other problems associated with locoweed ingestion include reproductive failure, abortion, birth defects, weight loss, and enhanced susceptibility to brisket disease at high elevations.

Locoweed poisoning affects all animals, but because of the transient nature of the poisoning, animals removed from the locoweed early in the toxicosis will recover. In the final stages of locoism, central nervous system tissue shows swelling of axonal hillocks (meganeurites) and growth of new dendrites and synapses. This altered synaptic formation in nervous tissue in severely affected animals is permanent and may be the cause of some irreversible neurological signs. Because of neurological dysfunction and apparent permanence of some lesions in the nervous system, horses are believed to be unpredictable and therefore unsafe to use for riding, but they may remain reproductively sound once they have recovered from the poisoning.

Prevention of Poisoning The most effective management strategy is to avoid livestock access to locoweeds during critical periods when they are more palatable than associated forage.

11.2.2 Nitro-Containing *Astragalus* (Milkvetches)

There are more than 260 species of nitro-containing *Astragalus* and are frequently referred to as milkvetches. Nitro-toxins are therefore the most common toxins in the

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Astragalus, followed by swainsonine (loco) and selenium. The aliphatic nitro-containing *Astragalus* are distributed throughout North America, with substantial livestock losses of cattle or sheep. Examples of these include *A. emoryanus* (emory milkvetch), *A. tetrapterus* (four-winged milkvetch), *A. pterocarpus* (winged milkvetch) and *A. miser* var. serotinus, *A. miser* var. oblongifolius, and *A. miser* var. hylophylus (collectively referred to as timber milkvetch).

Toxic Principles The toxic principles are β-D-glycosides of 3-nitro-1-propanol (NPOH) or 3-nitropropionic acid (NPA).

Mechanism of Toxicity The glycoside conversion occurs more readily in the ruminant because of the microflora and is apparently the reason for increased toxicity in ruminants. The glycoside (miserotoxin) is metabolized to the highly toxic NPOH in the gastrointestinal (GI) tract of ruminants. Thus, NPOH is absorbed in the gut and apparently converted to NPA by the liver. Further metabolism yields inorganic nitrite and an unidentified metabolite that may be involved in toxicity. It appears that NPOH is more rapidly absorbed from the gut than is NPA; therefore, forage containing the alcohol form is the most toxic.

Toxicity The nitro-containing *Astragalus* species cause an acute and chronic type of poisoning in sheep and cattle. The acute form results in weakness, increased heart rate, respiratory distress, coma, and death. Although blood methemoglobin is high (induced from nitro-toxin metabolism to nitrites) and a contributing factor to the respiratory difficulties, administration of methylene blue in cattle does not prevent death. Therefore, the methemoglobinemia is apparently not the primary cause of death. The chronic form is the most frequent form of poisoning observed and follows a course of general weakness, incoordination, central nervous system involvement resulting in knuckling of the fetlocks, goose stepping, clicking of the hooves, "cracker heels" progressing to paralysis, and death. A respiratory syndrome is also present in the chronic and acute forms, with emphysema-like signs causing the animals to force respiration: "roaring disease." Sheep manifest the respiratory syndrome more than the central nervous syndrome and are more resistant to poisoning compared to cattle.

Prevention and Treatment There is no preferred treatment for milkvetch poisoning, although treatment with methylene blue appears to reverse the methemoglobinemia but does not prevent death in cattle. Oxidation of NPOH to NPA was prevented if alcohol dehydrogenase was saturated with ethanol or inhibited with 4-methylpyrazole before NPOH was given. This suggests that NPOH is a good substrate for the enzyme alcohol dehydrogenase. This information could be useful in acute cases; however, its value in treatment of poisoning in the field is unknown. Livestock losses can be reduced by decreasing the density of the *Astragalus* species with herbicides or avoiding grazing livestock on infested areas when the plant is most poisonous.

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11.2.3 Seleniferous *Astragalus*

Approximately 22–24 species of *Astragalus* are known to accumulate selenium (Se) that creates most of the subacute or chronic toxicity problems for livestock. The species most associated with selenium poisoning include *A. bisulcatus* (two-grooved milkvetch), *A. praelongus* (stinking milkvetch), *A. pattersonii* (Patterson milkvetch), *A. pectinatus* (tiny-leaved milkvetch), and *A. racemosus* (alkali milkvetch). Acute cases of selenium poisoning are rare and usually involve animals that have been exposed by one of the following three methods:

(a) Livestock graze forages that have accumulated selenium from seleniferous soils.
(b) Selenium toxicosis occurs from environmental contamination from agricultural drain water, from reclaimed soils from phosphate or ore mining, or from fly ash.
(c) Acute selenosis can be caused by accidental overdosing with organic selenium or Bo-Se in the treatment of white muscle disease or by misformulated feed mixes.

Toxicity Selenium poisoning is known as selenosis. It may be acute, subacute, or chronic. The signs of acute selenium poisoning include diarrhea, unusual postures, increased temperature and heart rate, dyspnea, tachypnea, respiratory distress, prostration, and death. Gross pathological findings are usually limited to pulmonary congestion and hemorrhage and pulmonary edema. Histologically, multifocal myocardial necrosis and pulmonary alveolar vasculitis are common.

Chronic selenium poisoning is common and referred to as alkali disease because most areas with high concentrations of available selenium are alkaline in nature. Chronic selenosis occurs from prolonged ingestion of seleniferous forages containing 5–40 ppm Se. Clinical signs include rough coat, hair or wool loss, poor growth, emaciation, abnormal hoof growth and lameness, dermatitis, and depressed reproduction. In swine, a condition of paralysis (poliomyelomalacia or polioencephalomalacia) often occurs with cervical or lumbar involvement. The description of a second chronic syndrome in cattle called "blind staggers" has been redefined and is now believed to be polioencephalomalacia induced by high-sulfate water or high-sulfate forage sources. Selenium is found in plants in both inorganic and organic forms. The organic forms are more bioavailable than the inorganic forms, resulting in higher tissue concentrations when administered at equivalent doses. Although a dramatic difference in tissue selenium uptake between organic (selenomethionine) and plant (*A. bisulcatus*) forms and inorganic (sodium selenate) forms occurs, the clinical and pathological syndromes are similar, that is, poliomyelomalacia in pigs and pulmonary edema and hemorrhage in sheep.

Prevention and Treatment There is no treatment for selenium poisoning except removal of the source, allowing spontaneous recovery in chronic cases.

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11.3 Larkspurs (*Delphinium* spp.)

There are more than 80 wild species of larkspurs, and a larger number of domestic horticultural varieties. Some commonly available larkspurs include *D. nelsonii*, *D. bicolor*, *D. andersonii*, *D. tricorne*, *D. virescens*, *D. geyeri*, *D. barbeyi*, *D. occidentale*, *D. glaucescens*, *D. trolliifolium*, and *D. robustum*. The larkspurs are a major cause of cattle deaths than by any other poisonous plant except locoweed.

Toxic Principles Toxic principles are norditerpenoid alkaloids, which occur as one of two chemical structural types—the 7,8-methylenedioxylycoctonine (MDL) type and the N-(methylsuccinimido) anthranoyllycoctonine (MSAL) type (Fig. 11.2). The MSAL-type alkaloids are much more toxic. The structure formulae are given in Fig. 11.2.

Mechanism of Toxicity The primary result of larkspur toxicosis is neuromuscular paralysis from blockage at the post-synaptic neuromuscular junction at α1 nicotinic site. The toxins also elicit central effects in mice and rats.

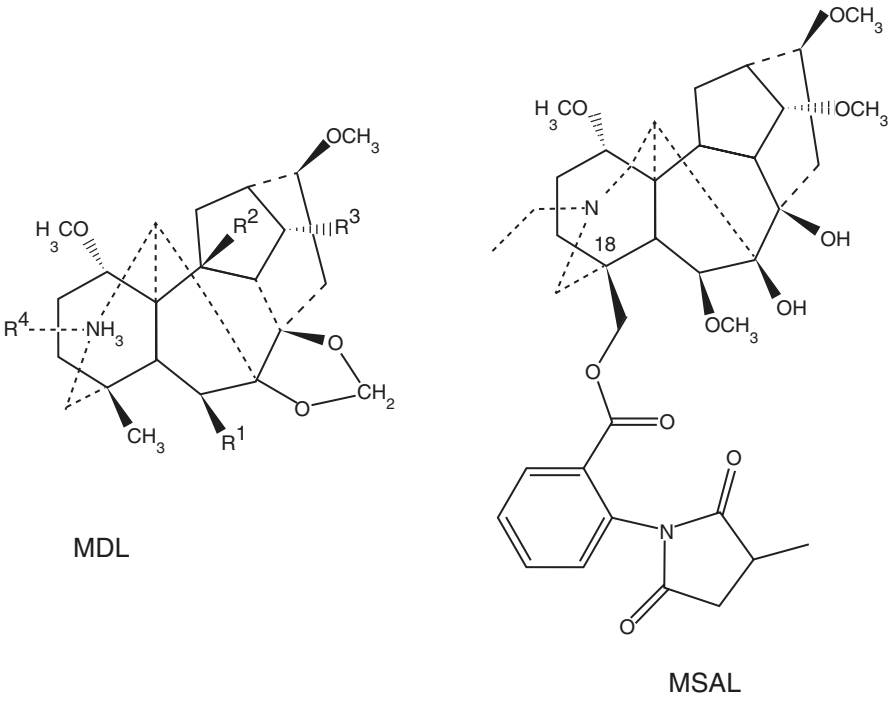


Fig. 11.2 Structure formulae MDL and MSAL

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Toxicity Larkspurs (*Delphinium* spp.) are a serious toxic problem for cattle. The toxicity of larkspur plants is due to norditerpenoid alkaloids. Tall larkspur species vary substantially in toxicity, with a relative ranking (most to least toxic, based on the MSAL alkaloid content) of *D. glaucum* (*D. brownii* in Canada), *D. barbeyi*, *D. glaucescens*, and *D. occidentale*. Toxicity declines rapidly in tall larkspurs once pods begin to shatter. MSAL-type alkaloids are much more toxic than the MDL-type alkaloids. The primary result of larkspur toxicosis is neuromuscular paralysis from blockage at the post-synaptic neuromuscular junction. Therefore, clinical signs of intoxication include muscular weakness and trembling, straddled stance, periodic collapse into sternal recumbency, respiratory difficulty, rapid and irregular heartbeat, and collapse but not death.

Prevention and Treatment Sheep can be herded into or bedded on the patches to reduce larkspur availability or acceptability to cattle on tall larkspur-infested ranges where larkspur grows as discrete patches. It is recommended that animals not be watered or provided mineral supplementation in areas that have high densities of larkspurs.

If less than a lethal dose is ingested, the animal would likely recover despite any treatment, unless bloat or aspiration pneumonia occurred during recumbency. Treatment for overt poisoning is usually symptomatic, and recovery is often spontaneous if animals are not stressed further by driving. The cholinergic drug physostigmine has been successfully used under field and pen conditions to reverse clinical symptoms of larkspur. Similarly, IV administration of neostigmine significantly reduced clinical signs in cattle.

11.4 Lupines (*Lupinus* spp.)

Lupines belong to the Leguminosae family, and the *Lupinus* genus contains more than 150 species of annual, perennial, or soft woody shrub lupines. The lupines are rich in alkaloids, responsible for most of the toxic and teratogenic properties. There are domestic lupines that through plant breeding are low in alkaloid content and have been selected for ornamental purposes or for animal and human food. Different lupines produce varying toxic syndromes in a given species of livestock, apparently because the alkaloid profile varies remarkably among species. Season and environment influence alkaloid concentration in a given species of lupine. Generally, alkaloid content is highest in young plants and in mature seeds. Alkaloids are not lost upon drying, so wild hay may be highly toxic if young lupine plants or especially seed pods are present. Only those range lupines known to cause poisoning or birth defects are discussed here.

Toxic Principles Most lupine species contain quinolizidine alkaloids, a few contain piperidine alkaloids, and some contain both. The specific alkaloids responsible for crooked calf syndrome are anagyrine, ammodendrine, or N-methyl ammodendrine (Fig. 11.3).

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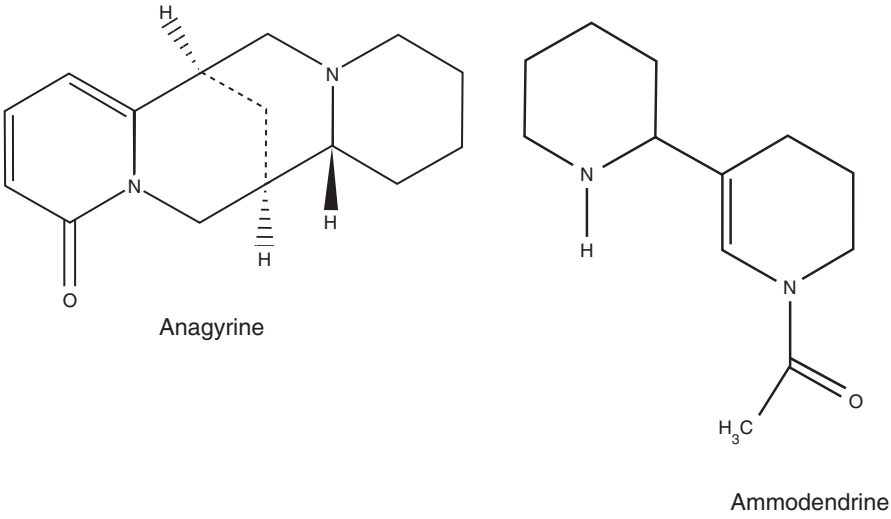


Fig. 11.3 Structure formulae of anagyrine and ammodendrine or N-methyl ammodendrine

Toxicity It is known that chemical profile and concentration differ, resulting in changing levels of toxicity within and between species and populations. Stockmen have long recognized the toxicity of lupines, *L. caudatus* and *L. leucophyllus*, when livestock, particularly sheep, were poisoned in the fall by the pods and seeds of lupine. Major losses in sheep were reported in the 1950s, and individual flock losses of hundreds and even thousands were reported. Lupines are also poisonous to other livestock, and field cases of poisoning in cattle, horses, and goats have been reported. Clinical signs of poisoning are those of muscular weakness (neuromuscular blockade) beginning with nervousness, frequent urination and defecation, depression, frothing at the mouth, relaxation of the nictitating membrane, ataxia, muscular fasciculations, weakness, lethargy, collapse, sternal recumbency followed by lateral recumbency, respiratory failure, and death. Death usually results from respiratory paralysis. However, the most recognized condition of lupine ingestion is the "crooked calf syndrome," a congenital condition in calves resulting in skeletal contracture-type malformations and cleft palate after their mothers have grazed lupines during sensitive periods of pregnancy. The anagyrine-containing lupines only caused birth defects in cattle and did not affect sheep or goats; however, the piperidine-containing lupine *L. formosus* induced similar birth defects in cattle and goats. Dystocia may occur when calves are severely deformed.

Prevention of Poisoning A reduction in incidence can be expected and has been achieved by using one or more of the following: (1) coordinating grazing periods according to plant growth stage, (2) changing time of breeding by either advancing or delaying or changing from spring to fall calving, (3) reducing lupine populations through herbicide treatment, and (4) intermittent grazing between clean pastures and lupine pastures to break the cycle of lupine ingestion. Treatment for overt

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poisoning is usually symptomatic, and recovery is often spontaneous if animals are not stressed further by driving. Once the animal is observed showing muscular tremors, it should be allowed to drop back and proceed at its own pace. Poisoned animals should never be forced to continue moving because this will exacerbate the clinical effects and can result in death.

11.5 Poison Hemlock (*Conium maculatum*)

Poison hemlock grows in waste areas where adequate moisture will sustain the biennial stands. Four species are recognized worldwide. Historically, poison hemlock has been associated with human poisoning more than livestock. Multiple *Conium* species are few worldwide, and only one species, *C. maculatum*, is described in the United States. *Conium maculatum* is a biennial plant 1–2.5 m tall (Fig. 11.4). The stems are stout, rigid, smooth, and hollow except at the nodes.

Toxic Principles Two alkaloids, coniine and γ-coniceine, are prevalent and likely responsible for toxicity and teratogenicity of the plant. γ-Coniceine is the predominant alkaloid in the early vegetative stage of plant growth. Coniine predominates in late growth and is found mainly in the seeds. γ-Coniceine is seven or eight times more toxic than coniine in mice. This makes the early growth plant most dangerous. Seeds are also very toxic and can contaminate poultry and swine cereal grains.



Fig. 11.4 Poison hemlock plant (*Conium maculatum*). (https://upload.wikimedia.org/wikipedia/commons/thumb/b/b2/Conium.jpg/220px-Conium.jpg)

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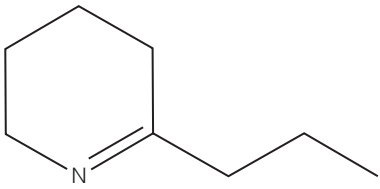


Fig. 11.5 Structure of γ-coniceine toxin

Toxic Principles Two alkaloids, coniine and γ-coniceine (Fig. 11.5), are prevalent and likely responsible for toxicity and teratogenicity of the plant. γ-Coniceine is the predominant alkaloid in the early vegetative stage of plant growth and is a biochemical precursor to the other *Conium* alkaloids.

Mechanism of Toxicity The mechanism of action of the *Conium* alkaloids is twofold. The most serious effect occurs at the neuromuscular junction, where they act as nondepolarizing blockers like curare. Systemically, the toxins cause biphasic nicotinic effects, including salivation, mydriasis, and tachycardia, followed by bradycardia as a result of their action at the autonomic ganglia. The teratogenic effects are undoubtedly related to the neuromuscular effects on the fetus and have been shown to be related to reduction in fetal movement. Likewise, cleft palate is caused by the tongue interfering in palate closure during the reduced fetal movement and occurs during days 30–40 of gestation in swine, days 32–41 in goats, and days 40–50 in cattle.

Toxicity The clinical signs of toxicity are the same in all species and include initial stimulation (nervousness) resulting in frequent urination and defecation (no diarrhea), rapid pulse, temporarily impaired vision from the nictitating membrane covering the eyes, muscular weakness, muscle fasciculations, ataxia, incoordination followed by depression, recumbency, collapse, and death from respiratory failure. *Conium* plant and seeds are teratogenic, causing contracture-type skeletal defects and cleft palate like those of lupine. Field cases of teratogenesis have been reported in cattle and swine and experimentally induced in cattle, swine, sheep, and goats. Birth defects include arthrogryposis (twisting of front legs), scoliosis (deviation of spine), torticollis (twisted neck), and cleft palate. Field cases of skeletal defects and cleft palate in swine and cattle have been confirmed experimentally.

In cattle, the susceptible period for *Conium*-induced terata is the same as that described for lupine and is between day 40 and day 70 of gestation. The defects, susceptible period of pregnancy, and probable mechanism of action are the same as those of crooked calf disease induced by lupines.

Prevention of Poisoning Prevention of poisoning is based on recognizing the plant and its toxicity and avoidance of livestock exposure when hungry. If a lethal dose has not been ingested, the clinical signs will pass spontaneously, and a full recovery can be expected. Avoidance of stressing animals poisoned on *Conium* is recommended. However, if lethal doses have been ingested, supporting respiration, gastric lavage, and activated charcoal are recommended.

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11.6 Water Hemlock (*Cicuta* spp.)

There are approximately 20 species of water hemlock (*Cicuta* spp.) throughout the world, and all are poisonous. Water hemlock is often confused with poison hemlock; in fact, there are similar plant characteristics, and both belong to the Umbelliferae family. However, their toxic effects are dramatically different, and when toxicoses occur, differentiation between the two genera is important. The most common water hemlock species include *C. bulbifera*, *C. bolanderi*, *C. californica*, *C. douglasii*, *C. machenziana*, *C. occidentalis*, *C. vagans*, and *Cicuta virosa* (Fig. 11.6). Tubers are the most toxic part of the plant, especially in early spring. The parsnip-like roots extending from the tuber are two to four times less toxic, and as the vegetative parts of the plant grow and mature, they become less toxic.

Toxic Principle The toxic principle in water hemlock is a long-chain, highly unsaturated alcohol called cicutoxin. This oily substance has a parsnip-like odor (Fig. 11.7).



Fig. 11.6 *Cicuta virosa*. (https://www.alamy.com/stock-photo-cowbane-water-hemlock-cicuta-virosa-blooming-germany-76119971.html)

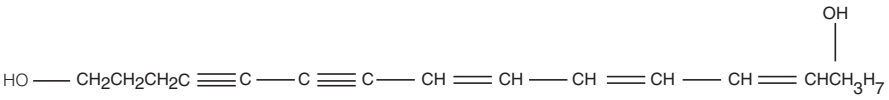


Fig. 11.7 Structure formula of cicutoxin

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Toxicity Clinical signs of poisoning appear within 10–15 min after ingestion and progress from nervousness, frothing, ataxia, dyspnea, muscular tremors, and weakness to involuntary, spastic head and neck movements accompanied by rapid eye blinking and partial occlusion of the eyes from the nictitating membranes. Water hemlock acts on the central nervous system as a stimulant, inducing violent grand mal. This is quickly followed by collapse and intermittent grand mal seizures lasting 1–2 min each followed by relaxation periods of 8–10 min. Depending on the dosage, recovery may occur or seizures continue until death from exhaustion or respiratory failure. Upon necropsy, gross lesions are confined to pale areas in heart muscle and skeletal muscles, particularly the long digital extensor muscle groups.

Prevention and Treatment Prevention of poisoning is accomplished by recognizing the plant and avoiding exposing animals to it early in the spring or when in flower/seed stage. Successful treatment with barbiturates or perhaps tranquilizers prevents death and the lesions and serum chemistry changes; however, treatment must be prompt. This treatment has been successful in humans, but in animals, it has never been demonstrated in the field and would require a veterinarian to be on sight soon after the ingestion of this plant.

11.7 Ponderosa Pine Needles (*Pinus* spp.)

Ponderosa pine (*Pinus ponderosa*) is one of the most prevalent species of *Pinus*. During early growth, the bark is dark brown to black, hence the name "black jack" pine. Older trees have a bark of cinnamon brown to yellow, hence the name "yellow" pine. Ponderosa pine is a three-needled pine, although groups of two and three can be found on the same tree. The needles of ponderosa pine have been known for years to induce abortion in pregnant cows when grazed, particularly during the last trimester of pregnancy. Occasional toxicosis in pregnant cows occurs; however, cases of toxicosis in non-pregnant cows, steers, or bulls are not reported. There are several varieties of *Pinus* spp. that are commonly found. Other genera and species have also been implicated in abortions, such as Monterey cypress, Korean pine, and California juniper and lodgepole pine.

