PART I

# INTRODUCTION

CHAPTER 1

# Introduction to Toxicology

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Since the publication of the 3rd edition of this textbook (2004) major changes have been initiated in toxicology as the tools of molecular biology, genomics, proteomics, metabolomics, bioinformatics, and systems biology are increasingly brought to bear on the critical areas of mode of action, toxicity testing, and risk analysis. Chapter 2 provides information on new methodology and Part VIII—New Approaches in Toxicology is composed of two chapters of commentary on the current and expected impact of these new methods. While the traditional aspects and subdisciplines of toxicology, as outlined below, are still active and viable, during the next few years all are likely to be impacted and their development accelerated by these new approaches.

## 1.1 DEFINITION AND SCOPE

Toxicology can be defined as that branch of science that deals with poisons, and a poison can be defined as any substance that causes a harmful effect when administered, either by accident or by design, to a living organism. By convention, toxicology also includes the study of harmful effects caused by physical phenomena, such as radiation of various kinds, noise, and so on. In practice, however, many complications exist beyond these simple definitions, both in bringing more precise definition to the meaning of poison and to the measurement of toxic effects. Broader definitions of toxicology, such as "the study of the detection, occurrence, properties, effects, and regulation of toxic substances," although more descriptive, do not resolve the difficulties. Toxicity itself can rarely, if ever, be defined as a single molecular event, but is, rather, a cascade of events starting with exposure, proceeding through distribution and metabolism, and ending with interaction with cellular macromolecules (usually DNA or protein) and the expression of a toxic end point (Figure 1.1). This sequence may be mitigated by excretion and repair. It is to the complications, and to the science behind them and their resolution, that this textbook is dedicated, particular to the *how* and *why* certain substances cause disruptions in biologic systems that result in toxic effects. Taken together, these

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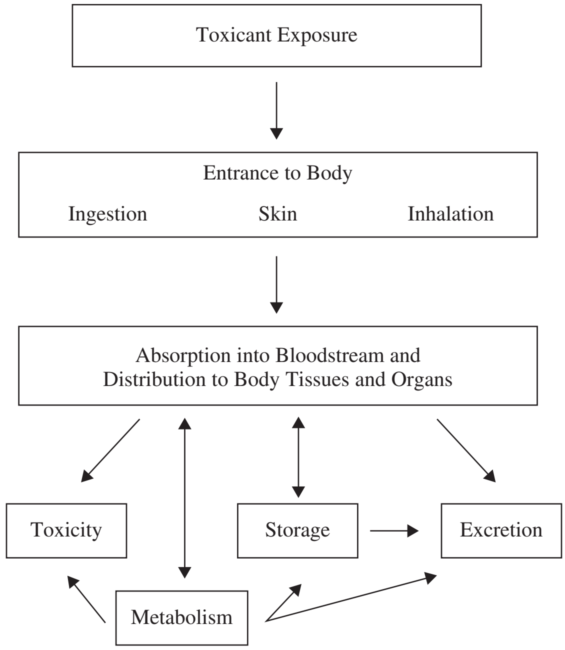


**Figure 1.1** Fate and effect of toxicants in the body.

difficulties and their resolution circumscribe the perimeter of the science of toxicology.

The study of toxicology serves society in many ways, not only to protect humans and the environment from the deleterious effects of toxicants, but also to facilitate the development of more selective toxicants such as anticancer and other clinical drugs, pesticides, and so forth.

Poison is a quantitative concept, almost any substance being harmful at some doses but, at the same time, being without harmful effect at some lower dose. Between these two limits, there is a range of possible effects, from subtle long-term chronic toxicity to immediate lethality. Vinyl chloride may be taken as an example. It is a potent hepatotoxicant at high doses, a carcinogen with a long latent period at lower doses, and apparently without effect at very low doses. Clinical drugs are even more poignant examples because, although therapeutic and highly beneficial at some doses, they are not without deleterious side effects and may be lethal at higher doses. Aspirin (acetylsalicylic acid), for example, is a relatively safe drug at recommended doses and is taken by millions of people worldwide. At the same time, chronic use can cause deleterious effects on the gastric mucosa, and it is fatal at a dose of about 0.2–0.5 g/kg. Approximately 15% of reported accidental deaths from poisoning in children result from ingestion of salicylates, particularly aspirin.