Toxic Principles The active toxin in ponderosa pine is labdane derivative—isocupressic acid (ICA) (Fig. 11.8). Two related derivatives (succinyl ICA and acetyl ICA) also contribute to the induction of abortion after hydrolytic conversion to ICA in the rumen. Other related labdane acids (agathic acid, imbricatoloic acid, and dihydroagathic acid) are found in ponderosa pine needles at low levels.

Toxicity Pine needles, pine bark, and new growth tips of branches are all abortifacient, and new growth tips are also toxic. The primary toxicological effects of ponderosa pine needles in cattle are abortion and complications associated with abortion, such as retained fetal membranes, metritis, and occasional overt toxicosis and death. The abortions generally occur in the last trimester of pregnancy in the

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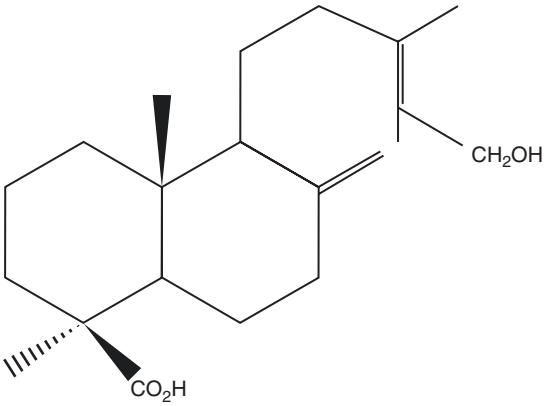


Fig. 11.8 Isocupressic acid (active principle of ponderosa pine)

late fall, winter, or early spring. Abortions are generally characterized by weak uterine contractions, uterine bleeding, incomplete cervical dilation, dystocia, birth of weak but viable calves, agalactia, and retained fetal membranes. These syndromes seem to occur depending on the amount of pine needles eaten. Pine needles will induce abortion in buffalo, but cows, steers, or bulls are apparently unaffected by pine needles; likewise, sheep, goats (pregnant or not), and horses can graze pine needles with impunity and experience no adverse effects. Extensive vasoconstriction of the caruncular vascular bed with accompanying necrosis and hemorrhage are the only reported pathological changes in maternal tissues.

Prevention and Treatment The only recommendation to prevent pine needle abortion is to avoid grazing pregnant cows around pine trees, especially in the third trimester. There is no known treatment for cattle once ingestion of pine needles has occurred. Supportive therapy (antibiotic treatment or uterine infusion for retained fetal membranes) is recommended for cows that have aborted, and intensive care of the calf may save its life.

11.8 Rayless Goldenrod (*Haplopappus heterophyllus*)

Rayless goldenrod (*Haplopappus heterophyllus*) is a very toxic plant. The disease associated with toxicity has been referred to as "milk sickness" or "trembles" (the same as white snake-root in the Midwest) because the toxin tremetone (Fig. 11.9), a mixture of ketones and alcohols, is excreted in the milk and subsequently results in poisoning of humans and nursing offspring. *Haplopappus acradenius* was implicated in poisoning in cattle in Southern California. The plant grows abundantly on alkaline and gypsic soils in western Texas and the Pecos River Valley.

Toxic Principles Tremetone (5-acetyl-2,3-dihydro-2-isopropenyl-benzofuran) was thought to be the principle toxic factor; however, 11 different compounds have now been isolated and identified.

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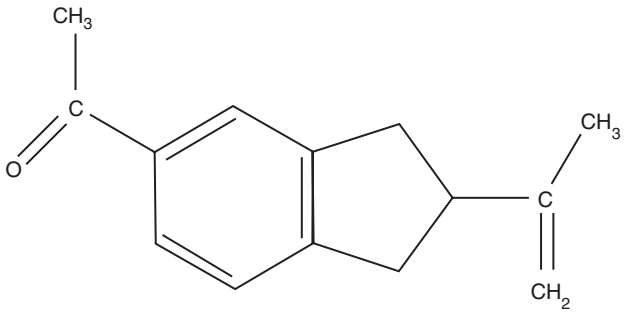


Fig. 11.9 Structure of tremetone

Toxicity Clinical signs begin with depression or inactivity, followed by noticeable trembling of the fine muscles of the nose and legs. Most cases of poisoning reported constipation, nausea, vomition, rapid labored respiration, progressive muscular weakness, stiff gait, standing in a humped-up position, dribbling urine, inability to stand, coma, and death. Signs are similar in cattle, sheep, and goats. The disease is often more acute and severe in horses than in cattle, and horses may die of heart failure after subacute ingestion of white snakeroot and presumably rayless goldenrod. Cattle have also been poisoned on a related plant (*Haplopappus acradenius*) in Southern California.

Prevention and Treatment Rayless goldenrod is not readily palatable, and toxicity results from animals being forced to graze the plant due to lack of good-quality forage. Treatment is generally symptomatic and supportive, providing dry bedding, good shelter, and fresh feed and water. Activated charcoal and saline cathartic may be beneficial. Treatment may include fluids, B vitamins, ketosis therapy, and tube feeding.

11.9 Broom Snakeweed (*Gutierrezia* spp.)

Broom snakeweed (Fig. 11.10) causes significant loss to cattle, sheep, and goat due to abortions and toxicoses. There are some similarities with ponderosa pine needles, except pine needles apparently affect only cattle. There are two major species of broom snakeweed, *Gutierrezia sarothrae* (perennial snakeweed or turpentine weed) and *G. microcephala* (threadleaf broomweed). These plants are short-lived perennial half shrubs ranging from 15 to 60 cm tall.

Toxic Principles The crude resin content of broom snakeweed, which includes the diterpene acids and other monoterpenes.

Toxicity The snakeweeds are toxic and abortifacient to cattle, sheep, and goats. Abortions and retained fetal membranes in cattle are among the most serious problems in livestock.

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Fig. 11.10 Snake weed plant. (https://image.shutterstock.com/image-photo/polygonum-bistorta-superba-snakeroot-snakeweed-260nw-1103976884.jpg)

Prevention and Treatment Broom snakeweed is usually not palatable to most large ungulates; cattle will not graze snakeweed unless all other vegetation is depleted. Treatment of sick animals is only symptomatic, providing supplementation to weak calves and antibiotic therapy to cows with retained fetal membranes to avoid infection.

11.10 Halogeton (*Halogeton glomeratus*)

Halogeton is a noxious and poisonous weed. It does not have flowers but, rather, bracteoles formed in the axils of leaves from which seed clusters develop. There were many instances of large, catastrophic sheep losses; sometimes entire bands of sheep died overnight from halogeton poisoning. It takes up sodium and potassium from saline soils, forming the respective oxalates. These oxalates provide an important metabolic function to maintain high cell sap osmotic potential to allow the plant to take up saline water. Oxalates accumulate during the growing season, reaching peak concentration in the fall (20–36% of plant dry weight). Soluble oxalates leach out of the senescent foliage during the winter and accumulate on the soil surface, increasing its salinity. Thus, halogeton modifies its environment, making it more saline to meet its requirements, while exceeding the tolerance limits of associated species.

Toxic Principles The toxins are sodium and potassium oxalates.

Mechanism of Toxicity Poisoning occurs when sheep consume more oxalates than what the body can detoxify. If they reach the bloodstream, they precipitate the Ca from the blood, creating Ca oxalate crystals, causing hypocalcemia resulting in shock and death. The Ca oxalate crystals also physically damage the tubules of the kidney. The Na oxalates interfere with two key enzymes (succinic dehydrogenase and lactic dehydrogenase) in the Krebs cycle, disrupting energy metabolism. Combined, they cause rapid and acute death.

Toxicity Signs of poisoning include depression, anorexia, weakness, incoordination, recumbency, blood-tinged nasal discharge, coma, and rapid death. Gross pathologic changes include hemorrhage and edema of the rumen wall, hyperemia of the abomasal wall, and intestinal mucosa and ascites. Morphologic changes include hemorrhage and calcium oxalate crystal formation in the rumen wall and oxalate crystals with accompanying cellular damage in the renal tubules of the kidney.

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Prevention and Treatment Provide good feed following trucking or trailing. Introduce sheep gradually to halogeton to allow rumen microbes to adjust. Animals can be drenched with water to flush oxalates out in the urine, or including dicalcium phosphate in the drench provides Ca that will combine with oxalates in the rumen and can be excreted. Intravenous injection of calcium gluconate can maintain blood Ca levels, but the forming Ca oxalate crystals will continue to damage kidneys. Provide symptomatic treatment.

11.11 Pyrrolizidine Alkaloid-Containing Plants

Pyrrolizidine alkaloid (PA)-containing plants are numerous and worldwide in distribution and have toxic significance. Three plant families predominate in PA-producing genera and species: Compositeae (*Senecio* spp.), Leguminosae (*Crotalaria* spp.), and Boraginaceae (*Heliotropium*, *Cynoglossum*, *Amsinckia*, *Echium*, and *Symphytum* spp.). More than 150 PAs have been identified and structural characteristics elucidated. The PAs contain the pyrrolizidine nucleus (and can be represented by the basic structures of senecionine and heliotrine). A few selected species of PA-producing genera and species include *Cynoglossum officinale*, *Echium vulgare*, *Symphytum officinale*, *Senecio brasiliensis*, *Senecio cineraria*, *Senecio glabellus*, *Senecio integerrimus*, *Senecio jacobaea*, *Senecio longilobus*, *Senecio spartioides*, *Senecio riddellii*, and *Senecio vulgaris* (Fig. 11.11).

Toxic Principle Toxic principle is pyrrolizidine alkaloid (Fig. 11.12).



Fig. 11.11 *Senicio* sp. (http://poisonousplants.ansci.cornell.edu/images/senecio2.jpg)

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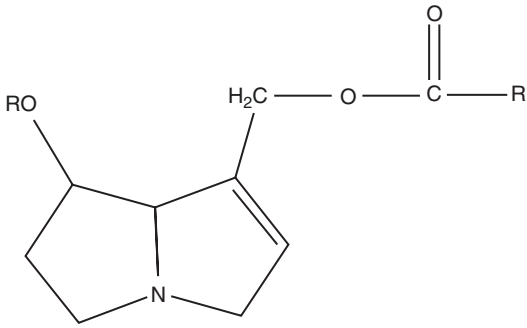


Fig. 11.12 Structure formula of Pyrrolizidine alkaloid

Mechanism of Toxicity All PAs have almost similar mechanism of toxicity. Their potency varies due to their bioactivation in the liver to toxic metabolites called pyrroles. These pyrroles are powerful alkylating agents that react with cellular proteins and cross-link DNA, resulting in cellular dysfunction, abnormal mitosis, and tissue necrosis. Detoxification mechanisms of PAs generally involve the liver and GI tract. Evidence of ruminal detoxification in sheep suggests this contributes to the reduced toxicity in that species. There are also substantial species-specific differences in the rate of PA metabolism. Both probably contribute to species susceptibility. For example, *Echium* and *Heliotropium* PAs are easily degraded by certain rumen microflora, but there is little evidence of ruminal degradation of *Senecio* PAs.

Toxicity The primary toxic effect is hepatic damage; however, many alkaloid and species-specific extrahepatic lesions have been described. Small amounts of pyrrole may enter the blood and be transported to other tissues, but there is debate on this issue because most pyrroles are super-reactive and not likely to make it into the circulation. When PA metabolites circulate, they are probably protein adducts that may be recycled. Some alkaloids (monocrotaline) may come off their carrier blood proteins and damage other tissues such as lung. Pigs seem more prone to develop extrahepatic lesions. Toxicity of *Senecio*, *Heliotropium*, and *Echium* is largely confined to the liver, whereas *Crotalaria* will also cause significant lung damage. Typical histologic lesions are swelling of hepatocytes, hepatocyte necrosis, periportal necrosis, megalocytosis (enlarged parenchymal cells), karyomegaly (enlarged nuclei) fibrosis, bile duct proliferation, and vascular fibrosis and occlusion.

In most species affected by PA poisoning, the liver becomes hard, fibrotic, and smaller. Because of decreased bile secretion, bilirubin levels in the blood rise, causing jaundice. Common clinical signs include ill thrift, depression, diarrhea, prolapsed rectum, ascites, edema in the GI tract, photosensitization, and aberrant behavior. In horses, "head pressing" or walking in straight lines regardless of obstacles in the path may occur. These neurological signs in horses are due to elevated blood ammonia from reduced liver function. PA poisoning may cause elevated blood ammonia, resulting in spongy degeneration of the central nervous system.

Cows are most sensitive, followed by horses, goats, and sheep, respectively. In small laboratory animals, rats are most sensitive, followed by rabbits, hamsters,

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guinea pigs, and gerbils, respectively. Among avian species, chickens and turkeys are highly susceptible, whereas Japanese quail are resistant.

Prevention and Treatment There are no proven effective methods of prevention or treatment. Avoid access to the plant or control plant populations with herbicides or through biological control. Resistance to PA toxicosis in some species suggests that the possibility may exist to increase resistance to PAs. Use of antioxidants such as butylated hydroxytoluene (BHT) and ethoxyquin induced increased detoxifying enzymes such as glutathione S-transferase, and epoxide hydrolase may be useful. Zinc salts have been shown to provide some protection against hepatotoxicosis.

11.12 Photosensitizing Plants

Photosensitizing plants are too numerous resulting in losses to the livestock industry. Photosensitization is the development of abnormally high reactivity to ultraviolet radiation or natural sunlight in the skin or mucous membranes. The syndrome in livestock has been defined as primary and secondary photosensitization. Photosensitizing plants occur throughout the world and are common in the diets of livestock and people.

Toxic Principles Toxic principles of some selected plants causing primary and secondary photosensitization are summarized in Tables 11.1 and 11.2.

11.12.1 Primary Photosensitization

Several plants responsible for primary photosensitization are weedy in nature and can contaminate pastures and feed. The photoreactive agent is absorbed directly from the plant and reaches the peripheral circulation and skin. For example, hypericin and fagopyrin are polyphenolic derivatives from St. John's Wort (Fig. 11.13) and buckwheat, respectively (Table 11.1), and are primary photodynamic agents.

Toxicity The photoactive reagents in the plant reacts with the ultraviolet rays of the sun and results in sunburn, particularly of unprotected areas of the body. Primary photosensitization does not induce hepatic damage. Most agents are ingested, but some may induce lesions through skin contact.

Table 11.1 Some selected photosensitizing plants along with their toxic principles that cause primary photosensitizers

Name of the plant	Common name	Toxin
Hypericum perforatum	St. John's wort, Klamath weed	Hypericin
Fagopyrum sagittatum	Buckwheat	Fagopyrin
Cymopterus watsoni	Spring parsley	Furocoumarins

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Table 11.2 Some selected photosensitizing plants along with their toxic principles that cause secondary photosensitizers

Name of the plant	Common name	Toxin
Solanum elaeagnifolium	Silverleaf nightshade	Solanine and solanidine
S. nigrum	Black nightshade	Tropane and glycoalkaloids
S. dulcamara	Bittersweet, climbing nightshade	Glycoalkaloids
Datura wrightii	Sacred datura	Tropane alkaloids
D. stramonium	Jimson weed, thorn apple	Tropane alkaloids
Capsicum annum	Green or chili pepper	Capsaicinoids
Lycopersicon esculentum	Tomato	Glycoalkaloids
Hyoscyamus niger	Black henbane	Tropane alkaloids, calystegins



Fig. 11.13 *Hypericum* sp. (St. John Wort). (https://upload.wikimedia.org/wikipedia/commons/thumb/1/14/Hypericum_olympicum_Liberec_1.jpg/220px-Hypericum_olympicum_)

11.12.2 Secondary Photosensitization

In secondary or hepatogenous photosensitization, the photoreactive agent is phylloerythrin, a degradation product of chlorophyll. Phylloerythrin is produced in the stomach of animals, especially ruminants, and absorbed into the bloodstream. In normal animals, the hepatocytes conjugate phylloerythrin and excrete it in the bile. However, if the liver is damaged or bile secretion is impaired, phylloerythrin accumulates in the liver, the blood, and subsequently the skin, causing photosensitivity. This is the most common cause of photosensitization in livestock and horses. Because chlorophyll is almost always present in the diet of livestock, the etiologic agent of secondary photosensitization is the hepatotoxic agent. The dermatologic signs of photosensitization in livestock are similar regardless of the plant or toxicant involved. Degree of severity varies, depending on the amount of toxin or reactive phylloerythrin in the skin, degree of exposure to sunlight, and amount of normal physical photoprotection (hair and pigmentation).

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Toxicity Signs of toxicity in most animals are restlessness or discomfort from irritated skin, followed by photophobia, squinting, tearing, erythema, itching, and sloughing of skin in exposed areas (i.e., lips, ears, eyelids, udder, external genitalia, or white pigmented areas). Swelling in the head and ears (edema) of sheep after ingestion of *Tetradymia* has been referred to as big head. It was determined that sheep grazing black sagebrush (*Artemisia nova*) before *Tetradymia* were three times more likely to develop this photosensitization. Tissue sloughing and serum leakage may occur where tissue damage is extensive. Primary photosensitization rarely results in death. However, in secondary or hepatogenic photosensitization, the severity of liver damage and secondary metabolic and neurologic changes of hepatic failure may ultimately result in death. Recovery may leave sun-burned animals debilitated from scar tissue formation and wool or hair loss.

Prevention and Treatment Prevention of poisoning lies in controlling plants with photosensitizing potential and providing adequate quality forage to animals. Treatment after poisoning involves removing animals from sun exposure, treating areas of necrosis and sunburn, antibiotic therapy, and supplementing young animals when access to sunburned udders is prevented because of nursing discomfort to dams.

11.13 Bracken Fern (*Pteridium* and *Aquilinum*)

The bracken fern family is worldwide in distribution and includes approximately 20 genera and more than 400 species. The bracken fern most associated with toxicosis is *Pteridium aquilinum* (Kuhn). Important species of bracken plant (Fig. 11.14) include *Pteridium aquilinum*, *Pteridium arachnoideum*, *Pteridium caudatum*, *Pteridium centraliafricanum*, *Pteridium esculantum*, *Pteridium falcatum*, *Pteridium feei*, *Pteridium lineare*, *Pteridium revolutum*, *Pteridium tauricum*, and *Pteridium yunnanense*.

Toxic Principles The major toxin is the sesquiterpene glucoside (Fig. 11.15), ptaquiloside. Other toxins, carcinogens, and mutagens may also be implicated in the disease conditions.

Toxicity Bracken causes a wide range of syndromes in livestock, including thiamine deficiency in monogastrics, acute hemorrhagic disease associated with bone marrow aplasia and ulceration of the upper GI tract, "bright blindness" progressive retinal degeneration, and neoplasia of the urinary bladder and upper digestive tract. The major toxin is the sesquiterpene glucoside, ptaquiloside. The toxin is transferred through milk of cows grazing the plant. Epidemiological evidence suggests that some cancers in humans probably result from primary or secondary consumption of the carcinogens. Ptaquilosides form adducts with DNA, binding to certain base sequences, resulting in mutated codons associated with known oncogenes.

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Fig. 11.14 *Pteridium aquilinum* (Bracken fern). (Reproduced from: https://www.ars.usda.gov/arsuserfiles/images/docs/9859_10053/Bracken%20Fern%20Photo.bmp)

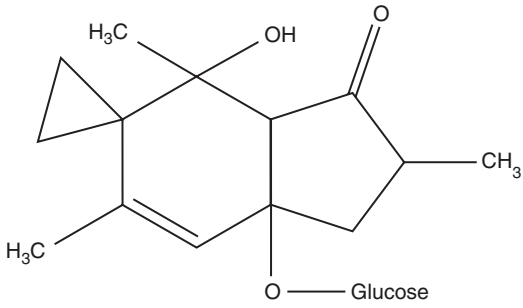


Fig. 11.15 Sesquiterpene glucoside—ptaquiloside

Lesions in horses poisoned by bracken fern are indicative of thiamine deficiency and include congestion of the brain, a swollen and edematous cerebrum grossly, and necrosis of some neurons microscopically. Acute hemorrhagic disease in cattle is characterized by extensive hemorrhage of the mucous membranes and subcutaneous hemorrhage and edema.

Prevention and Treatment Administration of thiamine parenterally followed by decreasing doses during the next few days may be useful. Symptomatic care with good feed and freshwater accompanied by administration of a laxative but not mineral oil is helpful. In ruminants, the bone marrow suppression and deficiency of blood platelets and neutrophils is best treated with antimicrobials to counteract any bacterial infection that might occur because of diminished immune function. Good veterinary care, symptomatic treatment, clean water, and quality feed in a quiet and clean environment are recommended.

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11.14 *Cannabis sativa* (Cannabaceae Family)

Cannabis sativa is commonly known as marijuana, marihuana, bhang, hashish, ganja, and sinsemilla.

The term marijuana refers to the dried leaves and flowers of the Indian hemp plant (cannabis). It is an illicit drug plant, and its leaves, flowers, and seeds contain several cannabinoids that are favored by some people for their psychoactive properties. Originally, the plant *Cannabis sativa* was an annual herb that was native to Asia, but it has spread throughout the world. Marijuana and hemp both come from the same cannabis species but are genetically distinct and are further distinguished by use, chemical makeup, and cultivation methods; they have been employed for thousands of years as a source of fiber to make rope in Asia and in the Middle East as a medicinal and recreational drug. Only since the 1960s and 1970s has the recreational use of marijuana become common in the Eastern world. The most common cause of intoxication in dogs and cats is unintentional ingestion of a cannabis product, but it may also occur after the exposure to marijuana smoke.

Toxic Principles The main psychoactive ingredient in the plant is the complex chemical delta-9-tetrahydrocannabinol (THC). Chemical structure of THC is given in Fig. 11.16.

Toxicity The pharmacological effect of this agent is to produce central nervous system (CNS) depression and derangement. The greatest concentration of the active ingredient is in the flowering tops of the female plant, whereas leaves are less potent and seeds contain little of the active ingredient. The animal most affected is the dog or other pet animal. Animals show behavioral abnormalities and hyperexcitability. The main clinical signs in the poisoned dog are vomiting, salivation, incoordination, alternating somnolence and hyperactivity, muscular weakness, and hyperthermia. Moreover, CNS and respiratory depression is another important sign in the dog. This is followed by coma and possibly death.

Prevention and Treatment The best way to avoid illness secondary to toxic exposure to any substance, including marijuana, is through prevention. For exposures occurring less than 2 hours before presentation, emesis is induced to clear the stomach of the intoxicant. Once vomiting is under control, administration of activated

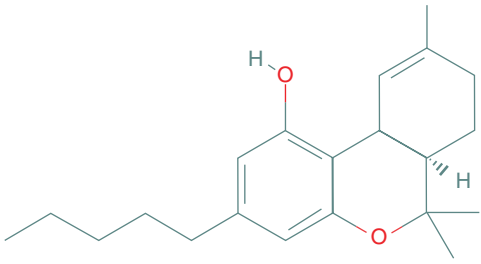


Fig. 11.16 Structure of delta-9-tetrahydrocannabinol (THC)

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charcoal can reduce absorption of certain toxins and speeds their evacuation through the gastrointestinal tract. Provided a pet is not vomiting or comatose, administration of activated charcoal is a component to treating many cases of toxic exposure because of its ability to reduce enterohepatic recirculation of a toxic substance. Enterohepatic recirculation occurs after a toxin enters the bloodstream through the digestive tract, gets processed by the liver, and then is excreted back into the small intestine via the bile from the gall bladder. Animals showing more profound sedation, ataxia, hypothermia, vomiting, or other clinical signs should be provided with intravenous fluids, thermoregulatory support, and anti-nausea and antacid medications that promote a more rapid recovery and positive outcome.

11.15 *Colchicum autumnale* L

The common names are autumn crocus, meadow saffron, and naked ladies. The plant is common in Eurasia and Africa. It belongs to the family Liciacea with height 15–30 cm, with basal, slender leaves; and long, tubular, flowers are pink, violet/lavender, or white in color. All parts of plant including seeds (Fig. 11.17) are highly poisonous.

Imran Usman Enterprises. http://iue.weebly.com/colchicum-bitter.html.

Toxic Principles Alkaloid colchicines and demecolcine (Figs. 11.18 and 11.19).

Mechanism of Action The alkaloid is a microtubule-depolymerizing drug like vinblastine. It binds to microtubule plus end to suppress microtubule dynamics.

Toxicity The plant *C. autumnale* contains the alkaloids colchicine and colchiceine of which the former is more toxic. The colchicine exists in all parts of the plant, but



Fig. 11.17 Colchicum plant seeds. Imran Usman Enterprises. (http://iue.weebly.com/colchicum-bitter.html)

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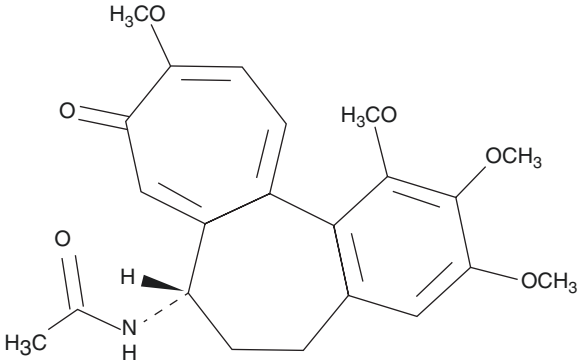


Fig. 11.18 Chemical structure of colchicine

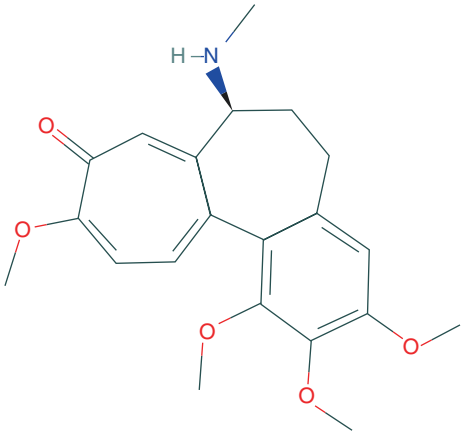


Fig. 11.19 Chemical structure of demecolcine

its highest concentration is in the bulb. Colchicine has a purgative effect. At higher doses, colchicine is a potent gastrointestinal toxin and causes intractable multiorgan failure. Poisoning of animals in the spring involves ingestion of the young leaves, whereas in the autumn the flowers of plants growing wild in pastures are implicated.

Poisoning primarily affects cattle but can also affect horses and pigs raised on pasture. Clinical signs appear approximately 48 h after ingestion. In cattle, the clinical signs of intoxication are predominantly related to the digestive tract and are characterized by salivation, dysphagia, colic, abdominal pain, diarrhea, and fetid feces that are green or black with tenesmus. Death occurs from cardiorespiratory failure and may be delayed for several days depending of the amount of plant ingested. The visible postmortem finding is gastroenteritis. Lesions that appear are edema and intestinal bleeding. In the horse, abdominal and thoracic serous effusions also occur.

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Treatment Emesis to prevent the absorption of the colchicine into the bloodstream is useful. Activated charcoal will be given to attempt to soak up as much of the toxin as possible. Gastric lavage under general sedation should be carried out to remove as much toxin from the patient's stomach as possible. There is no antidote to colchicine, so treatment beyond that is supportive. The supportive treatment is likely to include IV fluids for dehydration and combinations of electrolytes and sugars to adjust for any imbalances. Oxygen may also be given to the dog if breathing is becoming difficult.

11.16 Datura

Datura belongs to the family Solanaceae, and the common names are thorn apple, stinkweed, angel's trumpet, and Jamestown weed. It is a vegetable deliriant type of cerebral poison. The botanical name is *Datura stramonium*. Commonly there are two varieties of plants: *Datura alba* (with white flower) and *Datura nigra* (with blackish or purple flowers). A view of the plant along with fruits, seeds, and flower is shown in Fig. 11.20. The following are the common *Datura* species to which pets may be exposed:

(a) *Datura stramonium* (jimsonweed or Jamestown weed)
(b) *Datura metaloides* (thorn apple, apple of Peru, and tolguacha)
(c) *Datura arborea* (trumpet vine and angel's trumpet)

These species and others are grown as ornamentals, such as trumpet vine, or occur as weeds. The plants vary in appearance, but all have large, tubular flowers ranging in color from white to lavender. The fruit is an ovoid spiny capsule, giving rise to the common name, thorn apple. Most of the plants emit an objectionable odor.

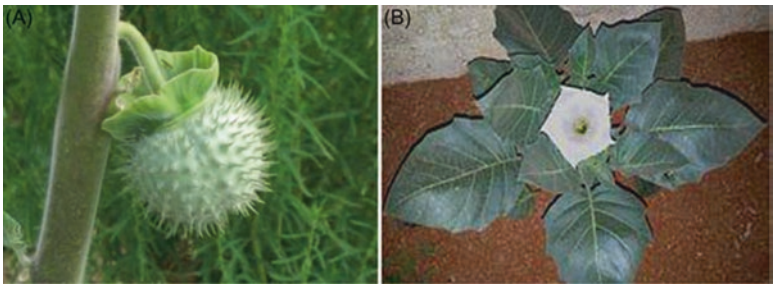


Fig. 11.20 Datura plant with fruit ((**a**) Available at https://en.wikimedia.org/wiki/Datura. https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcQwo6dpzsVfDuCrxI3PXk0X2AFIQOjhE2z3fap0ik54O2es6b8y0w and plant flower (**b**). Available at Wikipedia Commons. https://en.wikimedia.org/wiki/Datura. https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTvymhAMXDIuD_pDJJLeH7hplfJSbdIVpwfLd74hYGvWg5PddLY)

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Toxic Principles The active principles are alkaloids such as hyoscine (scopolamine), hyoscyamine, and atropine.

Toxicity The foliage may contain as much as 0.25–0.7% alkaloids. The seeds are likely to be the source of toxicity for pets. Pets are likely to consume toxic material accidentally if their owners are careless in handling the plant. Occasionally, a person may deliberately give the material to his or her animals. Clinical signs associated with Datura poisoning are similar to those caused by an overdose of atropine. The signs may occur a few moments after ingestion or may not appear for several hours. The poisoning has an acute course in which there is a weak, rapid pulse and heartbeat; disturbances of vision (dilated pupils due to mydriatic effects of Datura); dry mouth; incoordination; convulsions; and coma.

Treatment Treatment methods include gastric lavage and the administration of activated charcoal, if possible. The drug physostigmine is used to reverse the effect of the poisons. Benzodiazepines can be given to curb the patient's agitation, and supportive care with oxygen, hydration, and symptomatic treatment is often provided.

11.17 Oleander Plants (Apocynaceae Family)

Oleanders are commonly known as rosebay. Oleanders are widely cultivated in various parts of the world for their ornamental flowers. A general view of the plant is shown in Fig. 11.21. *Nerium* spp. (Oleander) is an evergreen shrub that thrives principally in subtropical regions.



Fig. 11.21 Oleander plant. (http://www.tbyil.com/oleander3.htm)

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Toxic Principles All parts of *N. oleander* contain very toxic cardiac glycosides (oleandrin, digitoxigenin, neriin, folinerin, and rosagenin).

Mechanism of Action Cardiac glycosides exert a positive inotropic effect on cardiac muscle that apparently exert a digitoxin-like effect (cardiotoxic potential). Their action is derived from inhibition of the plasmalemma (cell membrane) Na1/K1-ATPase.

Toxicity Toxins may also be inhaled in smoke when plants are burned. Human poisoning occasionally occurs from eating hot dogs roasted on sticks from nearby oleander plants. This extremely toxic plant can poison livestock and humans at any time of the year. The lethal dose in horses, donkeys, and calves is 30–50 mg/kg BW. Clinical signs of toxicity include severe gastroenteritis, diarrhea, abdominal pain, sweating, and weakness. These signs appear within a few hours after eating the leaves. Cardiac irregularities are common, often characterized by increased heart rate. However, a slower heart rate is often detected in the later stages. In comparison with other species, turkey poults have not been found to be very sensitive to Oleander. Histopathological examination revealed myocardial degeneration.

Treatment Gastric lavage and the administration of activated charcoal and supportive care with oxygen, hydration, and symptomatic treatment is often provided. Drugs like antiemetics, gastroprotectants, and medications to help improve the condition of the heart are used. Severely affected canines may need a temporary pacemaker if the heart is not responding to drug therapy. Digoxin immune fab treatment restores sinus rhythm and is the only proven therapy for yellow oleander poisoning.

11.18 *Aconitum napellus*

Aconitum napellus plant belongs to the family Ranunculaceae (Fig. 11.22). It is grown in the garden, and the common names are monkshood, blue rocket, wolf's bane, mithazaha/mitha vish (meaning "sweet poison" in Hindi), etc. The whole plant is poisonous; however, roots are highly toxic. The plant has blue or white flowers bilaterally symmetrical with a prominent upper hood, which gives the genus its name. The perennial herb has palmate leaves and a tuberous root. Cases of poisoning in European countries are not common. However, it should be remembered that these plants are potentially poisonous.

Toxic Principles The toxic principles are diterpene alkaloids known as aconitine, misaconitine, and hypaconitine. These alkaloids are sparingly soluble in water and considered as the most virulent poison with sweetish taste. Other alkaloids present in small quantities in the plant are picraconitine, pseudoaconitine, and aconine.

Toxicity Alkaloid content and composition varies throughout the year. The alkaloid content is highest when plants are flowering (June and July). Horses, donkeys,

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Fig. 11.22 Aconite plant with leaves and flowers. (Available at Antosh, G., 2012. Aconite Plant: How to Grow Monkshood Plants. Plant-Care.com. http://www.plant-care.com/aconite-plant.html)

and goats are more sensitive to aconitum than sheep. The plant is not usually eaten (acrid test), and field poisoning is uncommon. Aconitine may also be present when forage or hay are contaminated by it. The clinical signs induced by this plant include vomiting, colic, bradypnea and dyspnea, muscular weakness, paralysis, and pupillary dilatation (mydriasis). In cattle muscle weakness, staggering gait, excessive salivation and bloating and eventually recumbency with inability to stand due to muscle paralysis followed by death. Death is due to asphyxia, and the postmortem findings are those associated with suffocation. The lesions are not specific, usually appearing to be gastric and renal congestion.

Prevention and Treatment There is no proven treatment for monkshood poisoning. Affected animals should be stressed as little as possible, and possibly have a better chance of survival if they are herded away from the source of the plants without stressful attempts at treatment. Symptomatic treatment with intravenous fluids and relief of rumen bloat should be undertaken as necessary.

11.19 *Ricinus communis*

The plant *Ricinus communis* belongs to the family Euphorbiaceae. It is commonly known as castor bean, arandi, and moleean. The plant has large, palmately lobed leaves, and it is a robust annual (in southern regions) or perennial (in tropics and subtropics regions) woody herb. It is cultivated and occasionally escapes and persists in pinelands, waste places, and roadsides. Seeds are oval/round in shape and are of two types: (1) larger in size, red in color with brown blotches (yields 40% oil)

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and (2) small in size, gray in color with glossy bright, polished, brown mottling (yields 37% oil) (Fig. 11.23).

Toxic Principle The poisonous principle is a phytotoxin called ricin (Fig. 11.24).

Toxicity Cases of ricin poisoning occurred in different animal species, mostly in domestic animals. Intoxications of animals were caused either by the unprocessed plant seeds or by processed castor cake as it is used as a by-product in organic fertilizer. Horses are most susceptible to poisoning; however, intoxications of other animals, especially dogs, have been observed either by the unprocessed plant seeds or by processed castor cake products. All parts of the plant are toxic, especially the seeds. Toxicity is seen most often in spring and summer. Depending on the amount consumed, symptoms appear from several hours to days after animals consume the toxin. Violent purgation in the form of straining and bloody diarrhea is the classical sign. Other signs are dullness, abdominal pain, weakness, trembling, and incoordination.

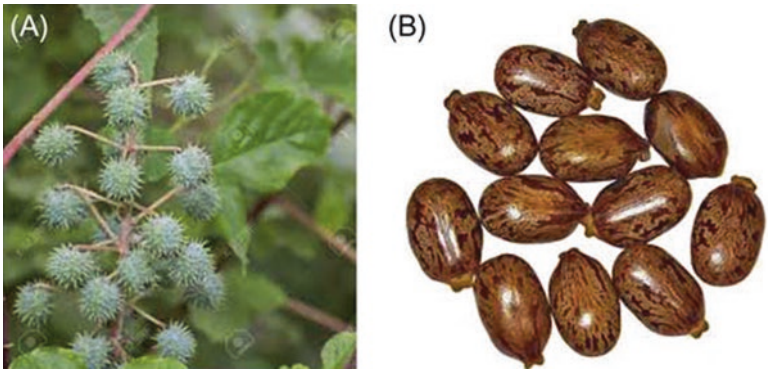


Fig. 11.23 Castor plant leaves and pods (**a**) and seeds (**b**). ((**a**) Available at Horseback Riding worldwide. http://www.horsebackridingworldwide.com/the-castor-oilplantricinus/. (**b**) Available at Indo Exports. http://indoexports.tradeget.com/F38632/castor_bean_seeds.html)

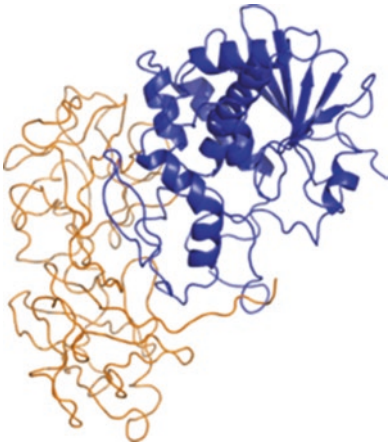


Fig. 11.24 Structure of ricin. (https://upload.wikimedia.org/wikipedia/commons/thumb/e/e4/Ricin_structure.png/220px-Ricin_structure.png)

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Treatment Currently, no approved specific therapy or antidote against ricin intoxication is available. The treatment focuses on supportive medicine and involves application of intravenous fluids and suppression of hypertension. To prevent further absorption of the toxin, treatment with activated charcoal or gastric lavage has been used depending on the time of admission after oral ingestion.

11.20 *Lantana* Poisoning

Lantana belongs to the family Verbenaceae. It is a genus comprising about 150 species of perennial flowering plants. They are native to tropical regions of the America and Africa but exist as introduced species in numerous areas, especially in the Australian-Pacific region. *Lantana* (*Lantana camara* and *Lantana montevidensis*) is a shrub and is commonly known as red sage, wild sage, yellow sage, and shrub verbena that was once grown as garden ornamentals and is now a major weed across all states and territories of India and Australia. Triterpenoids (liver toxins) are found in all parts of the plant. Animals in pastures with sufficient forage will often avoid Lantana plant (Fig. 11.25), perhaps because of its pungent aroma and taste, but animals unfamiliar to the plant may ingest enough to affect them. Fifty to ninety percent of animals newly exposed may be affected. Foliage and ripe berries contain the toxic substances with the toxins being in higher concentrations in the green berries.

Toxic Principles *Lantana* plant contains lantadene A and B (the major toxins involved in poisoning) as well as other structurally and toxicologically related pentacyclic triterpene acids (Fig. 11.26), including reduced lantadene A, dihydrolantadene A, and icterogenin.



Fig. 11.25 Lantana plant. (https://encrypted-tbn3.gstatic.com/images?q5tbn:ANd9GcRpqqJ2Ulc1omPTNIRRrLC_PX1HuJ-M-2bTD9zGpmXPuNBiqLpGkg)

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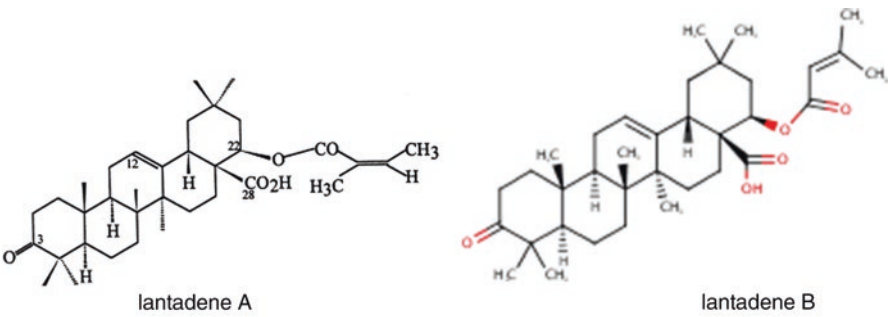


Fig. 11.26 Toxins of *Lantana*



Fig. 11.27 Cattle may become sun sensitive, and their skin may blister after eating *Lantana*. (https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTYFusbgzVM6FWagvdZ_-8t2kmv3LRcKiE7GImwNTq-XhoD9pfxjg)

Toxicity All variants of lantana are thought to be toxic with the red-flowered forms most toxic to stock. Most cases of lantana poisoning occur when animals are introduced to an area where toxic forms of lantana grow or during droughts when other feed sources are scarce. Species affected include cattle, sheep, horses, dogs, guinea pigs, and rabbits. Symptoms include depression, vomiting, diarrhea, weakness, and possible liver failure (which occur more commonly with farm animals). The plant is also toxic to dogs and cats. Liver failure is more common in livestock. The major clinical effect of *Lantana* toxicosis is excessive skin sensitivity to sunlight (photosensitization); the onset of this often takes place in 1–2 days (Fig. 11.27) after consumption of a toxic dose (1% or more of animal's body weight). Jaundice is usually prominent, animals usually become in appetent, and they often exhibit decreased digestive tract motility and constipation. Other signs may include sluggishness, weakness, and transient, sometimes bloody, diarrhea. In acute cases, death occurs in 2–4 days. Subacute poisoning is more common and may result in death after

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1–3 weeks of illness and weight loss. Raw photosensitized surface areas are susceptible to invasions by blow fly maggots and bacteria. In severely affected cattle, lesions may appear at the muzzle, mouth, and nostrils. Ulceration may be present in the cheeks, tongue, and gums, whereas swelling, hardening, and peeling of mucous membranes and deeper tissues occur in the nostrils. Dogs usually do not ingest a fatal dose, but unless the dog is treated immediately, he can deteriorate and die within 1–3 weeks. A fatal dose causes death in 2–4 days.

Treatment Effective treatment may include giving intravenous fluids and encouraging the animal to eat, and provide proper shade. Activated charcoal is effective. A second dose may be required 24 hr after the first if the animal has not improved. Skin damage can be treated with antibiotics and sunscreens. The outlook for recovery is good.

11.21 *Descurainia pinnata*

Descurainia pinnata belongs to the family Brassicaceae. It is a species of flowering plant in the mustard family known by the common name western tansy mustard. It is native to North America, where it is widespread and found in varied habitats. It is a hardy plant which easily becomes weedy, and can spring up in disturbed, barren sites with bad soil. This is a hairy, heavily branched, mustard-like annual which is quite variable in appearance. There are several subspecies which vary from each other, and individuals within a subspecies may look different depending on the climate they endure. At the tips of the stem branches are tiny yellow flowers (Fig. 11.28).



Fig. 11.28 Tansy mustard plant (*Descurainia pinnata*). (Reproduced from Pxhere https://pxhere.com/en/photo/1351550)

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Toxic Principle The toxic principle of tansy mustard is not known. All parts of the plant contain poisonous levels of nitrate. The seeds contain isoallyl thiocyanates and irritant oils.

Toxicity Western tansy mustard is toxic to livestock, causing blindness, staggering, and loss of ability to swallow. Continued ingestion of large quantities of western tansy mustard over long periods of time is required before symptoms appear. Livestock may consume western tansy mustard in large quantity if other forage is sparse. This is followed by an inability to use the tongue or to swallow. The disease is popularly termed "paralyzed tongue" or "wooden tongue." Because of blindness, animals may wander aimlessly until exhausted or stand pushing against a solid object in their path for hours. Because of the inability to swallow, animals may be observed standing at water unable to drink or unsuccessfully grazing forage. Animals become thinner and weaker and will die if not treated.

Treatment Most animals will recover if removed from the tansy mustard or flixweed. Severely affected animals need symptomatic treatment including water and electrolytes via stomach tube. Large doses of thiamin (or thiamine) may help resolve the blindness.

11.22 Plants Containing Cyanogenic Glycosides

Plants containing cyanogenic glycosides are widespread in nature and are responsible for multiple disease conditions in animals and human population. The ubiquitous nature of plants containing cyanogenic glycosides is represented by more than 2500 species found within most plant families including the Rosaceae, Leguminoseae, Gramineae, Araceae, Poaceae, Compositeae, Euphorbiaceae, and Passifloraceae.

The plant species that commonly cause poisoning in livestock include *Sorghum* spp. (Fig. 11.29) (Johnson grass, sudan grass, and *S. bicolor*, the common cereal grain crop referred to as "sorghum" or the synonyms—durra, jowari, and milo), *Acacia greggii* (guajillo), *Amelanchier alnifolia* (western service berry), *Linum* spp. (linseeds and flaxes), *Sambucus nigra* (elderberry), *Suckleya suckleyana* (poison suckleya), *Triglochin maritime* and *T. palustris* (marsh arrow grasses), *Mannihot esculentum* (cassava), *Prunus* genus until proved otherwise (apricot, peach, chokecherry, pincherry, wild black cherry (Fig. 11.30), ornamental cherry, peaches, nectarines, apricots, almonds, bird cherries, black thorn, cherry laurels [commercial orchard species are often specifically bred for low cyanide content; however, ornamental members of this genus are often highly poisonous]), *Nandina domestica* (heavenly or sacred bamboo), *Phaseolus lunatus* (Lima beans), *Trifolium* sp. (clovers; often, pasture species have been bred for low cyanide content), *Zea mays* (corn), *Eucalyptus* spp. (gum trees), *Hydrangea* spp. (hydrangeas), *Pteridium aquilinum* (bracken fern), *Bahia oppositifolia* (bahia), and *Chaenomeles* spp. (flowering quince).