The importance of dose is well illustrated by metals that are essential in the diet but are toxic at higher doses. Thus, iron, copper, magnesium, cobalt, manganese, and zinc can be present in the diet at too low a level (deficiency), at an appropriate level (maintenance), or at too high a level (toxic). The question of dose–response relationships is fundamental to toxicology (see Section 1.4).

The definition of a poison, or toxicant, also involves a qualitative biological aspect because a compound, toxic to one species or genetic strain, may be relatively harmless to another. For example, carbon tetrachloride, a potent hepatotoxicant in many species, is relatively harmless to the chicken. Certain strains of rabbit can eat *Belladonna* with impunity while others cannot. Compounds may be toxic under some circumstances but not others or, perhaps, toxic in combination with another compound but nontoxic alone. The methylenedioxyphenyl insecticide synergists, such as piperonyl butoxide, are of low toxicity to both insects and mammals when administered alone, but are, by virtue of their ability to inhibit xenobiotic-metabolizing enzymes, capable of causing dramatic increases in the toxicity of other compounds.

The measurement of toxicity is also complex. Toxicity may be acute or chronic, and may vary from one organ to another as well as with age, genetics, gender, diet, physiological condition, or the health status of the organism. As opposed to experimental animals, which are highly inbred, genetic variation is a most important factor in human toxicity since the human population is highly outbred and shows extensive genetic variation. Even the simplest measure of toxicity, the $LD_{50}$ (lethal dose; the dose required to kill 50% of a population under stated conditions) is highly dependent on the extent to which the above variables are controlled. $LD_{50}$ values, as a result, vary markedly from one laboratory to another.

Exposure of humans and other organisms to toxicants may result from many activities: intentional ingestion, occupational exposure, environmental exposure, as well as accidental and intentional (suicidal or homicidal) 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. Experimental methods of administration such as injection may also give highly variable results; thus, the toxicity from intravenous (IV), intraperitoneal (IP), intramuscular (IM), or subcutaneous (SC) injection of a given compound may be quite different. Thus, toxicity may vary as much as 10-fold with the route of administration. Following exposure, there are multiple possible routes of metabolism, both detoxifying and activating, and multiple possible toxic end points (Figure 1.1).

Attempts to define the scope of toxicology, including that which follows, must take into account that the various subdisciplines are not mutually exclusive and are frequently interdependent. Due to overlapping of mechanisms as well as use and chemical classes of toxicants, clear division into subjects of equal extent or importance is not possible.

Many specialized terms are used in the various subdisciplines of toxicology as illustrated in the *Dictionary of Toxicology*, 2nd edition (Hodgson et al., 1998). However, some terms are of particular importance to toxicology in general; these and some more recent terms are defined in the glossary to be found at the end of this volume.

Although B through F (following) include subdivisions that encompass essentially all of the many aspects of toxicology, there are two new approaches (A, following) that serve to integrate the discipline as a whole.

A. Integrative Approaches

1. *Bioinformatics*. In the narrow and original meaning, bioinformatics was the application of information technology to molecular biology. While this is still

the most important aspect of bioinformatics, it is increasingly applied to other fields of biology, including molecular and other aspects of toxicology. It is characterized by computationally intensive methodology and includes the design of large databases and the development of techniques for their manipulation, including data mining.

2. *Systems Biology*. Although systems biology has been defined in a number of ways, some involving quite simple approaches to limited problems, in the currently most commonly accepted sense, it is an integrative approach to biological structure and function that will be of increasing importance to biology in general and toxicology in particular. In large part, biology has been reductionist throughout its history, studying organs as components of organisms, cells as components of organs, enzymes, nucleic acids, and so on, as components of cells, with the goal of describing function at the molecular level. Systems biology, on the other hand, is holistic and has the objective of discerning interactions between components of biological systems and describing these interactions in rigorous mathematical models. Furthermore, the proponents of systems biology aim to integrate these models at higher and higher levels or organization in order to develop an integrated model of the entire organism.

   Clearly, systems biology is in its infancy; however, the ultimate value of having an integrative model that could clarify all of the effects, from the most proximate to the ultimate, of a toxicant on a living organism, will provide enormous benefits not only for fundamental studies but in such applied areas as human health risk assessment.