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Fig. 11.29 *Sorghum* plant. (https://encrypted-tbn3.gstatic.com/images?q5tbn:ANd9GcQbNK2mB5DW6iKUp5LffIPrLyaf_pBPWIx2VZwshNVg02UlXdm5)



Fig. 11.30 Prunus spp. Common name: Wild cherries, black cherry, bitter cherry, choke cherry, and pin cherry. (Reproduced from Department of Parks & Recreation, LA County)

Some unfavorable conditions lead to dangerous levels of cyanogenic glycosides in plants. These conditions include:

(a) Periods of rapid regrowth following stunting, for example, after drought breaks, if a crop is eaten back and then allowed to regrow or if a crop is harvested for hay and then allowed to regrow (levels are highest in young plants with green, growing shoots)
(b) Frosted or wilted plants that have a transient increase in glycoside levels
(c) Herbicide-treated plants that have a transient increase in glycoside levels
(d) High nitrogen and low phosphorus levels in the soil

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(e) Plant species, such as sorghum, which can contain more prussic acid than sudan grass—varieties vary in their prussic acid potential
(f) Plants that are wet with dew or light rain

Toxic Principles More than 50 cyanogenic glycosides which yield hydrogen cyanide (hydrocyanic acid or prussic acid) have been identified, and some of the more common ones include amygdalin and prunasin.

Mechanism of Toxicity As a glycoside, the cyanogenic glycosides in plants are relatively nontoxic to plants or animals. Cyanogenic glycosides only become toxic when the free hydrogen cyanide (HCN) is cleaved from the glycoside through a two-step enzymatic process. In the plant, the glycosides and enzymes are in different plant compartments, thus protecting the plant cells from HCN toxicity. The glycosides are usually contained within cellular vacuoles whereas the enzymes (glycosidases, lyases) are found in the plant cytosol. When plant cells are damaged or stressed through crushing, chewing, frost, drought, etc., the glycoside comes in direct contact with the enzymes, and the HCN levels increase quickly. HCN or prussic acid, as it is frequently called, is highly poisonous to all animals because of its ability to block cellular respiration. The free HCN is readily absorbed through the gut and lungs, and the cyanide ion (CN_2) has a strong affinity to bind with the trivalent iron component of the cytochrome oxidase molecule preventing cellular respiration and death from histotoxic anoxia. Tissues that heavily depend on aerobic metabolism such as the heart and brain are particularly susceptible to these effects. Cyanide also binds to other heme-containing enzymes, such as members of the cytochrome p450 family, and to myoglobin. However, these tissue cyanide "sinks" do not provide sufficient protection from histotoxic anoxia.

Toxicity Toxicity can result from accidental, improper, or malicious use or exposure. However, in livestock species, the most frequent cause of acute and chronic cyanide poisoning is ingestion of plants that either constitutively contain cyanogenic glycosides or are induced to produce cyanogenic glycosides and cyanolipids as a protective response to environmental conditions.

Acute Cyanide Poisoning Dyspnea follows shortly, with tachycardia. The classic "bitter almond" breath smell may be present. Salivation, excess lacrimation, and voiding of urine and feces may occur. Vomiting may occur, especially in pigs. Muscle fasciculation is common and progresses to generalized spasms and coma before death. Animals may stagger and struggle before collapse. In other cases, sudden unexpected death may ensue. Mucous membranes are bright red but may become cyanotic terminally. Venous blood is classically described as "cherry red" because of the presence of high venous blood pO_2; however, this color rapidly changes after death. Cardiac arrhythmias are common due to myocardial histotoxic hypoxia. Death occurs during severe asphyxial convulsions. The heart may continue to beat for several minutes after struggling, and breathing stops. Ruminant animals (cattle and sheep) are more susceptible to prussic acid poisoning than

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monogastric animals (horses and pigs) because lower pH in the stomach of the monogastric animals helps to destroy the enzymes that convert cyanogenic glycosides to prussic acid.

Poachers use cyanide to kill the animals such as zebra, birds, and cheetah, and even elephants are poisoned by cyanide (Fig. 11.31).

Chronic Cyanide Poisoning There are at least two forms of chronic cyanide poisoning in domestic animals:

(a) Hypothyroidism due to disruption of iodide uptake by the follicular thyroid cell sodium-iodide symporter by thiocyanate, a metabolite in the detoxification of cyanide. Chronic cyanogenic glycoside hypothyroidism will present as hypothyroidism with or without goiter.
(b) Chronic cyanide and plant cyanide metabolite (e.g., various glutamyl β-cyanoalanines) –associated neuropathy toxidromes (e.g., equine sorghum cystitis ataxia syndrome, cystitis ataxia syndromes in cattle, sheep, and goats) that are typically associated with posterior ataxia or incoordination that may progress to irreversible flaccid paralysis, cystitis secondary to urinary incontinence, and hind limb urine scalding and alopecia. Death, although uncommon, is often associated with pyelonephritis. Late-term abortion and musculoskeletal teratogenesis may also occur.

Treatment Treatment consists of use of various nitrites. Inhaled amyl nitrite followed by IV injection of a nitrite salt (typically sodium nitrite). Cyanide bound to methemoglobin can then be detoxified by rhodanese to thiocyanate. Treatment with nitrites is usually followed up by injection of sodium thiosulfate. Oral dosing with sodium thiosulfate into the rumen and/or stomach has also been suggested because



Fig. 11.31 Poachers used cyanide to kill the animals, the picture of zebra. (Reproduced from https://commons.wikimedia.org/wiki/File:Hartmanns_Mountain_Zebra_Resting.jpg)

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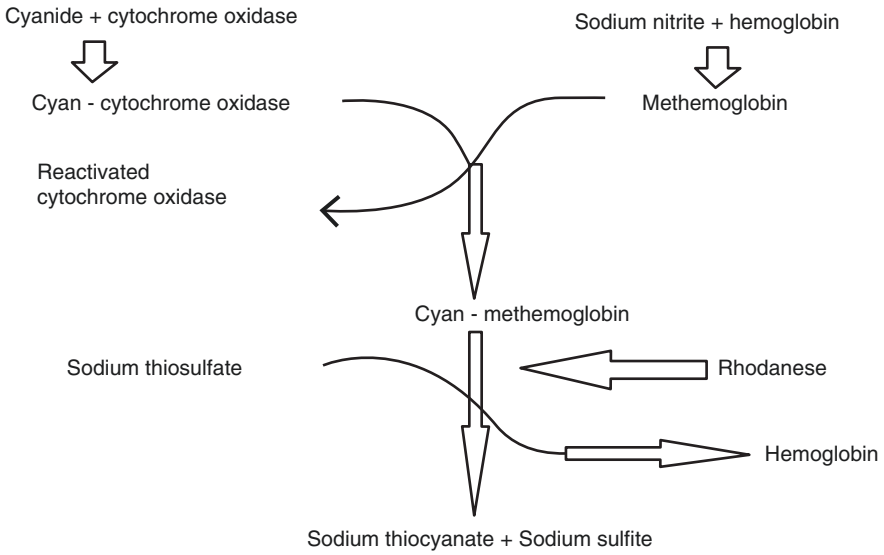


Fig. 11.32 Mechanism of action of sodium nitrite in cyanide poisoning

the reaction between thiosulfate and cyanide can also occur nonenzymatically, and this may reduce any ongoing production of cyanide in the rumen/stomach environments. The figure shows that cyan-cytochrome oxidase has more affinity for methemoglobin to form cyan-methemoglobin. Sodium thiosulfate reacts with cyan-methemoglobin to release hemoglobin (Fig. 11.32). Therefore, the goal of treatment is to break the cyanide-cytochrome c oxidase bond and reestablish the mitochondrial electron transport chain.

11.23 Nitrate- and Nitrite-Accumulating Plants

Nitrate poisoning is a commonly encountered disease state in herbivores. Ruminants are the most susceptible to acute nitrate poisoning. Microflora in the rumen reduces nitrates to nitrites and then ammonia for microbial growth. Excess intake of nitrates may overwhelm further reduction capacity, allowing toxic amounts of nitrite to accumulate and be absorbed into the blood, where it causes the formation of methemoglobin. Thus, even though the clinical syndrome is referred to as nitrate poisoning, it is actually poisoning by the nitrite ion. Nitrate poisoning is occasionally a problem of fertilized pastures of ryegrass (*Lolium multiflorum*), oats (*Avena* spp.), turnips (*Brassica rapa*), or wheat (*Triticum* spp.), pigweed (*Amaranthus* spp.), dock (*Rumex* spp.), nightshades (*Solanum* spp.; Fig. 11.33), and lambsquarter (*Chenopodium* spp.; Fig. 11.34). Potentially troublesome crop plants include corn, sorghum, oats, barley, beet tops, and wheat.

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Fig. 11.33 *Solanum* species—nightshades. (https://upload.wikimedia.org/wikipedia/commons/3/3a/Lycianthes_rantonnei.jpg)



Fig. 11.34 *Chenopodium* species. (http://upload.wikimedia.org/wikipedia/commons/b/b2/Chenopodium_album_a1.jpg)

Mechanism of Action The nitrite anion causes vasodilation and oxidizes ferrous iron (Fe2+) in hemoglobin to the ferric iron (Fe3+) state forming methemoglobin, which then cannot accept molecular oxygen. The formation of methemoglobin is likely rapid with the cumulative development occurring as nitrite is absorbed. As the percentage of methemoglobinemia rises, oxygen starvation of tissues increases and blood becomes chocolate brown in color.

Toxicity Clinical signs of nitrate-nitrite toxicosis in cattle include weakness, cyanosis of mucous membranes, tremors, ataxia, collapse, tachypnea, dyspnea, abortions, and death. Affected animals may remain standing but then collapse and die within minutes. Dead animals may be found in sternal recumbency or lying on their side. Blood is generally dark and may have an obvious brown color. In cattle, abortions may occur in the herd 2–10 days after acute nitrate toxicosis. Less oxygen is

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available to the fetus because of decreased vascular perfusion (decreased arterial pressure) and methemoglobinemia in the cow, and nitrite induces methemoglobinemia in fetal blood. Bovine abortion has been reported to occur with forages containing 0.61–1% nitrate. Necropsy findings were cyanosis, dark colored blood, and pulmonary congestion and edema.

Monogastric animals are less susceptible to the toxic effects of nitrate ingestion. Horses and rabbits can convert some nitrate to nitrite in the large bowel, but are much less sensitive than ruminants, with nitrate toxicosis in horses being rarely reported. Other monogastric species are susceptible to the systemic toxic effects of nitrites, when ingested as nitrites from non-plant sources.

Treatment Methylene blue is used to treat severe methemoglobinemia. Lower dosages of methylene blue can be used in all species, but only ruminants can safely tolerate higher dosages. If additional exposure or absorption occurs during therapy, retreating with methylene blue every 6–8 h should be considered. Rumen lavage with cold water and antibiotics may stop the continuing microbial production of nitrite.

11.24 Toxicity of Yew (*Taxus* spp.) Alkaloids

Common varieties of yews plants (*Taxus* spp., Taxaceae family) such as yew (*Taxus baccata*), American yew (*Taxus canadensis*), Japanese yew (*Taxus cuspidata*), and Pacific or Western yew (*Taxus brevifolia*) can be highly toxic and have been implicated in numerous human and animal poisonings. The poisonous taxine alkaloids are present in the foliage, bark, and seeds of the plants but not in the fleshy scarlet aril (berry).

Toxic Principles Alkaloid "taxines" having two major types of taxine alkaloids—taxine A and taxine B—are the principle toxins.

Mechanism of Action Both taxines A and B have inotropic effects while eliciting marked changes in atrioventricular conduction that leads to atrioventricular conduction blocks and complete diastolic cardiac arrest. Taxine B is more cardiotoxic than taxine A. Mechanism of action of taxines is primarily based on calcium channel antagonistic properties. Therefore, it is likely that the toxicity of taxines in animals and humans also occurs through the same mechanism.

Toxicity Poisoning in animals is often accidental. Yew intoxication has been reported in cattle, horses, sheep, goats, and dogs. Adverse clinical signs in animals can vary depending on the amount of yew ingested. However, in most cases of acute poisoning, animals are often found dead within 24 h or less after ingestion without demonstrating abnormal behavior or adverse signs of toxicity. In subacute poisonings, which have been reported infrequently, clinical signs may include ataxia, bradycardia, dyspnea, muscle tremors, recumbency, and convulsions leading to collapse and death.

Treatment Symptomatic treatment is advocated. Usually death is the first adverse clinical sign in animals that have eaten toxic amounts of yew; therefore, opportunities to treat exposed animals are rare.

11.25 *Senna occidentalis* (Fabaceae Family)

The species *Senna occidentalis* belongs to the genus *Senna*. Vernacular names include septic weed, coffee senna, coffeeweed, Mogdad coffee, negro-coffee, senna coffee, Stephanie coffee, stinking weed, or styptic weed. The plant is annual undershrub, subglabrous, fetid, few feet high (Fig. 11.35).

Toxic Principles The plant contains anthraquinones. The roots contain emodin, and the seeds contain chrysarobin (1,8-dihydroxy-3-methyl-9-anthrone) and N-methylmorpholine.

Toxicity *Senna occidentalis* is a toxic leguminous plant found in many tropical and subtropical regions of the world. The plant is reported to be poisonous to cattle and other species. The seeds are the most toxic part of the plant and may be present in animal rations. In calves, dyspnea, neutrophilia, and tachycardia from consumption of the plant have been reported. Horses and pigs also may be affected. After eating the plant for a few days, animals develop diarrhea, show evidence of weakness, and display a swaying, stumbling gait that is related to the developing muscle lesions. The disease progresses rapidly, and most of the animals affected become recumbent and develop myoglobinuria and high concentrations of muscle-origin enzymes in serum. Recumbent animals may live for several days, but usually do not recover.



Fig. 11.35 *Senna occidentalis* flower. (https://upload.wikimedia.org/wikipedia/commons/thumb/9/99/Senna_occidentalis.jpg/330px-Senna_occidentalis.jpg)

The morbidity rate may reach 60%. In swine pig farms, when animals were fed grains contaminated with seeds, several pigs showed a short period of reduced weight gain and a progressively wobbly, unsteady gait followed by death. Seeds have been shown to be toxic for laying hens, which show marked reduction in egg production and yolk leaking and dysplasia of the inner layer of the vitelline membrane.

11.26 Strychnine Poisoning

Strychnine is a bitter alkaloid substance that is extracted from the seeds of *Strychnos nux-vomica* trees (Fig. 11.36). In the past, strychnine has been used as a pesticide to control rats, moles, gophers, and coyotes. Strychnine is highly toxic to most domestic animals. Their use as indoor pesticides has been eliminated since 1989. Malicious or accidental strychnine poisoning, although not very common, occurs mainly in small animals, especially dogs and occasionally cats, and rarely in livestock. Most poisonings occur when nontarget species consume commercial baits.

Toxic Principles Plant contains alkaloids such as strychnine and brucine.

Toxicity Strychnine is quickly absorbed from the gastrointestinal tract, causing rapid onset of clinical signs. Strychnine is highly toxic to all animals. Early signs, which may often be overlooked, consist of apprehension, nervousness, tenseness, and stiffness. Vomiting is possible but uncommon. Severe tetanic seizures may appear spontaneously or may be initiated by stimuli such as touch, sound, or a sudden bright light. An extreme and overpowering extensor rigidity causes the animal to assume a "sawhorse" stance. Hyperthermia (104–106 °F [40°–41 °C]) due to stiffness and seizures is often present in dogs. The mucous membranes become cyanotic and the pupils are dilated. Strychnine acts on the animal's nervous system

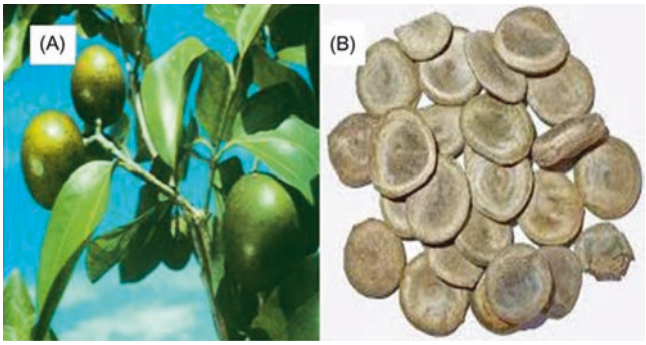


Fig. 11.36 *Strychnine* plant along with fruits (**a**) and seeds (**b**). ((**a**) Available at The Poison Diaries. http://thepoisondiaries.tumblr.com/post/36597628648/strychnosnuxvomica. (**b**) Available at Wikimedia Commons. https://en.wikipedia.org/wiki/Strychnos_nux-vomica)

to cause profound stimulation with severe muscle spasms and seizures. Frequency of the seizures increases, and death eventually occurs from exhaustion or asphyxiation during seizures.

Treatment Strychnine can cause a very rapid onset of clinical signs. The opportunity to induce vomiting (in order to remove the poison from the stomach) is often lost. Once clinical signs are present, vomiting is not induced, because it could cause more harm than good. Muscle stiffness, tremors, and seizures can sometimes be managed with injectable drugs such as anticonvulsants and muscle relaxants. Supportive care may include administration of intravenous fluids; correction of high body temperatures induced by the muscle tremors and seizures; and respiratory support with oxygen or acidification of urine with ammonium chloride may be useful for ion trapping and urinary excretion of the alkaloid.

11.27 Mushroom Poisoning

It is not clear how many of the mushrooms worldwide contain potentially toxic compounds. New species are being discovered continuously, and for many species, toxicity data are unavailable. Animals are at much greater risk of exposure to toxic mushrooms than humans; mushroom poisonings in animals are most likely underreported. Three genera—*Amanita*, *Galerina*, and *Lepiota*—are known to contain hepatotoxic cyclopeptides, with *Amanita phalloides*, the ubiquitous death cap or death angel, and *Galerina sulpices* being considered the most toxic worldwide. *A. phalloides* (Fig. 11.36) is the species most frequently resulting in fatalities in humans and probably dogs (Fig. 11.37).



Fig. 11.37 The toxic mushroom *Amanita phalloides*. (https://thumb1.shutterstock.com/display_pic_with_logo/163922440/772763140/stock-photo-death-cap-mushroom-amanita-phalloides-772763140.jpg)

Mechanism of Action Amanitins exert their toxicity by inhibiting nuclear RNA polymerase II. The decrease in mRNA and associated decrease in protein synthesis result in hepatocyte necrosis. Cells with a high metabolic rate, such as hepatocytes, crypt cells, and proximal convoluted tubules of the kidneys, are most commonly affected.

Toxicity Amanitins are extremely toxic, and poisonings have been observed in dogs, horses, and cattle. The symptoms usually appear within a few hours of ingesting the mushrooms, and include nausea, vomiting, cramps, and diarrhea, which normally pass after the irritant had been expelled. Members of *Amanita* genera cause hypoglycemia and hepatic and renal failures. Considering the average concentration of amanitins per mushroom, one *A. phalloides* mushroom has the potential to kill a dog or horse.

Treatment With no proven antidotes to treat mushroom poisonings, treatment is primarily directed at decontamination, mushroom identification when possible, and intensive supportive care.

11.28 Questions and Answers

11.28.1 Short Questions and Answers

Exercises 1

Q.1. How poisonous plants are responsible for toxicity in animals?
- Many plants commonly used as food possess toxic parts, are toxic unless processed, or are toxic at certain stages of their lives. Some only pose a serious threat to certain animals (such as cats, dogs, or livestock) or certain types of people (such as infants, the elderly, or individuals with pathological vulnerabilities). Most of these food plants are safe for the average adult to eat in modest quantities.

Q.2. Name the active toxic principle(s) of *Abrus precatorius*.
- Active principles are N-methyltryptophan, glycyrrhizin (lypolytic enzyme—the active principle of liquorice), abrin (toxalbumin also known as phytotoxin), abrine (amino acid), abralin (glucoside), and abric acid.

Q.3. Name the active toxic principle(s) of Croton plant.
- Seed and oil extracted from the seeds are extremely toxic. Seed oil is known to have tumor-promoting diesters. Active principles are crotin (toxalbumin) and crotonoside (glycoside).

Q.4. What are toxic principles of *Calotropis* plant?
- Toxic parts include stem, branches, leaves, and the milky white latex (madar juice). Important toxic principles are uscharin, calotoxin, calotropin, and gigantin.

Q.5. What are the important toxic principles of *Semecarpus anacardium*?
- Semicarpol (monohydroxy phenol compound) and bhilawanol (alkaloid).

Q.6. What are the important principles of *Capsicum annum*?
- Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is an active component of chili peppers. It is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact.

Q.7. What is the toxic principle of *Eucalyptus globus* plant?
- Eucalyptol (cineole).

Q.8. What are the important toxic principles of *Colchicum* plant?
- Alkaloid colchicines and demecolcin.

Q.9. What are the important oleander plants?
(a) *Nerium odourum*: Common names—white/pink kaner.
(b) *Cerbera thevetia*: Common names—yellow, that is, peela kaner, exile, and bastard.
(c) Cerbera odollum: Common names—dabur, dhakur, and pilikibir. All parts of the plant are poisonous, especially fruit with kernels or seeds and the nectar from the flowers, which yields poisonous honey.

Q.10. What are the toxic principles of *Nerium odourum*?
- Nerium odourum has nerin, containing cardiac glycosides: (1) neriodorin, (2) neriodorein, (3) karabin, (4) oleandrin, (5) folinerin, and (6) rosagerin.

Q.11. What are the toxic principles of *Cerbera thevetia*?
- *Cerbera thevetia* has glycosides: (1) thevetin (one-eighth as potent as ouabain which is similar in action to digitalis), (2) thevitoxin (less toxic than thevetin), (3) nerifolin (more potent than thevetin), (4) peruvoside, (5) ruvoside, and (6) cerberin.

Q.12. What are the toxic principles of *Cerbera odollum*?
- *Cerbera odollum* contains glycoside cerberin.

Q.13. Describe in brief the mode of action of Oleanders plants?
- Oleanders act like digitalis; toxic doses can produce malignant dysrhythmias and cardiac failure, cardiac arrest, and convulsions. Toxic principles are absorbed easily via skin and GI route.

Q.14. What are the toxic principles of aconite plant?
- Toxic principles are diterpene alkaloids known as:
  (a) Aconitine
  (b) Misaconitine
  (c) Hypaconitine.
  These alkaloids are sparingly soluble in water and are considered as most virulent poisons with sweetish taste. Other alkaloids present in small quantities in the plant are picraconitine, pseudoaconitine, and aconine.

Q.15. What is the mode of action of aconite toxins?
- Diterpene alkaloids are known as cardiac and neurotoxins that can cause conduction block and paralysis through their action on voltage-sensitive sodium channels in the axons. This can result in initial neurological stimulation, followed by depression of myocardium, smooth and skeletal

muscles, CNS, and peripheral nervous system. Aconite is absorbed via skin and oral route. Symptoms generally appear within 30–90 min after ingestion of the poison and lasts up to approximately 30 h.

Q.16. What are the toxic principles of nicotine plant?
- Lobeline is the chief constituent of nicotine plant (Indian tobacco), obtained from the leaves and tops of *Lobelia inflatea*, an alkaloid similar to nicotine, but less potent than nicotine, and is used in antismoking tablets and lozenges.

Q.17. What is the source of strychnine?
- Strychnine is a spinal poison obtained from *Strychnos nux-vomica*, kuchila plant. It contains alkaloids such as *stichnine*, *brucine*, *and loganine*.

Q.18. What are invasive plants?
- Invasive plants are plant species that can be harmful when introduced to new environments. These plants can reproduce quickly and thrive in different habitats. Invasive plants can grow in natural areas (forests, grasslands, and wetlands), managed areas (cultivated fields, gardens, lawns, and pastures), and areas where the soil and vegetation have been disturbed (ditches, rights of way, and roadsides).

Q.19. Why phenothiazine tranquilizers are contraindicated in *Datura* intoxication?
- In *Datura* intoxication, anticholinergic symptoms are seen. As phenothiazines also possess anticholinergic activity, they are contraindicated for controlling CNS excitation in *Datura* intoxication.

Q.20. What is prussic acid poisoning?
- Prussic acid is also known as hydrocyanic acid (HCN). Prussic acid is not normally present in plants but under certain conditions, several common plants can accumulate large quantities of cyanogenic glycosides which can convert to prussic acid. It is a potent, rapidly acting poison, which enters the bloodstream of affected animals and is transported through the body. It then inhibits oxygen utilization by the cells so that, in effect, the animal dies from asphyxia.

11.28.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. Which of the following plants are carcinogenic?
(a) American hellebore
(b) Bracken fern
(c) Buttercup
(d) Tung nut

Q.2. All of the following are true of grayanotoxins *except* _____.
(a) They are present in rhododendron.
(b) They can contaminate honey.
(c) They cause bradycardia.
(d) They block the neuromuscular junction.

Q.3. Plant molecules that react as bases and usually contain nitrogen in a heterocyclic structure are known as _____.
(a) Alkaloids
(b) Terpenes
(c) Resins
(d) Glycosides

Q.4. Plant molecules that are created from isoprene units with varying functional groups are known as _____.
(a) Terpenes
(b) Amines
(c) Alkaloids
(d) Phenols

Q.5. Plant molecules that are hydrolyzed to a sugar and a nonsugar moiety are known as _____.
(a) Glycosides
(b) Alkaloids
(c) Resins
(d) Terpene

Q.6. Toxic minerals that may accumulate in plants include all of the following *except* _____.
(a) Cadmium
(b) Magnesium
(c) Copper
(d) Selenium

Q.7. *Brassica oleracea* (kale) contains _____.
(a) Cardiac glycoside
(b) Cyanogenic glycoside
(c) Goitrogenic glycoside
(d) Steroid glycoside

Q.8. A plant toxin that can be highly transmitted through milk is _____.
(a) Oxalate
(b) Cyanide
(c) Nitrate
(d) Tremetol

Q.9. An antidote is available for the toxin present in _____.
(a) Azalea
(b) Pigweed
(c) Veratrum
(d) Apple seeds

Q.10. Which of the following plant toxins is classified as an alcohol?
(a) Nicotine
(b) Ranunculus
(c) Dogbane
(d) Tremetol

Q.11. Amygdalin is found in the highest amount in the seeds of _____.
(a) Bitter almond
(b) Tomato
(c) Pear
(d) Plum

Q.12. Strychnine blocks _____.
(a) Glycine-gated chloride channel
(b) Glutamate receptors
(c) GABA receptors
(d) Voltage-gated sodium channels

Q.13. The toxin found in species of *Capsicum* has been known to be useful in the therapy of _____.
(a) Skin cancer
(b) Depression
(c) Chronic pain
(d) Decubitus ulcers

Q.14. All of the following are true of curare *except* _____.
(a) It was a South American arrow poison.
(b) It is a neuromuscular blocking agent.
(c) It can be used clinically.
(d) It is CNS toxic.

Q.15. Swainsonine _____.
(a) Is present in *Vinca* species
(b) Is a glycoprotein
(c) Causes abortions in livestock
(d) None of the above

Q.16. The veratrum and lupine alkaloids are _____.
(a) Teratogenic
(b) Components of marketed pharmaceuticals
(c) Used as insecticides
(d) Poisons that Socrates drank

Exercise 3

Q.17. The part of the plant that does not accumulate fluoride is _____.
(a) Seed
(b) Stem
(c) Leaf
(d) Flower

Q.18. Fluoride interferes with the following element(s) in the body:
(a) Calcium
(b) Magnesium
(c) Manganese
(d) Phosphorus

Q.19. Which form of fluorosis is seen if the animal is exposed to fluorine during early stages of life?
(a) Skeletal
(b) Dental
(c) Both
(d) Not affected

Q.20. Which of the following form of phosphorus is toxic?
(a) White
(b) Red
(c) Yellow
(d) Black

Answers

Exercise 2

1. b	11. a
2. d	12. a
3. a	13. c
4. a	14. d
5. a	15. c
6. b	16. a
7. c	17. a
8. d	18. a, b, and c
9. d	19. c
10. d	20. a and c

11.28.3 Fill in the Blanks

Exercise 3

Q.1. *Abrus precatorius* is commonly known as _____ or _____.
Q.2. The toxicity due to seeds of *Abrus precatorius* is commonly referred to as _____ poisoning.
Q.3. The toxic principle present in the seeds of *Abrus precatorius* is _____.
Q.4. *Ricinus communis* is commonly referred to as _____.
Q.5. The toxic principle present in the seeds of *Ricinus communis* is _____.

Q.6. The toxic principles abrin and ricin belong to the class of glycoproteins known as _____.
Q.7. The toxic principle present in castor bean which causes hemagglutination and hemolysis is _____.
Q.8. The species of animal that is more susceptible to abrin and ricin poisoning is _____.
Q.9. At the cellular level, lectins (abrin and ricin) act by inhibiting _____ preventing protein synthesis.
Q.10. The toxic plant whose flowers are known as "angel's trumpets" or "moonflowers" is _____.

Answers

Exercise 3

1. Rosary pea or rathi
2. Sui/needle
3. Abrin
4. Castor bean
5. Ricin
6. Lectins
7. RCA (*Ricinus communis* agglutinin)
8. Horse
9. Ribosomes
10. *Datura stramonium*

11.28.4 True or False Statements

Write (T) for true and (F) for false statement.

Exercise 4

Q.1. The chronic selenium poisoning is also known as blind staggers.
Q.2. Selenium toxicity occurs when the pasture contains more than 5 ppm of selenium.
Q.3. The toxicity of nitrates is six to ten times more than nitrite.
Q.4. Lantadin A and B from *Lanatana camera* causes secondary photosensitization.
Q.5. *Aster* sp. is an example of indicator plant which contains high concentration of selenium.
Q.6. Nitrate poisoning can cause abortion in cattle.
Q.7. There is a treatment for water hemlock (cicutoxin) poison.

Answers

Exercise 4

1. False
2. True
3. False
4. True
5. False
6. True
7. False

11.28.5 Match the Statements

Match the column A with column B.

Exercise 5

Column A	Column B
Q.1. Apricot	A. Anticholinergic
Q.2. Water hemlock	b. Nausea and vomiting
Q.3. Lupine	c. Soluble oxalate
Q.4. Cactus	d. Seizures and tremors
Q.5. Poinsettia	e. CNS cognitive
Q.6. Digitalis purpurea	f. Photosensitivity inducing
Q.7. Jimsonweed	g. Cyanide
Q.8. St. John's wort	h. Contact irritant dermatitis
Q.9. Rhubarb	i. Hepatotoxic and teratogenic
Q.10. Marijuana	j. Cardiac arrhythmias

Answers

Exercise 5

Q.1	g. Cyanide
Q.2	d. Seizures and tremors
Q.3	i. Hepatotoxic and teratogenic
Q.4	h. Contact irritant dermatitis
Q.5	b. Nausea and vomiting
Q.6	j. Cardiac arrhythmias
Q.7	a. Anticholinergic
Q.8	f. Photosensitivity inducing
Q.9	c. Soluble oxalate
Q.10	e. CNS cognitive

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Feed Contaminant Toxicity

12

Abstract

This chapter focuses attention on feed contaminant toxicity that results from toxins such as melanine, cyanuric acid, ionophores, and ureas (nonprotein nitrogen) that represent significant risks to farm livestock and pet animals. In addition, animal feeds and forages contain a wide range of contaminants and toxins arising from anthropogenic and natural sources such as nitrates, heavy metals, radionuclides, mycotoxins, pesticide residues, plant toxins, antibiotic, microbials, coccidiostats, and so forth. Feed and fodder also get contaminated with insect fragments and excreta. Sometimes a compound itself is not toxic, but presence of other ingredients makes the compound toxic. For example, melamine, by itself, has relatively low toxicity. The combination of melamine and cyanuric acid is markedly more toxic to most domestic animals than either compound when given alone.

Keywords

Feed contaminants · Melanine · Cyanuric acid · Ionophores · Ureas (nonprotein nitrogen) · Question and answer bank · Multiple choice questions

12.1 Introduction

This chapter is limited to a review of contaminants and toxins such as melanine, cyanuric acid, ionophores, and ureas (nonprotein nitrogen) that represent significant risks to farm livestock and pet animals. Contamination of mycotoxins, in cereals, has been discussed earlier under appropriate headings and various chapters of this book. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements relevant to adverse effects of feed contaminants in animals.

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Key Points

- Animal feeds and forages contain a wide range of contaminants and toxins arising from anthropogenic and natural sources.
- Common contaminants include nitrates, heavy metals, radionuclides, mycotoxins, pesticide residues, plant toxins, antibiotics and microbial pathogens, coccidiostats, etc.
- Feed and fodder also get contaminated with insect fragments and excreta.
- Melamine, by itself, has relatively low toxicity. The combination of melamine and cyanuric acid is markedly more toxic to most domestic animals than either compound when given alone.

12.2 Melamine and Cyanuric Acid

Melamine, or 1,3,5-triazine-2,4,6-triamine, is a small, nitrogen-rich molecule used in the manufacture of plastics, adhesives, cleaners, and yellow dye. Melamine is sometimes illegally added to food products in order to increase the apparent protein content. Melamine ingested in large doses may cause stones and illness without significant ingestion of cyanuric acid or other melamine-related chemicals. The melamine contamination crisis highlighted the evolving nature of international commerce in food, including animal feed and pet food, and the need for a review of the policies used to protect against food and feed risks. Therefore, the US Congress passed legislation in 2007 to give FDA more mechanisms to keep pet food and animal feed safe.

Mechanism of Action Both melamine and cyanuric acid are relatively nontoxic when given individually; however, they cause crystal formation in renal tubules of mammals when given together. Melamine and cyanuric acid crystallize, forming a molecular lattice structure, at a pH of 5.8.

Toxicity Melamine, by itself, has relatively low toxicity. The combination of melamine and cyanuric acid is markedly more toxic to most domestic animals than either compound when given alone. Early clinical signs of vomiting and inappetence are apparent in cats and dogs ingesting contaminated food, followed later by evidence of renal failure. The most common clinical signs in cats and dogs are inappetence, vomiting, polyuria, polydipsia, and lethargy. Urinalysis revealed the presence of circular green-brown crystals in urine sediment. Renal tubular necrosis with evidence of rupture and regeneration may be observed.

Treatment and Prognosis The basic treatment regimens for crystalluria and urolithiasis related to melamine ingestion include fluid therapy and supportive care in both veterinary and pediatric patients. Increased water intake and fluid therapy may be used to increase urine output. Alkalization of the urine by sodium bicarbonate or

potassium citrate is advocated. Antispasmodic drugs, such as anisodamine (7β-hydroxyhyoscyamine, is an anticholinergic and $\alpha_1$adrenergic receptor antagonist) or atropine, may be used.

12.3 Ionophore Toxicity

12.3.1 Toxic Myopathies in Ruminants and Pigs

Ionophores are commonly added to ruminant feeds for their growth promotion and coccidiostat properties. Horses, however, are ten times more sensitive to the toxic effects of ionophores in feed than cattle. When equine feeds are inadvertently contaminated with ionophores or horses eat cattle feed, some animals may die acutely with colic-like signs, myoglobinuria, hypokalemia, cardiac arrhythmia, and tachypnea. Cardiomyopathy is the most common chronic sequela.

Feed concentrations of 100 g/ton and 400 g/ton have been fatal to sheep and cattle, respectively. Newborn calves dosed with 100 mg lasalocid tid for cryptosporidiosis experience muscle necrosis. Other ionophores include naracin, salinomycin, and laidlomycin. At necropsy, pale areas of myocardial necrosis and pulmonary congestion are usually prominent in cattle. Pigs and sheep tend to have mainly skeletal muscle lesions that appear quite similar grossly and histologically to those of nutritional myodegeneration. Diagnosis requires history of exposure with development of characteristic clinical and pathologic alterations.

12.3.2 Toxic Myopathy in Poultry

Ionophore toxicity in poultry causes muscle damage with incoordination, leg weakness, diarrhea, dyspnea, and reduced feed intake and weight. Stunting may also occur. Type I ("red muscle" or oxidative) fibers are most susceptible, and lesions are most prominent in the leg musculature. Lesions may also be found in heart and gizzard muscle. Adult birds (chickens, turkeys, ratites) and birds with no previous exposure are more sensitive to ionophore coccidiostats. Ionophores promote movement of cations across the cell membrane, causing disruption of the ionic equilibrium, increased intracytoplasmic concentration of Ca2+, and cell death. The toxic dose of ionophores is decreased if they are used in conjunction with tiamulin, erythromycin, or chloramphenicol. Salinomycin at the dose recommended for chickens (60 g/ton) is toxic for turkeys; doses >15 g/ton are toxic in turkeys. Monensin (100 g/ton) and lasalocid (100 g/ton) at the dose recommended for chickens are not toxic to turkeys.

12.3.3 Nonprotein Nitrogen Poisoning

Poisoning by ingestion of excess urea or other sources of nonprotein nitrogen (NPN) is usually acute, rapidly progressive, and highly fatal. NPN is any source of nitrogen not present in a polypeptide (precipitable protein) form. Sources of NPN have

different toxicities in various species, but mature ruminants are affected most commonly. After ingestion, NPN undergoes hydrolysis and releases excess ammonia (NH_3) into the GI tract, which is absorbed and leads to hyperammonemia.

Ruminants are most sensitive, because urease is normally present in the functional rumen after 50 days of age. Dietary exposure of unacclimated ruminants to 0.3–0.5 g of urea/kg body weight may cause adverse effects; dosages of 1–1.5 g/kg are usually lethal. Urease activity in the equine cecum is ~25% that of the rumen, and horses may receive NPN as a feed additive; however, horses are more sensitive to urea than other monogastrics, and dosages ≥4 g/kg can be lethal. Ammonium salts at 0.3–0.5 g/kg may be toxic in all species and ages of farm animals; dosages ≥1.5 g/kg usually are fatal. Pigs and neonatal calves are generally unaffected by ingestion of urea except for a transient diuresis. Wild birds (silver gulls) reportedly have been poisoned after consuming water contaminated with urea fertilizer spillage.

A related CNS disorder in cattle fed ammoniated high-quality hay, silage, molasses, and protein blocks is thought to be caused by formation of 4-methylimidazole (4-MI) through the action of NH_3 on soluble carbohydrates (reducing sugars) in these feedstuffs. Cattle fed dietary components containing 4-MI develop a syndrome known as the "bovine bonkers syndrome," named for the wildly aberrant behavior exhibited. Signs relate to CNS effects, with stampeding, ear twitching, trembling, champing, salivating, and convulsions. Because nursing calves are affected, the toxic principle apparently is excreted in milk. Ammoniated low-quality forages do not have sufficient concentrations of reducing sugars to form 4-MI and thus serve as a relatively safe nitrogen source for acclimated animals.

Another related disorder involves accidental excessive exposure of ruminants (cattle and sheep) to raw soybeans. Soybeans have high concentrations of both carbohydrates and proteins, as well as urease. Overconsumption can cause acute carbohydrate fermentation and excessive ammonia release, resulting in ammonia toxicosis and lactic acidosis. Affected animals have engorged rumens with a gray, amorphous mass inside.

Toxicity The period from urea ingestion to onset of clinical signs is 20–60 min in cattle, 30–90 min in sheep, and longer in horses. Early signs include muscle tremors (especially of face and ears), exophthalmia, abdominal pain, frothy salivation, polyuria, and bruxism. Tremors progress to incoordination and weakness. Pulmonary edema leads to marked salivation, dyspnea, and gasping.

Horses may exhibit head pressing; cattle are often agitated, hyperirritable, aggressive, and belligerent as toxicosis progresses; sheep usually appear depressed. An early sign in cattle is ruminal atony; as toxicosis progresses, ruminal tympany is usually evident, and violent struggling and bellowing, a marked jugular pulse, severe twitching, tetanic spasms, and convulsions may be seen. As death nears, animals become cyanotic, dyspneic, anuric, and hyperthermic. Regurgitation may occur, especially in sheep. Death related to excess NPN usually occurs within 2 h in cattle, 4 h in sheep, and 3–12 h in horses. Survivors recover in 12–24 h with no sequelae.

Treatment Affected animals should be treated by ruminal infusion of 5% acetic acid (vinegar, in sheep, goats, and in cattle). Administration of cold water lowers the rumen temperature and dilutes the reacting media, which slows urease activity. In severely affected valuable animals, removed rumen contents should be replaced with a hay slurry, and a transfer of some rumen contents from a healthy animal may serve as an inoculum to restore normal function. Ruminal tympany should be corrected if indicated, and a trocar may be installed to prevent recurrence.

Supportive therapy such as IV isotonic saline solutions, IV calcium gluconate, and magnesium solutions to relieve tetanic seizures is advocated. Convulsions may also be controlled with sodium pentobarbital or other injectable anesthetic agents.

12.4 Questions and Answers

12.4.1 Short Questions and Answers

Exercise 1

Q.1. What kind of material is melamine?
Melamine resin or melamine formaldehyde (also shortened to melamine) is a hard, thermosetting plastic material made from melamine and formaldehyde by polymerization. In its butylated form, it is dissolved in n-butanol and xylene.

Q.2. Is melamine toxic?
Melamine is a widely used industrial chemical not considered acutely toxic with a high LD(50) in animals. The recent outbreak in infants showed that melamine ingested in large doses may cause stones and illness without significant ingestion of cyanuric acid or other melamine-related chemicals.

Q.3. What is nonprotein nitrogen?
Nonprotein nitrogen (or NPN) is a term used in animal nutrition to refer collectively to components such as urea, biuret, and ammonia, which are not proteins but can be converted into proteins by microbes in the ruminant stomach.

Q.4. Why nonprotein nitrogen is added in the animal diet?
Due to their lower cost compared to plant and animal proteins their inclusion in a diet can result in economic gain,

Q.5. Why ruminants are most sensitive to nonprotein nitrogen than other species?
Ruminants are most sensitive, because urease is normally present in the functional rumen after 50 days of age.

Q.6. What is “bovine bonkers syndrome,” in cattle?
Cattle fed dietary components containing high content of nonprotein nitrogen develop a syndrome known as the “bovine bonkers syndrome,” named for the wildly aberrant behavior exhibited. Signs relate to CNS effects,

with stampeding, ear twitching, trembling, champing, salivating, and convulsions.

Q.7. How does ammonia poisoning occur in animals?

It is caused by abrupt addition of feed-grade urea or ammonium salts to the ruminant diet. Mature ruminants are most susceptible, as they convert nonprotein nitrogen to ammonia, which is toxic. Toxic symptoms include muscle tremors, weakness, difficulty breathing, and death.

Q.8. Why the pH of the blood is acidic in urea poisoning?

Liver detoxification of ammonia to urea requires bicarbonate (HCO32), which depletes blood $HCO3^{-}$ buffer leading to acidosis. Blood pH changes from 7.4 to 7.0.

Q.9. What are fertilizers?

- A fertilizer is any material of natural or synthetic origin (other than liming materials) that is applied to soils or to plant tissues to supply one or more plant nutrients essential to the growth of plants.

Q.10. How fertilizers are extracted and purified from natural deposits?

- Many fertilizers are extracted and purified from natural deposits in the earth. Materials such as sulpomag, muriate of potash, and triple super phosphate are all produced from naturally occurring minerals

12.4.2 Multiple Choice Questions

Exercise 2

Q.1. The toxicity produced by excessive ingestion of urea in cattle is due to _____.

(a) Urea itself
(b) Ammonia
(c) Urea as well as ammonia

Q.2. Which of the following age group is more resistant to urea toxicity?

(a) Calf
(b) Heifer
(c) Bull
(d) Cow

Q.3. In ruminants, urea toxicosis is characterized by:

(a) **Ruminal alkalosis, systemic acidosis, and elevated blood ammonia levels**
(b) Ruminal acidosis, systemic alkalosis, and elevated blood ammonia levels
(c) Ruminal alkalosis, systemic alkalosis, and elevated blood ammonia levels
(d) Ruminal acidosis, systemic alkalosis, and decreased blood ammonia levels
(e) Ruminal alkalosis, systemic alkalosis, and elevated blood urea nitrogen levels

Q.4. Which of the following reason(s) contribute to the susceptibility of ruminants for urea poisoning?
(a) Urease present in plants
(b) Alkaline pH of rumen
(c) Acidic pH of stomach
(d) Urease activity of rumen

Q.5. Which of the following age group is more resistant to urea toxicity?
(a) Calf
(b) Heifer
(c) Bull
(d) Cow

Answers

Exercise 2

1. b.	4. a and b.
2. a.	5. a.
3. a.	

12.4.3 Fill in the Blanks

Exercise 3

Q.1. _____ is used in the production of melamine resins**.**
Q.2. Melamine is combined with _____ and other agents to produce melamine resins.
Q.3. Both melamine and cyanuric acid were relatively _____ when given individually.
Q.4. Horses are _____ to the toxic effects of ionophores in feed than cattle.
Q.5. Adult birds (chickens, turkeys, ratites) and birds with no previous exposure are more _____ to ionophore coccidiostats.
Q.6. After ingestion, nonprotein nitrogen undergoes hydrolysis and releases excess _____ into the GI tract.
Q.7. Nonprotein nitrogen (or NPN) which are not proteins can be converted into proteins by _____ in the ruminant stomach.
Q.8. Apart from dietary sources, animals get exposed to urea from _____.
Q.9. Excessive use of ammonium nitrate and urea fertilizers in plants can result in _____ poisoning in animals.
Q.10. Ammonia exerts its toxic effect by inhibition of _____.

Answers

Exercise 3

1. Melamine	6. Ammonia (NH3)
2. Formaldehyde	7. Microbes
3. Nontoxic	8. Fertilizers
4. More sensitive	9. Nitrate
5. Sensitive	10. Citric acid cycle

12.4.4 True or False Statements

Write (T) for true and (F) for false statement.

Exercise 4

Q.1. Melamine is also used in some fertilizers.
Q.2. Cyanuric acid is a structural analog of melamine.
Q.3. Melamine is used in the production of cyanuric acid, typically by reaction with formaldehyde.
Q.4. Cyanuric acid may be found as an impurity of melamine.
Q.5. Melamine and melanin are the same.
Q.6. Combination of melamine and cyanuric acid in diet is very safe.
Q.7. Ionophores are commonly added to ruminant feeds in increase milk production.
Q.8. Adult birds (chickens, turkeys, ratites) and birds with no previous exposure are resistant to ionophore coccidiostats.

Answers

Exercise 4

1. T.	5. F.
2. T.	6. F.
3. F.	7. F.
4. T.	8. F .

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Food Hazards

13

Abstract

This chapter is limited to a review of the food hazards as a result from accidental or deliberate consumption of large quantities of avocado, beard doughs, chocolate, macadamia nuts, xylitol, and raisins and grapes that represent significant risks to farm livestock and pet animals. Food safety hazards associated with animal feed can be biological, chemical, or physical. Each hazard is associated with particular sources and routes of contamination and exposure. Hazards may also be introduced with source materials or via carryover or contamination of products during handling, storage, and transportation. However, the role of water as a potential source of hazards should not be overlooked.

Keywords

Toxicity of avocado · Beard doughs · Chocolate · Macadamia nuts · Xylitol · Raisin and grape toxicity · Question and answer bank · Multiple choice questions

13.1 Introduction

This chapter is limited to a review of the food hazards as a result from accidental or deliberate consumption of large quantities of avocado, beard doughs, chocolate, macadamia nuts, xylitol, and raisins and grapes that represent significant risks to farm livestock and pet animals. Contamination of food or hazards associated with biological (microbial, plants, and animal sources), chemical (metal, pesticides, or environmental chemicals), or physical means has been discussed earlier under appropriate headings and in various chapters of this book, as related to their adverse effects in animals. This chapter also highlights the key points about the subject matter followed by sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true or false statements as relevant to food hazards in animals.

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Key Points

- Food safety hazards associated with animal feed can be biological, chemical, or physical.
- Each hazard is associated with particular sources and routes of contamination and exposure.
- The role of water as a potential source of hazards should not be overlooked.
- Hazards may be introduced with source materials or via carryover or contamination of products during handling, storage, and transportation.
- The presence of a hazard may also result from accidental or deliberate (e.g., fraud or bioterrorism) human intervention.
- Avocado causes necrosis and hemorrhage of mammary gland epithelium of lactating mammals and myocardial necrosis in birds and mammals.
- Chocolate is derived from the roasted seeds of *Theobroma cacao*. Chocolate poisoning occurs most commonly in dogs and may result in potentially life-threatening cardiac arrhythmias and CNS dysfunction.
- Unbaked yeast containing dough can result in multiple problems if a pet ingests it.
- Ingestion of macadamia nuts by dogs may lead to vomiting, ataxia, weakness, hyperthermia, and depression.

13.2 Avocado Poisoning

Ingestion of fruit, leaves, stems, and seeds of avocado (Fig. 13.1) has been associated with toxicosis in animals; leaves are the most toxic part. The Guatemalan varieties of avocado have been most commonly associated with toxicosis.

Toxic Principle Toxic principle in avocado is persin, a fungicidal toxin which is an oil-soluble compound structurally similar to a fatty acid (Fig. 13.2), and it leaches into the body of the fruit from the seeds.

Toxicity In general, non-lactating mammals, or at higher doses, myocardial insufficiency may develop within 24–48 h of ingestion and is characterized by lethargy, respiratory distress, subcutaneous edema, cyanosis, cough, exercise intolerance, and death. Horses may develop edema of the head, tongue, and brisket. Birds develop lethargy, dyspnea, anorexia, subcutaneous edema of the neck and pectoral regions, and may die. Goats and sheep develop severe mastitis and cardiac injury. Myocardial injury, mastitis, and colic have been reported in horses ingesting avocado fruit and/or leaves. In lactating mice, mastitis and myocardial necrosis have been observed.

Histopathologic lesions in the mammary gland include degeneration and necrosis of secretory epithelium, with interstitial edema and hemorrhage. Myocardial



Fig. 13.1 Avocado fruit and foliage. (https://upload.wikimedia.org/wikipedia/commons/thumb/f/f2/Persea_americana_fruit_2.JPG/220px-Persea_americana_fruit_2.JPG)

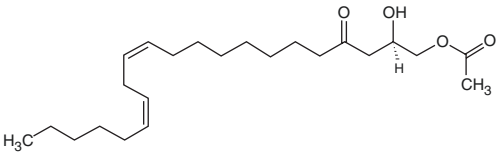


Fig. 13.2 Structure of persin

lesions include degeneration and necrosis of myocardial fibers, which are most pronounced in ventricular walls and septum; interstitial hemorrhage and/or edema may be present. In horses, symmetric ischemic myopathy of the head muscles and tongue, as well as ischemic myelomalacia of the lumbar spinal cord, has been described.

Treatment Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics may benefit animals with mastitis. Treatment for congestive heart failure (e.g., diuretics, antiarrhythmic drugs) may be of benefit but may not be economically feasible in livestock.

13.3 Chocolate Poisoning

Chocolate is derived from the roasted seeds of *Theobroma cacao*. Chocolate toxicosis may result in potentially life-threatening cardiac arrhythmias and CNS dysfunction. Chocolate poisoning occurs most commonly in dogs, although many species are susceptible. Contributing factors include indiscriminate eating habits and

readily available sources of chocolate. Deaths have also been reported in livestock fed cocoa by-products and in animals consuming mulch from cocoa bean hulls. Serious poisoning happens more frequently in domestic animals, which metabolize theobromine much more slowly than humans, and can easily consume enough chocolate to cause poisoning. The most common victims of theobromine poisoning are dogs, for which it can be fatal. The toxic dose for cats is even lower than for dogs However, cats are less prone to eating chocolate since they are unable to taste sweetness. Theobromine is less toxic to rats, mice, and humans.

Toxic Principle The primary toxic principles in chocolate are the methylxanthines theobromine (Fig. 13.3) (3,7-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine).

Toxicity Clinical signs of chocolate toxicosis usually occur within 6–12 h of ingestion. Initial signs may include polydipsia, vomiting, diarrhea, abdominal distention, and restlessness. Signs may progress to hyperactivity, polyuria, ataxia, rigidity, tremors, and seizures. Tachycardia, premature ventricular contractions, tachypnea, cyanosis, hypertension, hyperthermia, bradycardia, hypotension, or coma may occur. Hypokalemia may occur late in the course of the toxicosis, contributing to cardiac dysfunction. Death is generally due to cardiac arrhythmias, hyperthermia, or respiratory failure. The high fat content of chocolate products may trigger pancreatitis in susceptible animals. Hyperemia, hemorrhages, or congestion of multiple organs may occur as agonal changes. Severe arrhythmias may result in pulmonary edema or congestion.

Treatment Methocarbamol or diazepam may be used for tremors and/or mild seizures; barbiturates may be required for severe seizures. Arrhythmias should be treated as needed: propranolol or metoprolol for tachyarrhythmias, atropine for bradyarrhythmias, and lidocaine for refractory ventricular tachyarrhythmias. Fluid diuresis may assist in stabilizing cardiovascular function and hastening urinary excretion of methylxanthines.

Decontamination should be performed. Induction of emesis using apomorphine or hydrogen peroxide should be initiated; in animals that have been sedated because of seizure activity, gastric lavage may be considered. Activated charcoal should be administered; because of the enterohepatic recirculation of methylxanthines, repeated doses should be administered every 12 h in symptomatic animals for as long as signs are present. In addition, symptomatic treatment such as maintenance of thermoregulation, correcting acid-base and electrolyte abnormalities, monitoring cardiac status via electrocardiography, and placing a urinary catheter may be necessary.

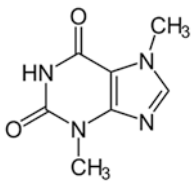


Fig. 13.3 Structure of theobromine

13.4 Beard Doughs

Ingestion of unbaked yeast containing dough can result in multiple problems in pets. The warm, moist environment of the stomach serves as an efficient incubator for the replication of yeast within the dough. The expanding dough mass causes the stomach to distend, resulting in vascular compromise to the gastric wall similar to that seen in gastric dilatation/volvulus. With sufficient gastric distention, respiratory compromise occurs. Yeast fermentation products include ethanol, which is absorbed into the bloodstream, resulting in inebriation and metabolic acidosis.

Toxicity As ethanol intoxication develops, the animal becomes ataxic and disoriented. Eventually, profound CNS depression, weakness, recumbency, coma, hypothermia, or seizures may be seen. Death is usually due to the effects of the alcohol rather than from gastric distention; however, the potential for dough to trigger gastric dilatation/volvulus in susceptible dog breeds should not be overlooked.

Treatment Induce vomiting if the dough was recently ingested. To stop the rising of the dough, a cold-water gastric lavage may be performed. Animals presenting with signs of alcohol toxicosis should be stabilized and any life-threatening conditions corrected before attempts to remove the dough are made. Alcohol toxicosis is managed by correcting acid-base abnormalities, managing cardiac arrhythmias as needed, and maintaining normal body temperature. Providing fluid diuresis to enhance alcohol elimination may be helpful. Anecdotally, yohimbine has been used to stimulate severely comatose dogs with alcohol toxicosis.

13.5 Macadamia Nuts

Macadamia is a genus of four species of trees indigenous to Australia and constituting part of the plant family Proteaceae. Macadamia nuts are cultivated from *Macadamia integrifolia* in the continental USA and *M. tetraphylla* in Hawaii and Australia. These species are commercially important for their fruit, the macadamia nut (Fig. 13.4). Other names include Queensland nut, bush nut, maroochi nut, bauple nut, and Hawaii nut.

Toxicity Clinical signs after ingestion of macadamia nuts by dogs have been associated with tremors that may be secondary to muscle weakness. Macadamia nuts may be identified in vomitus or feces. Syndrome characterized by vomiting, ataxia, weakness, hyperthermia, and depression.

Treatment Activated charcoal may be of benefit with large ingestions. Severely affected dogs may be given supportive treatment such as fluids, analgesics, or antipyretics.



Fig. 13.4 Macadamia nuts. (https://upload.wikimedia.org/wikipedia/commons/thumb/9/96/Macadamia_nuts_on_tree.JPG/220px-Macadamia_nuts_on_tree.JPG)

13.6 Xylitol

Xylitol, a sugar substitute used in sugar-free gum, oral care products, and baked goods, is gaining popularity. Xylitol consumption is considered harmless to people but is known to cause life-threatening toxicoses in dogs.

Toxicity Clinical signs of hypoglycemia include vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma. Signs of liver injury include depression, vomiting, icterus, and coagulopathy; other findings include hyperbilirubinemia, thrombocytopenia, and hyperphosphatemia. Not all dogs that develop xylitol-induced liver injury develop hypoglycemia.

Treatment Treatment includes dextrose supplementation for hypoglycemia and aggressive monitoring, treatment, and supportive care for dogs experiencing hepatotoxicosis.

13.7 Raisins and Grapes

Recently, veterinarians discovered that grapes, raisins, and currants (fruits from *Vitis* species) can cause kidney failure in dogs.

Toxicity The most common early symptom of grape or raisin toxicity is vomiting, which is generally seen within 24 h followed by ingestion, lack of appetite, lethargy, and possibly diarrhea which can be also seen within the next 12–24 h. Signs of acute kidney failure include nausea, lack of appetite, vomiting, uremic breath, diarrhea, abdominal pain, excessive thirst, and excessive urination.

As the poisoning progresses, the kidneys may shut down and the dog will not produce any urine. Following this, the dog's blood pressure will increase dramatically and the dog will usually lapse into a coma. Once the kidneys have shut down and urine output has dropped, the prognosis is poor.

Treatment There is no antidote. The goal of treatment is to block absorption of the toxins and prevent or minimize damage to the kidneys. As grapes and raisins stay in the stomach for a prolonged period of time, inducing vomiting is of the utmost importance (even up to 4–6 h after ingestion). Decontamination and use of aggressive intravenous fluids to flush any absorbed toxins out of the body as quickly as possible help to maintain kidney function, and symptomatic treatment will be useful.

13.8 Questions and Answers

13.8.1 Short Questions

Exercise 1

Q.1. What is food poisoning?
Food poisoning is a vague term. It includes illnesses resulting from ingestion of all foods containing nonbacterial or bacterial products. The nonbacterial products include poisons delivered from plants and animals, and certain naturally occurring toxins. Foods containing such products are, by convention, known as poisonous foods.

Q.2. What is toxic type of food poisoning?
In toxic type, the food poisoning results from poisonous substances produced by multiplying organisms that have gained access to the prepared food, e.g., enterotoxin produced by the *Staphylococcus*.

Q.3. How much chocolate can a dog eat without dying?
Chocolate can be very toxic to your dog—but the amount and type of chocolate matters a lot. For example, Baking chocolate: Approximately 0.5 ounce for a 10-pound dog, 1 ounce for a 20-pound dog, and 1.5 ounces for a 30-pound dog. Dark chocolate: Approximately 1.5 ounces for a 10-pound dog, 3 ounces for a 20-pound dog, and 4.5 ounces for a 30-pound dog.

Q.4. Can cats eat chocolate?
No. Chocolate is very toxic to cats because it contains theobromine, a toxic substance. Chocolate can accelerated heart rate, and can lead to diarrhea, vomiting, coma, and death.

Q.5. What does chocolate contain?
Chocolate contains; milk powder, cacao butter, sugar, milk, flavonoids, alkaloids such as theobromine, phenethylamine, and caffeine.

Q.6. How long does it take for a dog to get sick from chocolate?
Signs of chocolate poisoning usually appear within 6–12 h. and may last up to 72 h; clinical signs include vomiting, diarrhea, and restlessness.

Q.7. Why is chocolate toxic to dogs but not humans?
The toxic component of chocolate is theobromine. Humans easily metabolize theobromine, but dogs process it much more slowly, allowing it to build up to toxic levels in their system. A small amount of chocolate will probably only upset stomach with vomiting or diarrhea.

Q.8. What does beard doughs contain?
Homemade and store-bought unbaked dough contains yeast (used for bread, dinner rolls, etc.).

Q.9. What are macadamia nuts good for?
Macadamia nuts contain 78 to 86 percent of the fat that is monounsaturated (good for heart). Monounsaturated fat helps lower cholesterol and decreases risk of heart disease and stroke.

Q.10. Are macadamia nuts and hazelnuts the same?
Sometimes called filberts or cobnuts, hazelnuts originated in Asia, while macadamias hail from Australia. Hazelnuts are a true nut in the botanical sense, while macadamias should really be classified as a seed. Their flavors are similar, with the taste of a hazelnut resembling a cross between almonds and macadamias.

Q.11. What types of grapes and raisins are toxic to dogs?
Poisoning has occurred in dogs following ingestion of seedless or seeded grape varieties, commercial or homegrown fruits, red or green grapes/raisins, organic or non-organic fruits, and grape pressings from wineries. Foods containing grapes, raisins, and currants (such as raisin bran cereal, trail mix, granola mix, baked goods) are all potential sources of poison.

Q.12. Why are raisins, grapes, and currants toxic?
Currently, it is not known why these fruits are toxic. Some researchers suspect that a mycotoxin (a toxic substance produced by a fungus or mold) may be the cause. Some suspect a salicylate (aspirin-like) drug may be naturally found in the grape, resulting in decreased blood flow to the kidneys. However, so far no toxic agent has been identified. Since it is currently unknown why these fruits are toxic, any exposure should be a cause for concern.

Q.13. Is there an antidote for raisin or grape toxicity?
No

Q.14. What do you mean by food hazards?
Hazard is defined as any biological, chemical (including radiological), or physical agent that has the potential to cause illness or injury in humans or animals. Biological hazards in animal food may include *Salmonella* spp. and *Listeria monocytogenes*.

13.8.2 Multiple Choice Questions

Exercise 2

Q.1. How can you tell if food has enough bacteria to cause food poisoning?
(a) It will smell.
(b) You cannot, it will appear normal.
(c) It will have a different color.
(d) It will taste different.

Q.2. The following feedstuff supports growth of aflatoxins:
(a) Groundnut cake
(b) Soybean cake
(c) Cotton seed meal
(d) All

Q.3. The concepts of "de minimis" as applied to food safety means --
(a) To find the smallest harmful dose.
(b) Only food colors 1/100 of the no-observed adverse-effect level (NOAEL) can be used.
(c) Pesticide residues can be present at the acceptable daily intake (ADI).
(d) The risk is so small it is of no concern.

Q.4. The primary reason for adding nitrates and nitrites to food is to --
(a) Prevent the growth of *C. botulinum*
(b) Give the meat a characteristic flavor
(c) Turn the meat a brown-red color
(d) Sweeten the food product

Q.5. Which of the following chemicals in food can cause significant neurological complications (may choose more than one)?
(a) Mercury
(b) Lead
(c) Cadmium
(d) Antimony

Q.6. Of those listed below, which is not a food-borne pathogen?
(a) Lectins
(b) Nematodes
(c) Bacteria
(d) Protozoans

Q.7. Where should raw meat be stored in a refrigerator?
(a) At the top
(b) In the middle
(c) At the bottom, below all other food

Q.8. What is the ideal temperature for pathogens to flourish?
(a) 10--°C
(b) 37--°C
(c) 55--°C
(d) 90--°C

Q.9. Which of the following is true about bacteria?
(a) Bacteria multiplies and grows faster in warm environments.
(b) Bacteria needs air to survive.
(c) Every type of bacteria can give people food poisoning.
(d) By freezing food you can kill bacteria.

Q.10. What is the correct temperature that frozen food should be kept at?
(a) 0-°C
(b) 15-°C or lower
(c) 18-°C or lower
(d) 20-°C or lower

Q.11. Which clinical sign in small animals is NOT caused by chocolate?
(a) Liver necrosis
(b) CNS stimulation (seizure)
(c) Tachycardia
(d) Vasoconstriction
(e) Vomiting

Answers

Exercise 2

1.b	7. c
2. d	8. b
3. d	9. a
4. a	10. c
5. a and b	11. a
6. a	

13.8.3 Fill in the Blanks

Exercise 3

Q.1. Toxic principle in avocado is _____.
Q.2. _____ varieties of avocado have been most commonly associated with toxicosis. Guatemalan
Q.3. Animal studies show that exposure to persin leads to _____ in certain types of _____. Apoptosis, breast cancer cells
Q.4. Persin is an oil-soluble compound structurally similar to a _____. fatty acid
Q.5. Chocolate is derived from the roasted seeds of _____. *Theobroma cacao*
Q.6. After high intake of avocado, goats and sheep develop severe _____ and _____. mastitis and cardiac injury
Q.7. The most common victims of theobromine poisoning are _____. dogs

Q.8. Domestic animals metabolize theobromine _____ than humans. slowly
Q.9. Molds generally grow in stored feedstuffs containing a moisture content more than _____.
Q.10. The maximum permitted level of zearalenone in feed is _____.

Answers

Exercise 3

1. Persin	6. Mastitis, cardiac injury
2. Guatemalan	7. Dogs
3. Apoptosis, breast cancer cells	8. Slowly
4. Fatty acid	9. 15%
5. *Theobroma cacao*	10. 10 ppb

13.8.4 True or False Statements

Write (T) for true and (F) for false statement.

Exercise 4

Q.1. Toxic principle in avocado is Ricin.
Q.2. Cows and goats are resistant to avocado toxicity.
Q.3. Chocolate is derived from the roasted seeds of castor plant.
Q.4. Methylxanthines in chocolate vary because of the natural variation of cocoa beans and variation within brands of chocolate products.
Q.5. Unbaked yeast containing bread dough is safe, if a pet ingests it.
Q.6. Theobromine (3,7-dimethylxanthine) is more safe than caffeine.
Q.7. Diazepam is contraindicated in poisoning by chocolate.
Q.8. Xylitol is also known as xylene.
Q.9. Theobromine is less toxic to rats, mice, and humans.
Q.10. HACCP is used to assess hazards by following the flow of foods.

Answers

Exercise 4

1. F	6. F
2. F	7. F
3. F	8. F
4. T	9. T
5. F	10. T

Further Reading

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Veterinary Drug Residue Hazards

14

Abstract

This chapter is limited to a review of the result of veterinary drugs and other chemicals in food-producing animals. Use of veterinary drug has the potential to generate residues in animal-derived products (meat, milk, eggs, and honey). In addition, degradation products, which are the result of the medicine breaking down into its component parts, also pose a health hazard to the consumer because these residues that remain in animal products make their way into the food chain. The major public health significances of drug residue include (a) development of antimicrobial drug resistance; (b) hypersensitivity reaction; (c) carcinogenicity, mutagenicity, and teratogenicity; and (d) disruption of intestinal normal flora. The residual amount ingested is in small amounts and may not necessarily be toxic.

Keywords

Veterinary drug residues · Public health · Antimicrobial drug resistance · Hypersensitivity reactions · Question and answer bank · Multiple choice questions

14.1 Introduction

The scope of this chapter is limited to a review of the result of veterinary drugs and other chemicals in food-producing animals. Use of veterinary drug has the potential to generate residues in animal-derived products (meat, milk, eggs, and honey) and poses a health hazard to the consumer. Contamination of food and feed or hazards associated with biological (microbial, plants, and animal sources), chemical (metal, pesticides, or environmental chemicals), or physical means has been discussed earlier under appropriate headings and in various chapters of this book. This chapter also highlights the key points about the subject matter and a few sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, and true/false statements as relevant to use of veterinary drugs.

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Key Points

- Tissue residue is the concentration of a chemical or compound in an organism's tissue or a portion of an organism's tissue.
- Tissue residue is also used in aquatic toxicology to help determine the fate of chemicals in aquatic systems, bioaccumulation of a substance, bioavailability of a substance, account for multiple routes of exposure (ingestion, absorption, inhalation), and address an organism's exposure to chemical mixtures.
- A tissue residue approach to toxicity testing is considered a more direct and less variable measure of chemical exposure and is less dependent on external environmental factors than measuring the concentration of a chemical in the exposure media.
- Tissue residue approaches are used for chemicals that bioaccumulate or for bioaccumulative chemicals.
- The organic compounds that are not easily metabolized by organisms and have long environmental persistence also leave residues in tissues such as polychlorinated dibenzodioxins, furans, biphenyls, DDT and its metabolites, and dieldrin.
- Veterinary drug residues are the very small amounts of veterinary medicines that can remain in animal products and therefore make their way into the food chain. These include any degradation products, which are the result of the medicine breaking down into its component parts.

14.2 Background

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal-derived products (meat, milk, eggs, and honey) and poses a health hazard to the consumer. Illegal drug residues in the nation's food supply are a concern to the Food and Drug Administration of each and every country. In the USA the Center for Veterinary Medicine's Division of Compliance is responsible for reviewing violative residues reported to the Agency by the USDA's Food Safety and Inspection Service. Preventing illegal drugs in the nation's food supply is important to everyone. The occurrence of residues in animal products are influenced by many factors that include:

(a) Drug's properties and their pharmacokinetic characteristics
(b) Physicochemical properties
(c) Biological processes of animals and their products

The most likely reason for drug residues might be due to improper drug usage and failure to keep the withdrawal period.

14.3 Public Health Significances

The major public health significances of drug residue include:

(a) Development of antimicrobial drug resistance
(b) Hypersensitivity reaction
(c) Carcinogenicity, mutagenicity, teratogenicity
(d) Disruption of intestinal normal flora

The residual amount ingested is in small amounts and not necessarily toxic. However, there is limited information on the magnitude of veterinary drug residue worldwide. Hence, an extensive work has to be carried out to determine the magnitude of the problem, to prevent the occurrence of veterinary drug residues, and to familiarize all animal health professionals with the knowledge of pharmacokinetics, pharmacodynamics, and toxicological effects of veterinary drugs to minimize the potential public health hazards due to drug residues in food of animal origin. The most common definitions relevant to drug residues include:

Maximum Residue Limits Maximum residue limit or maximum residue level/tolerance (MRL) is the maximum amount of a pesticide or drug (mainly veterinary pharmaceuticals) residue that is legally permitted or recognized as acceptable in or on food commodities and animal feeds. Although both the terms have the same meaning, in practice the term maximum residue limit is used for the pesticide residue, while the term maximum residue level is applicable for the drug residue.

Withdrawal Symptom The unpleasant physical reaction that accompanies the process of ceasing to take an addictive drug is known as withdrawal symptom.

Or

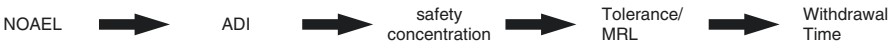
Abnormal physical or psychological features that follow the abrupt discontinuation of a drug that has the capability of producing physical dependence is called withdrawal symptom. For example, common opiates withdrawal symptoms include sweating, goose bumps, vomiting, anxiety, insomnia, and muscle pain.

The scientific advice developed by JMPR and JECFA aims to provide maximum residue levels for individual crops and plant and animal products, based on the results of scientific studies, so that these levels can be used by the relevant Codex committee to develop the draft MRLs, which may be adopted by the Codex Alimentarius Commission (CAC).

14.4 Withdrawal Times

Withdrawal times (periods) for meat and milk reflect the amount of time necessary for an animal to metabolize an administered product and the amount of time necessary for the product concentration level in the tissues to decrease to a safe, acceptable level. Every federally approved drug or animal health product has a withdrawal period printed on the product label or package insert.

The following steps are involved in setting withdrawal times:



- No-observed-adverse-effect level (NOAEL) is established in animals for the drug in question.
- Average daily intake (ADI) values are determined.

$$\text{ADI} = \left(\text{NOAEL} / 1000\right) \times \text{Ave.Body weight}$$

(ADI = Total dose of a drug that an average human can ingest on daily basis for entire life with no adverse effect)

- Safe concentration is arrived by dividing ADI with the amount of edible organ which is generally consumed in a day (e.g., muscle 300 g; liver 100 g). Safe concentration includes all metabolites of a drug.

$$\text{Safe concentration} = \text{ADI} / 300\left(\text{for muscle}\right)\text{ADI} / 100\left(\text{for liver}\right)$$

A marker residue which is sensitive and easy for detection is chosen (Parent compound or any of its metabolite).

- Tolerance level/maximum residue level is ascertained through estimation of marker residue. Tolerance (MRL) = the % of safe concentration represented by the marker residue.
- Studies are performed to know the time at which the target tissue is below tolerance, which is called withdrawal time. Withdrawal times apply only when the drug is used according to label instructions. The tolerance for extra label use of a drug is zero.
- Withdrawal times are applicable only when the drug is used according to label instructions. The tolerance for extra label use of a drug is zero (i.e., detection of extra label drug at any level leads to rejection of the product).

14.5 Questions and Answers

14.5.1 Short Questions

Exercise 1

Q.1. Who sets the withdrawal times and levels for drug residues in animal's products in the USA?

The Center for Veterinary Medicine (CVM) of Food and Drug Administration (FDA) sets the withdrawal times and limits for approved food animal drugs.

Q.2. Who sets the withdrawal times and limits for pesticide residues in animal's products in the USA?
In the USA, the Environmental Protection Agency (EPA) sets the withdrawal times and limits for pesticide residues in plant and animal products.

Q.3. How withdrawal time can be extrapolated from pharmacokinetic parameters?
Withdrawal time = $10 \times T_{1/2}$ ($T_{1/2}$ = half-life of the drug)

Q.4. What is the difference between "maximum residue level" and "maximum residue limit"?
"Maximum residue level" is used for drugs, whereas "maximum residue limit" is used for pesticides.

Q.5. What are the techniques used for detection of residues in foods?
Techniques such as ELISA, HPLC, LC, GC, paper chromatography

Q.6. What are the general classes of veterinary drugs that are found in animal products as residues?
The general classes of veterinary drugs found in animal products are antimicrobials, anti-inflammatory, growth promoters, anti-parasitic and insecticides, and tranquilizers.

Q.7. Which is the most common type of drug residue in animal products?
Antibiotics are the most frequently found drug residues followed by anti-inflammatory drugs.

Q.8. What are the hazards of drug residues in animal products?
The hazards of drug residues in animal products are as follows:

(a) Aesthetic issues: The presence of drugs in animal is not appealing for consumer.
(b) Allergic reactions: Certain drug residues like penicillin can cause allergic reaction in sensitive individuals at a level of 10 IU (0.6 μg).
(c) Development of antibiotic resistance in microorganisms.
(d) Direct toxic effects—cancer, reproductive and developmental effects. For example,
    (i) Clenbuterol residues were reported to have caused tachycardia, muscle tremor, headache, nausea and fever, and chills in humans.
    (ii) Furazolidone and its metabolites are banned by US FDA as they were reported to cause cancer in humans.
(e) Deleterious effects of hormone residues in humans. For example,
    (i) Diethylstilbestrol (DES): Vaginal clear cell adenocarcinoma in female offsprings exposed in utero; structural abnormalities of the uterus.
    (ii) International export barriers: Export of animal products need to comply with international standards for drug residues.

Q.9. In which type of animal drug residues are common?
Drug residues are most commonly found in dairy cattle (43%) followed by beef cattle (17%).

Q.10. What are the measures to be taken to prevent residues in animal products?
Measures to prevent drug residues include:

- Education of veterinary personnel, organizations, and government agencies involved in animal production
- Development of rapid screening methods for field use
- Avoiding irrational use of drugs in animals
- Processing of animal products, e.g., refrigeration completely destroys penicillins and pasteurization
- Causes loss of activity of most of the antibiotics
- Nationwide monitoring and surveillance for drug residues

14.5.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. A concentration of 0.01% is equivalent to how many parts per million (ppm)?
(a) 1 ppm
(b) 10 ppm
(c) 100 ppm
(d) 1000 ppm
(e) 10,000 ppm

Q.2. Heterocyclic amines and acrylamide are food contaminants which
(a) Are produced by microorganisms
(b) Are produced by the process of cooking
(c) Are considered as GRAS
(d) Are residues from animal feeds

Q.3. The concepts of "de minimis" as applied to food safety means
(a) Find the smallest harmful dose.
(b) Only food colors 1/100 of the no-observed-adverse-effect level (NOAEL) can be used.
(c) Pesticide residues can be present at the acceptable daily intake (ADI).
(d) The risk is so small it is of no concern.

Q.4. Which category of insecticidal compounds presents a problem of persistent residues in fatty tissues of animals?
(a) Carbamates
(b) Organochlorines
(c) Organophosphates
(d) Pyrethrins
(e) Juvenile hormones

Q.5. The most common type of drug residue in animal products is_____
(a) Antibiotic
(b) Metal
(c) Aflatoxin
(d) None

Answers

Exercise 2

1. c	4. b
2. b	5. a
3. d	

14.5.3 Fill in the Blanks

Exercise 3

Q.1. Heterocyclic amines and acrylamide are food contaminants which are produced by the process of _____.
Q.2. Category of insecticidal _____ compounds that presents a problem of persistent residues in fatty tissues of animals.
Q.3. The tolerance for extra label use of a drug is _____.
Q.4. Maximum acceptable/permitted amount of a drug present in feed and foods is known as _____.
Q.5. The highest dose of a compound which produces adverse effects but no mortality is called _____.

Answers

Exercise 3

1. Cooking	4. Maximum residue level (MRL) (for pesticides—maximum residue limit)
2. Organochlorines	5. Maximum tolerated dose or minimum toxic dose (MTD)
3. Zero	

14.5.4 True or False Statements

Write (T) for true and (F) for false statement.

Exercise 4

Q.1. The major public health significances of drug residue help in better growth.
Q.2. Safe concentration is arrived by dividing ADI with the amount of edible organ which is generally consumed in a day.
Q.3. The tolerance for extra label use of a drug is zero.

Q.4. Withdrawal time can be extrapolated from area under curve calculated from pharmacokinetic studies.
Q.5. Pesticides are the most frequently found drug residues followed by anti-inflammatory drugs. False
Q.6. Drug residues do not cause any allergic reaction in sensitive individuals.

Answers

Exercise 4

1. False	4. False
2. True	5. False
3. True	6. False

Further Reading

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Veterinary Clinical Toxicology

15

Abstract

The purpose of this chapter is to briefly describe veterinary clinical toxicology that combines the disciplines diagnostic toxicology, analytical chemistry, and prevention and treatment. Therefore, the answer is deceptively a simple question, did a chemical make an animal sick or kill it, and if so, which chemical? This seemingly simple question may be extremely challenging to answer because chemical testing is often required to confirm the diagnosis. For diagnosis of toxicosis, circumstantial evidence, history, clinical signs, lesions, laboratory examinations, and, in some cases, analytical procedures are valuable but do not replace a thorough clinical and postmortem examination. The most critical samples to be collected are generally stomach contents, liver, kidney, whole blood, plasma/serum, and urine, but exceptions exist, such as cerebral tissue for cholinesterase analysis. Prevention and treatment needs lifesaving measures using other measures such as prevention of further poison absorption, enhancement of poison elimination, supportive treatment, and specific antidote.

Keywords

Veterinary clinical toxicology · Diagnosis of toxicosis · Circumstantial evidence · Laboratory examinations · Analytical procedures · Treatment · Antidote · Question and answer bank · Multiple coice questions

15.1 Introduction

The purpose of this chapter is to briefly describe veterinary clinical toxicology that combines the disciplines diagnostic toxicology, analytical chemistry, and prevention and treatment. Therefore, the answer is deceptively a simple question, did a chemical make an animal sick or kill it, and if so, which chemical? This seemingly simple question may be extremely challenging to answer because chemical testing is often required to confirm the diagnosis. This chapter also highlights the key points

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about the subject matter and a few sample questions and answers that are in the format of short questions, multiple choice questions, fill in the blanks, true/false, and match the statements as relevant to the topic.

Key Points

- Veterinary clinical toxicology combines the disciplines diagnostic toxicology, analytical chemistry, and prevention and treatment.
- For diagnosis of toxicosis, circumstantial evidence, history, clinical signs, lesions, laboratory examinations, and, in some cases, analytical procedures are valuable but do not replace a thorough clinical and postmortem examination.
- Circumstantial evidence is valuable and should be noted but does not replace a thorough clinical and postmortem examination.
- Analytical procedure requires the detection, identification, and measurement of foreign compounds such as chemicals, pesticides, pharmaceuticals, drugs of abuse, natural toxins, etc. in biological and other specimens.
- Proper sample submission is critical to a successful toxicological analysis. Improper sample submission can jeopardize the process and cause erroneous results.
- The most critical samples to be collected are generally stomach contents, liver, kidney, whole blood, plasma/serum, and urine, but exceptions exist, such as cerebral tissue for cholinesterase analysis.
- Prevention and treatment needs lifesaving measures using other treatments for toxicosis such as prevention of further poison absorption, enhancement of poison elimination, supportive treatment, and specific antidote.

15.2 Diagnosis of Toxicosis

Diagnosis of a toxicosis, as with any disease, includes:

(a) History
(b) Clinical signs,
(c) Lesions,
(d) Laboratory examinations, and in some cases, analytical procedures.

Circumstantial evidence is valuable and should be noted but does not replace a thorough clinical and postmortem examination. Histories from animal owners may stress obvious factors and omit subtle, important details. “Sudden death” is often actually “tardy observation,” or sometimes the animal is simply found dead.

Pertinent data and samples should be submitted to the diagnostic laboratory. A complete history is necessary to develop the scheme of laboratory investigation and may be valuable in case of litigation. Information should be detailed. For example, a notation of CNS signs is insufficient; most animals exhibit some type of CNS signs before death. Exact actions and signs should be described. Examples of pertinent information include the following:

(a) Number of animals exposed/sick/dead, age, weight, and a chronology of morbidity and mortality.
(b) Clinical signs and course of the disease.
(c) Any prior disease conditions.
(d) Lesions seen at necropsy, with careful examination of ingesta.
(e) Response to treatment (medication should be listed to avoid analytic confusion).
(f) Related events, e.g., feed change, water source, other medications, feed additives, pesticide applications.
(g) Description of facilities (a drawing or digital photograph may be helpful), access to refuse, machinery, etc.
(h) Recent past locations and when moved. The diagnostic laboratory should be contacted if there are questions regarding the appropriate sample, amount, or container.

15.2.1 Collection of Samples

The toxicologist may also perform tests in the laboratory that is subject to frequent changes as better tests become available. The increasing availability of tests based on analytical procedures typically requires some type of sample preparation (which can be quite complex) prior to the actual analysis. Each veterinary diagnostic laboratory offers a unique set of diagnostic tests on newer molecular biology techniques is an excellent example of this trend. The protocols for sample collection and submission are therefore also subject to change. The practitioner and diagnostic laboratory staff *must* maintain good communication to complete their diagnostic efforts efficiently and provide optimal service to the client. Practitioners must be specific and clear in their test requests. The laboratory staff can provide guidance when there are questions regarding sample collection and handling, as well as offering assistance in interpretation of test results. The laboratory must also have a means of maintaining records of sample receipts and of reporting the results of the analyses. These chores are typically handled by a computer system known as Laboratory Information Management Systems, commonly abbreviated as "LIMS."

Most diagnostic laboratories publish user guidelines with preferred protocols for sample collection and submission.

15.2.2 Procedure for Submission of Samples

Regardless of the type of submission, a detailed case history should be included with the samples to assist laboratory personnel in determining a diagnosis. The information should include owner, species, breed, sex, age, animal identification, clinical signs, gross appearance (including size and location) of the lesion(s), previous treatment (if any), time of recurrence from any previous treatment, and morbidity/mortality in the group. If a zoonotic disease is suspected, this should also be clearly indicated on the submission form to alert laboratory personnel.

Proper sample submission is critical to a successful toxicological analysis. Improper sample submission can jeopardize the process and cause erroneous results. The components of proper sample submission are:

(a) Choice of appropriate test sample
(b) Ideal sample size
(c) Appropriate packaging
(d) Ideal shipping conditions
(e) Paperwork complete with history, clinical signs, clinical chemistry, feed labels, necropsy reports, or any other pertinent information

Proper fresh or frozen tissue samples should be submitted for the analysis. Whole blood should be kept refrigerated. Please strictly follow the guidelines for sample volume/size and shipping conditions specified in the available tests section of the VDL (Veterinary Diagnostic Laboratory), CD, or website. Some poisons are volatile at room temperature, while others are metabolized and lost if not packaged properly.

15.2.3 Samples for Toxicology Examination

If a known toxin is suspected, a specific analysis should always be requested—laboratories cannot just "check for poisoning." A complete description of clinical and epidemiologic findings may help differentiate poisoning from infectious diseases that can simulate poisoning. The most critical samples to be collected are generally stomach contents, liver, kidney, whole blood, plasma/serum, and urine, but exceptions exist, such as cerebral tissue for cholinesterase analysis (Table 15.1). For some investigations, the diagnosis requires analysis of like water, feed or food, bait, fence posts, animal bedding, nuts, coins, riverbed sediments, etc.

Chemical Analysis Tissues or fluids should be refrigerated. For some analyses, freezing is critical to prevent degradation of volatile chemicals, and in rare instances a chemical preservative is required.

Legal Action/ Forensic Sample All containers for shipment should be either sealed so that tampering can be detected or hand-carried to the laboratory and a receipt obtained. The chain of custody must be accurately documented.

Table 15.1 Guidelines for submitting samples for toxicologic examination

Suspected Poison or Analysis	Specimen Required	Comments
Ammonia	Whole blood or serum Urine Rumen contents	Frozen Frozen Frozen (or may add 1–2 drops saturated $HgCl_3$)
Anticoagulants (warfarin and related compounds)	Whole blood Liver Feed Stomach contents	Heparin or EDTA Refrigerated
Arsenic	Liver, kidney, urine, ingesta, feed	
Chlorates	Stomach contents Urine Feed	Frozen, in airtight container
Chlorinated hydrocarbons	Cerebrum Ingesta Body fat Liver Kidney	Use only glass containers Avoid contamination Refrigerated or frozen
Cholinesterase	Serum Cerebrum	Frozen
Copper (and Ni, Fe, Co, Cr, and Tl)	Kidney, liver, serum, feed, whole, blood, feces	
Cyanide	Forage, whole blood, liver	Rush to laboratory or ship promptly, frozen in airtight container
Dicoumarol	Forage, liver	
Ethylene glycol	Serum Urine Kidneys	Fresh plus fixed in formalin
Fluorides	Bone Water Forage Urine	Best to send affected bone(s)
Herbicides (many)	Treated weeds, urine, ingesta, liver, or kidney	
Ionophores	Feed Rumen contents Heart Skeletal muscle	Fixed in formalin Fixed in formalin
Lead (also Hg, Mo, Ni, and Tl)	Whole blood Kidney, liver, urine	Heparinized blood is preferred
Mercury and molybdenum	Whole blood Kidney, liver, feed	Heparinized blood is preferred
Mycotoxins	Grain, forages Liver, kidney	Laboratory personnel may advise for specific tests
Nitrate	Forage Water Body fluids (e.g., aqueous humor)	Refrigerated

(continued)

Table 15.1 (continued)

Suspected Poison or Analysis	Specimen Required	Comments
Organophosphates (and carbamates)	Feed Ingesta Urine	Samples of urine, blood, and stomach contents from clinically normal animals are also required
Oxalates	Fresh forage Kidney	Do not macerate; freeze Fixed in formalin
Phenols	Gastric or rumen contents	In airtight container
Polychlorinated (and polybrominated) biphenyls	Fat, cerebrum, feed	
Rumen pH	Ingesta	Frozen
Selenium	Whole blood Feed	Heparinized
Sodium (NaCl)	Brain, serum, CSF, feed	Other half fixed in formalin
Sodium fluoroacetate (1080)	Stomach contents Liver	Frozen
Strychnine (and some other convulsants such as bromethalin)	Liver, kidney, stomach contents	
Sulfates	Water Brain	Fixed in formalin
TDS (total dissolved solids)	Water	
Triaryl-PO4	Ingesta Feed	
Urea	Feed	Frozen
Vitamin A (also D and E)	Liver Serum	Frozen
Vitamin D_3 (rodenticides)	Kidney	
Zinc	Liver Kidney Serum	Use “trace minerals” tubes
Zinc phosphide	Liver Gastric contents	Frozen

Feed or Water If at all possible, a representative composite sample of the feed should be submitted from the suspect lot or shipment. In some instances, if an adequate amount of involved feed is available, some of it may be fed to experimental animals in an effort to reproduce the signs and lesions seen in the field cases.

15.2.4 Analytical Methods in Toxicology

Analytical toxicology is the detection, identification, and measurement of foreign compounds (xenobiotics) in biological and other specimens. Analytical methods are available for a very wide range of compounds: these may be chemicals, pesticides, pharmaceuticals, drugs of abuse and feeds, fodder, water, tissues, blood, urine, or natural toxins.

Analytical toxicology can assist in the diagnosis, management, prognosis, and prevention of poisoning. In addition, analytical toxicology laboratories may be involved in a range of other activities such as the assessment of exposure following chemical incidents, therapeutic drug monitoring, forensic analyses, and monitoring for drugs of abuse. They may also be involved in research, for example, in determining the pharmacokinetic and toxicokinetic properties of substances or the efficacy of new treatment regimens. Analytical procedures typically require some type of sample preparation (which can be quite complex) prior to the actual analysis. The analysis may be complicated by the normal chemical changes that occur during the decomposition of a cadaver. The autopsy and toxicologic analysis should be started as soon after death as possible. However, many poisons—such as arsenic, barbiturates, mercury, and strychnine—are extremely stable and may be detectable many years after death.

Forensic toxicology laboratories analyze specimens by using a variety of analytical procedures. Initially, nonspecific tests designed to determine the presence or absence of a class or group of analytes may be performed directly on the specimens. Examples of tests used to rapidly screen urine are the FPN (ferric chloride, perchloric and nitric acid) color test or phenothiazine drugs and immunoassays or the detection of amphetamines, benzodiazepines, and opiate derivatives, among others. Today, gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) are the most widely applied methodology in toxicology and are generally accepted as unequivocal identification of all drugs. The details of analytical procedures used for toxicology analysis of samples are beyond the scope of this chapter.

15.3 Principles of Therapy

At initial examination, certain immediate, lifesaving measures may be needed. Beyond this, treatment for toxicosis includes four basic principles:

(a) Prevention of further poison absorption
(b) Enhancement of poison elimination
(c) Supportive treatment
(d) Specific antidote

15.3.1 Prevention of Further Poison Absorption

During the early phases of poison treatment or intervention or a toxic exposure via the dermal (topical), oral, or inhalational route, a significant opportunity exists to prevent further absorption of the poison by minimizing the total amount that reaches the systemic circulation.

Topically applied toxicants usually can be removed by thorough washing with soap and water; clipping of the hair or wool may be necessary. Emesis is of value in dogs, cats, and pigs if done within a few hours of ingestion. Emesis is contraindicated when the swallowing reflex is absent; the animal is convulsing; corrosive

agents, volatile hydrocarbons, or petroleum distillates are involved; or risk of aspiration pneumonia is imminent. Oral emetics include syrup of ipecac and hydrogen peroxide. Apomorphine can be used parenterally in dogs.

Gastric lavage, using an endotracheal tube and the largest bore stomach tube possible, is done on the unconscious or anesthetized animal. The head is lowered to a 30° angle, and 10 mL of lavage fluid (water or saline) per kg of body weight is gently flushed into the stomach and then removed. This process is repeated until returned fluid is clear. A gastrotomy or rumenotomy may be necessary when lavage techniques are insufficient (or too slow in ruminants).

When the toxicant cannot be physically removed, certain agents administered orally can adsorb it and prevent its absorption from the alimentary tract. Activated charcoal effectively adsorbs a wide variety of compounds and usually is the adsorbent and detoxicant of choice when toxicosis is suspected. Sorbitol is sometimes added to activated charcoal to increase its palatability (in people) and to increase the GI transit time and flush out charcoal-bound toxins more rapidly. Activated charcoal should not be used in animals with known hypersensitivity or allergy to the drug. With administration of high doses, vomiting, constipation, or diarrhea may occur, and feces will appear black. Cathartics and laxatives may be indicated in some instances for more rapid elimination of the toxicant from the GI tract.

15.3.2 Enhancement of Poison Elimination

There are several methods available to enhance the elimination of specific poisons or drugs. For example, once the poisons/toxicants/drugs have been absorbed into the systemic circulation, the use of urinary alkalinization results in enhancement of the renal clearance of weak acids. The basic principle is to increase the pH of urinary filtrate to a level sufficient to ionize the weak acid and prevent renal tubule reabsorption of the molecule (ion trapping).

Serial oral administration of activated charcoal, also referred to as multiple-dose activated charcoal (MDAC), has been shown to increase the systemic clearance of various drug substances. The mechanism or the observed augmentation of nonrenal clearance caused by repeated doses of oral charcoal is thought to be transluminal efflux of the drug from the blood to the charcoal passing through the gastrointestinal tract. The activated charcoal in the gut lumen serves as a "sink" of the toxin. A concentration gradient is maintained and the toxin passes continuously into the gut lumen, where it is adsorbed to charcoal.

15.3.3 Supportive Treatment

Supportive therapy/treatment is often necessary until the toxicant can be metabolized and eliminated. The type of support required depends on the animal's clinical condition. Supportive efforts may include control of convulsive seizures, maintenance of respiration, treatment for shock, correction of electrolyte imbalance and fluid loss, and control of cardiac dysfunction, as well as alleviation of pain.

15.3.4 Specific Antidotes

A relatively small number of specific antidotes are available for clinical use in the treatment of poisoning. Specific antidotes for various toxicants work by various mechanisms.

(a) Some make complex with the toxicant (e.g., the oximes bind with organophosphorus insecticides, and EDTA chelates lead).
(b) Atropine, an antimuscarinic, anticholinergic agent, is used to pharmacologically antagonize at the receptor level the effects of organophosphate insecticides that produce lethal cholinergic, muscarinic effects.
(c) Certain agents exert their antidote effects by chemically reacting with biologic systems to increase detoxifying capacity of the toxin. For example, sodium nitrite is given to patients poisoned with cyanide to cause formation of methemoglobin, which serves as an alternative binding site or the cyanide ion, thereby making it less toxic to the body.

15.4 Questions and Answers

15.4.1 Short Questions and Answers

Exercise 1

Q.1. What are the objectives of analytical toxicology?
- Analytical toxicology is aimed at to provide support to clinical toxicology. In brief clinical toxicology includes DIMPLE which means:
  (a) Diagnosis (D)
  (b) Identification of poisons (I)
  (c) Management and treatment of poisoning (M)
  (d) Prognosis (P)
  (e) Law enforcement (L)
  (f) Education and research (E)

All the six indications mentioned above can be remembered by the mnemonic DIMPLE.

Q.2. What are general precautions to be followed by any investigator in toxicology laboratory?
(a) Strong acids or alkalis should always be added to water and not vice versa.
(b) Strong acids and alkalis should never be preserved together.
(c) Organic solvents should not be heated over a naked flame but in water bath.
(d) Use fume cup boards/hoods when organic solvents are heated.

Q.3. Which chelating agents are recommended for acute lead poisoning with signs of encephalopathy?
- Dimercaprol + Calcium EDT

Q.4. Define the term envenomation.
- Envenomation is the infusion of venom into another creature by the means of biting or stinging it.

Q.5. What is decontamination?
- Decontamination refers to:
  (a) Skin/eye decontamination
  (b) Gut evacuation
  (c) Administration of activated charcoal

Q.6. What are the methods used to increase elimination of poisons from the body?
The following methods are used to increase elimination of poisons from the body:
(a) Urinary alkalization,
(b) Multiple-dose activated charcoal
(c) Extracorporeal techniques
(d) Diaphoresis

Q.7. What are the three aims of emergency care when someone is bitten or stung by a poisonous animal?
- The aims of the emergency care are:
  (a) To minimize systemic absorption of the venom
  (b) To maintain life support
  (c) To facilitate the neutralization of the toxins by the immune system

Q.8. List groups of chemicals which are unnaturally produced toxicants:
(a) Pesticides
(b) Pharmaceuticals
(c) Food additives
(d) Solvents
(e) Environment contaminants

Q.9. Give four examples of naturally produced toxicants
(a) Plants (plant toxins)
(b) Fungus (mycotoxins)
(c) Bacterial (exotoxins)
(d) Animal/insects (venoms)

Q.10. What are the top 4 causes of poisonings for animal or human control centers?
- Pesticides > plants > household products > medicines

Q.11. In which season toxicant exposures have highest incidence?
- In summer _____may-august
  In December _____ (young and adult dogs)

Q.12. Name top 3 toxicant exposure agents causing death.
(a) Organophosphate insecticides
(b) Ethylene glycol (antifreeze)
(c) Anticoagulant rodenticides

Q.13. Indicate the circumstances under which activated charcoal should *not* be administered.
- It is ineffective in cases of heavy metal or corrosive chemical poisoning.

Q.14. Indicate the circumstances under which iso-osmotic laxative should *not* be administered.
- Suspected or proven obstruction or perforation of the bowel

Q.15. Indicate the circumstances under which penicillamine should *not* be administered.
- A person with a hypersensitivity to penicillamine

Q.16. Why strychnine is least toxic to chicken and pigeons?
- In birds and pigeon, strychnine is absorbed very slowly. Hence, strychnine is least toxic to chicken and pigeons. However, other avian species are easily affected.

Q.17. What is a chelating agent?
- A substance that binds strongly to metal ions, facilitating its elimination

Q.18. A delayed toxicity can include....
(a) Development of cancer (by carcinogens)
(b) Damage to the CNS by organophosphorus insecticides
(c) Toxic damage to the liver....
Can be reversible

Q.19. To manage unconscious poisoned patients, what can you do?
(a) Administer CPR
(b) Transport to clinical facilities
(c) *Do not* remove stomach contents by emesis

Q.20. The three major signs to monitor in the poisoned patients are...
(a) Cardiovascular
(b) Respiratory
(c) CNS

Q.21. What is the most effective way to reverse arrhythmia on the poisoned patient?
(a) Give sodium bicarbonate by IV
(b) Give lidocaine by IV

Q.22. Breath that smells of bitter almond is indicative of...
- Intoxication with cyanide

Q.23. For what purpose ipecac syrup is used?
- To induce emesis

Q.24. When Gastric lavage should be performed?
- Can be performed 4–6 hours after intoxication when hepatic recirculation occurs

Q.25. Chelating agents include....
- British Anti Lewisite (BAL) and Succimer

Q.26. Dispositional antidotes act by....
(a) Altering the metabolism of the drug
(b) Increasing the excretion of the drug

Q.27. To increase the renal excretion of an alkaline substance, you .....
- Acidify the urine with and infusion of NH_4Cl

Q.28. The use of ethanol in methanol intoxication is an example of....
- A dispositional antidote

Q.29. What is the antidote of copper poisoning?
- Stomach wash with potassium ferrocyanide 1% solution in water acts as an antidote by forming cupric ferrocyanide. Calcium EDTA or BAL is the recommended antidote. Maintain electrolyte and fluid balance.

Q.30. Name the agent(s) used in the treatment of poisoning by cyanide.
- Amyl nitrite, sodium nitrite, sodium thiosulfate

Q.31. Name the agent(s) used in the treatment of poisoning by lead.
- Penicillamine

Q.32. Name the agent(s) used in the treatment of poisoning by mercury.
- Penicillamine

Q.33. Name the agent(s) used in the treatment of poisoning by organophosphate pesticides.
- The organophosphate pesticides can be treated using atropine and pralidoxime iodide.

Q.34. Which four principles underlying the management of acute clinical overdose should be used?
- There are four principles underlying the management of clinical overdosage:
  (a) Life support
  (b) Client assessment
  (c) Drug decontamination/detoxification
  (d) Drug neutralization/elimination

Q.35. Name the specific antidote(s) for overdose of warfarin poisoning.
- Vitamin K

Q.36. Name the specific antidote(s) for overdose of digoxin poisoning.
- Digoxin antibody fragments

Q.37. Name the specific antidote(s) for overdose of pethidine poisoning.
- Narcotic antagonist, naloxone

Q.38. Name the specific antidote(s) for overdose of heparin toxicity.
- Protamine sulfate

Q.39. Describe in brief different mechanisms of specific antidotal therapy.
(a) Agents which specifically interact with the toxicant, e.g., iron (desferrioxamine), silver nitrate (sodium chloride), etc.
(b) Complex formation, e.g., methanol, fluoroacetate, heparin, etc.
(c) Metabolic activation, e.g., enhance metabolic conversion
(d) Pharmacological antidotes, e.g., morphine, warfarin, curare, etc.
(e) Enhancement of excretion of the toxicants, e.g., bromide, copper, lead, arsenic, etc.

Q.40. What is an antidote?
- An antidote is a medicine taken or given to counteract a particular poison which may be chemical, pharmacological, or physiological in nature.

Q.41. What is the mode of action of ciguatoxin toxicity?
- Ciguatoxin (found on warm-water, bottom-dwelling fish—including barracudas, sea bass, red snappers, grouper, and sturgeons, among others) binds to sodium channels and increases sodium channel permeability.

Q.42. Why ethylene toxicity causes renal toxicity?
- Ethylene glycol toxicity is caused by its conversion to oxalic acid, which causes renal toxicity.

Q.43. Why methanol toxicity causes renal and ocular toxicity?
- Methanol toxicity is caused by its conversion to formic acid, which causes both renal and ocular toxicity.

Q.44. Why fomepizole is a good option for alcohol poisoning?
- Fomepizole is an alcohol dehydrogenase inhibitor, which blocks the initial conversion of ethylene glycol to glycoaldehyde and methanol to formaldehyde, thus decreasing the precursors to oxalic and formic acid which are responsible for toxicity.

Q.45. How do herbicide paraquat act to cause lung toxicity?
- Paraquat acts on NADH to create superoxides.

Q.46. Which organ is most affected by Diquat herbicide?
- Kidney

Q.47. Which chelating agent is preferred for copper poisoning?
- Penicillamine

Q.48. How do methemoglobinemia cause cyanosis?
- Methemoglobinemia causes cyanosis due to the oxidation of the iron molecule in hemoglobin, thereby reducing its oxygen-carrying capacity.

Q.49. Why the pH of the blood is acidic in urea poisoning in animals?
- In the liver detoxification of ammonia to urea requires bicarbonate (HCO_{3-}), which depletes blood HCO_{3-} buffer leading to acidosis. Blood pH changes from 7.4 to 7.0.

Q.50. When removing an unabsorbed portion of a poison substance, which technique can be utilized?
(a) Gastric lavage
(b) Adsorption of the poison
(c) Cathartics
(d) Whole bowel irrigation

Q.51. The risk of intoxication from a toxicant in divided dose depends upon....
- Depends on the elimination rate

Q.52. A drug combination whose toxic effect can be described as: 3 + 0 = 5, refers to....
- Potentiation

Q.53. The ratio $TD1/ED_{99}$ of a therapeutic drug refers to....
- The Margin of Safety

Q.54. Name the technique for a patient that has been overdosed on coated tablets.
- Whole bowel irrigation

Q.55. How do you detect corneal poisoning? How do you treat it?
(a) Look for green stain in the cornea
(b) Use 2% Fluorescein (orange dye under blue light)

Q.56. Name the substances that prevent absorption of poison by their presence (act locally and not systemically).
(a) Physical antidotes
(b) Demulcents
(c) Activated charcoal

Q.57. Which salt is preferred to prevent an arrhythmia?
- $NHCO_3$ is preferred

Q.58. The administration of phenobarbital in warfarin poisoning...
- Increases the induction of microsomal enzymes that inactivate warfarin

Q.59. British anti-Lewisite (BAL) is _____
- A chemical agonist/chelating agent that is used for heavy metal intoxication

Q.60. Why does the lethal dose for chloroform have to be greater than toxic dose?
- The lethal dose is always greater than the toxic dose. A toxic dose causes physiological damage but does not cause death immediately.

Q.61. What is a quantal response?
- Is defined as an all-or-none response

Q.62. What is the purpose of advanced CNS support?
(a) Aimed at avoiding coma
(b) Aimed at avoiding convulsions

Q.63. Advanced respiratory life support includes _____
(a) Prolonged resuscitation over 20–30 minutes
(b) Use of doxapram

Q.64. In the intoxicated patient, does hypothermia provide any information?
- It is not informative.

15.4.2 Multiple Choice Questions

(Choose the correct statement; it may be one, two, or none.)

Exercise 2

Q.1. Toxicity associated with any chemical substance is referred to as _____
(a) Poisoning
(b) Intoxication
(c) Over dosage
(d) Toxicology

Q.2. Clinical toxicity, which is secondary to accidental exposure _____
(a) Toxicology
(b) Intoxication
(c) Poisoning
(d) Overdose

Q.3. Which of the following substances is not easily adsorbed by activated charcoal?
(a) Iron
(b) Ethanol
(c) Methanol
(d) All of the above

Q.4. The effect of Syrup Ipecac starts within 30 minutes of administration and lasts for approximately
(a) 30 minutes
(b) 1 hours
(c) 1 hours and 30 minutes
(d) 2 hours

Q.5. Which of the following procedure is contraindicated for patients who have ingested strong acids?
(a) Emesis
(b) Gastric lavage
(c) Whole bowel irrigation
(d) Both emesis and gastric lavage

Q.6. Which of the following technique is helpful in removing ethanol from body?
(a) Dialysis
(b) Activated charcoal
(c) Diuresis
(d) Hemoperfusion

Q.7. The most effective treatment in GI decontamination with acetaminophen is _____
(a) Emesis
(b) Gastric lavage
(c) Activated charcoal
(d) Dialysis

Q.8. Drug X is available as a 2.5% solution for intravenous administration. The desired dosage of this drug is 5 mg/kg. What volume of drug should be injected if the patient weighs 50 kg?
(a) 0.2 ml
(b) 1.0 ml
(c) 2.0 ml
(d) 10 ml
(e) 20 ml

Q.9. Thalidomide was accidentally discovered as _____
(a) Cardiotoxic agent
(b) Liver tonic
(c) A sedative/tranquilizer
(d) Cough mixture

Q.10. A target organ of toxicity is _____
(a) Lung
(b) Heart
(c) Reproductive system
(d) Kidney
(e) Liver

Q.11. A single large dose of N-nitrosodimethylamine fails to induce cancer in rats, but repeated dosing induces cancer because _____
(a) The single large dose is lethal, while the threshold for cancer induction can be exceeded by repeated smaller doses.
(b) The main DNA lesion from a single large dose can be repaired readily by methyltransferase, while repeated smaller doses can deplete the available repair enzyme, induce mutations in DNA, and effectively induce cancer.
(c) The enzyme system involved in detoxification of N-nitrosodimethylamine is depleted after repeated doses, allowing N-nitrosodimethylamine to build up and exceed the threshold for cancer induction.
(d) The enzyme system involved in conversion of N-nitrosodimethylamine to the active carcinogen is induced, and on subsequent repeated doses, more active carcinogen is produced.
(e) The initial dose of N-nitrosodimethylamine causes cell damage and, thus, high mitotic rates; subsequent small doses induce mutations in DNA and effectively induce cancer.

Q.12. Allergic contact dermatitis is _____
(a) A non-immune response caused by a direct action of an agent on the skin
(b) An immediate type I hypersensitivity reaction
(c) A delayed type IV hypersensitivity reaction
(d) Characterized by the intensity of reaction being proportional to the elicitation dose
(e) Not involved in photoallergic reactions

Q.13. Duration of ultra-short acting barbiturate is _____
(a) 3 hours
(b) 3 hours
(c) 15–20 minutes
(d) 0 minute

Q.14. Which of the following antidotes is *not* used in cyanide poisoning?
(a) Dicobalt EDTA
(b) Hydroxycobalamin
(c) Sodium nitrite
(d) Dimercaprol

Q.15. Extracorporeal elimination of drugs may be of use in all of the following *except*:
(a) Ethylene glycol
(b) Salicylates
(c) Atenolol
(d) Organophosphates

Q.16. Following aspirin overdose the initial acid base derangement is usually
(a) Respiratory acidosis
(b) Metabolic acidosis
(c) Respiratory alkalosis
(d) Metabolic alkalosis

Q.17. Which of the following pairs is *false* regarding drugs and their appropriateantidotes?
(a) Beta-blockers-glucagon
(b) Chloroquine-diazepam
(c) Isoniazid-pralidoxime
(d) Methanol-ethanol

Answers

Exercise 2

1. b	10. d
2. c	11. b
3. d	12. c
4. d	13. c
5. a & b	14. d
6. a	15. d
7. c	16. c
8. d	17. c
9. c	

15.4.3 Fill in the Blanks

Exercise 3

Q.1. The type of evidence seen at the time of poisoning is referred to as _____.
Q.2. The most common feed contaminant that can be expected during improper storage is _____.
Q.3. Pink coloration in urine is suggestive of poisoning due to _____.
Q.4. Phenols and cresols produce _____ coloration of urine.
Q.5. The symptoms or lesions that are characteristic to a particular toxicant are known as _____.
Q.6. The evidence that is obtained during postmortem examination is known as _____ evidence.
Q.7. Bitter almond smell of ruminal contents is suggestive of _____.
Q.8. Poisoning with phosphorus results in _____ odor during postmortem examination.
Q.9. The detection of toxic material in body using laboratory methods constitutes _____ evidence.

Q.10. The evidence that is obtained by feeding suspected material (feed) to healthy animals to ascertain the presence of toxicant is _____.
Q.11. The aim of treatment during poisoning is to _____ the threshold of the toxicant.
Q.12. The time versus concentration curve of toxicant in the body is shaped _____.
Q.13. The ascending phase of the time-concentration of toxicant curve represents _____.
Q.14. The descending phase of the time-concentration of toxicant curve represents _____.
Q.15. When emesis is contraindicated, the safest alternative is _____.
Q.16. The most commonly used adsorbing agent to bind toxicants in GIT is _____
Q.17. The type of diuretics or purgatives that are preferred in cases of poisoning is _____.
Q.18. When a large amount of toxicant is absorbed into the body or when renal failure occurs, the method of choice employed for elimination of the toxicant is _____.
Q.19. The mechanism involved in the enhanced elimination of acidic agents in alkalized urine and basic agents in acidified urine is _____.
Q.20. The substance which counteracts or neutralizes a toxicant is known as _____.

Answers

Exercise 3

1. Circumstantial evidence	11. Increase
2. Mycotoxins (aflatoxin)	12. Bell or inverted "U"
3. Phenothiazines	13. Absorption
4. Green	14. Excretion
5. Pathognomonic (symptom or lesion)	15. Gastric lavage
6. Pathological	16. Activated charcoal
7. Cyanide poisoning	17. Osmotic/saline type
8. Garlic-like	18. Dialysis
9. Analytical	19. Ion trapping
10. Experimental evidence	20. Antidote

15.4.4 True or False Statements

Wrtite (T) for true and (F) for false statement.

Exercise 4

Q.1. Porphyria is a congenital type of photosensitization.
Q.2. Spraying of 2,4-D in sugar beet is a predisposing factor for cyanide poisoning.

Q.3. Kidney is the tissue of choice for detection of most metals and sulfonamides.
Q.4. ANTU is less toxic when stomach is full than when it is empty.
Q.5. The toxicity of fluorocitrate is due to its conversion in body to highly toxic fluoroacetate.
Q.6. Biphasic reaction is a characteristic of carbamate poisoning.
Q.7. Cyanide poisoning could be detected if fresh rumen content contains 10 ppm HCN.
Q.8. Ochratoxin is primarily a hepatotoxic mycotoxin.
Q.9. Vit K is the best treatment for an animal showing signs of shock from warfarin toxin.
Q.10. Environmental toxicology does not deal with toxic effects on human

Answers

Exercise 4

1. T
2. F
3. T
4. F
5. F
6. F
7. F
8. F
9. F
10. F

15.4.5 Match the Statements

(Match the column A with column B)

Exercise 5

	Column A (poison)		Column B (antidote/antagonist
Q.1	Arsenic	a	Atropine / pralidoxime
Q.2	Cyanide	b	Fuller's
Q.3	Methanol	c	Dimercaprol
Q.4	Paraquat	d	Ethanol
Q.5	Parathion	e	Sodium nitrite /sodium thiosulfate
Q.6	Lead	f	N-acetyl cysteine
Q.7	Paracetamol	g	EDTA
Q.8	LSD	h	Gen-metal kidney
Q.9	Thalidomide	i	Abuse
Q.10	Copper	j	Teratogenicity

Answers

Exercise 5

Q.1	c	Dimercaprol
Q.2	e	Sodium nitrite/sodium thiosulfate
Q.3	d	Ethanol
Q.4	b	Fuller's earth
Q.5	a	Atropine/pralidoxime
Q.6	g	EDTA
Q.7	f	N-acetyl cysteine
Q.8	i	Abuse
Q.9	j	Teratogenicity
Q.10	h	Gun-metal kidney

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