B. Modes of Toxic Action. This includes the consideration, at the fundamental level of organ, cell, and molecular function, of all events leading to toxicity *in vivo*: uptake, distribution, metabolism, mode of action, and excretion. The term mechanism of toxic action is now more generally used to describe an important molecular event in the cascade of events leading from exposure to toxicity, such as the inhibition of acetylcholinesterase in the toxicity of organophosphorus and carbamate insecticides. Important aspects include the following:

1. *Biochemical and molecular toxicology* consider events at the biochemical and molecular levels, including enzymes that metabolize xenobiotics, generation of reactive intermediates, interaction of xenobiotics or their metabolites with macromolecules, gene expression in metabolism and modes of action, signaling pathways in toxic action, and so on.
2. *Behavioral toxicology* deals with the effects of toxicants on animal and human behavior, which is the final integrated expression of nervous function in the intact animal. This involves both the peripheral and central nervous systems, as well as effects mediated by other organ systems, such as the endocrine glands.
3. *Nutritional toxicology* deals with the effects of diet on the expression of toxicity and with the mechanisms of these effects.
4. *Carcinogenesis* includes the chemical, biochemical, and molecular events that lead to the large number of effects on cell growth collectively known as cancer.

5. *Teratogenesis* includes the chemical, biochemical, and molecular events that lead to deleterious effects on development.
6. *Mutagenesis* is concerned with toxic effects on the genetic material and the inheritance of these effects.
7. *Organ toxicity* considers effects at the level of organ function (e.g., neurotoxicity, hepatotoxicity, and nephrotoxicity).

C. Measurement of Toxicants and Toxicity. These important aspects deal primarily with analytical chemistry, bioassay, and applied mathematics, and are designed to provide the methodology to answer certain critically important questions. Is the substance likely to be toxic? What is its chemical identity? How much of it is present? How can we assay its toxic effect, and what is the minimum level at which this toxic effect can be detected? A number of important fields are included:

1. *Analytical toxicology* is a branch of analytical chemistry concerned with the identification and assay of toxic chemicals and their metabolites in biological and environmental materials.
2. *Genomics.* The sometimes stated distinction that genomics deals with genomes while molecular biology deals with single genes is unrealistic and unnecessary; it is more appropriate to regard genomics as an aspect of molecular biology that deals not only with genomes and gene expression but also such important aspects as genetic polymorphisms, particularly single nucleotide polymorphisms (SNPs). Techniques, such as microarrays, are now available to examine simultaneously the expression of very large numbers of genes.
3. *Proteomics* deals with the protein complement of organisms, the entire complement being known as the proteome. Thus, while genomics is concerned with gene expression, proteomics examines the products of the expressed genes.
4. *Metabolomics* is the next step in the sequence from genomics through proteomics and is concerned with the profile of small molecules produced by the metabolic processes of an organism. Changes in the profile in response to chemical stress are of importance to both fundamental and applied toxicology.
5. *Toxicity testing* involves the use of living systems to estimate toxic effects. It covers the gamut from short-term tests for genotoxicity such as the Ames test and cell culture techniques to the use of intact animals for a variety of tests from acute toxicity to lifetime chronic toxicity. Although the term "bioassay" is used properly only to describe the use of a living organism to quantitate the amount of a particular toxicant present, it is frequently used to describe any *in vivo* toxicity test.
6. *Toxicologic pathology* is that branch of pathology that deals with the effects of toxic agents manifested as changes in subcellular, cellular, tissue, or organ morphology.
7. *Structure-activity* studies are concerned with the relationship between the chemical and physical properties of a chemical and toxicity and, particularly, the use of such relationships as predictors of toxicity.

8. *Biomathematics and statistics* relate to many areas of toxicology. They deal with data analysis, the determination of significance, and the formulation of risk estimates and predictive models.
9. *Epidemiology*, as it applies to toxicology, is of great importance as it deals with the relationship between chemical exposure and human disease in actual populations, rather than in experimental settings.

D. Applied Toxicology. This includes the various aspects of toxicology as they apply in the field or the development of new methodology or new selective toxicants for early application in the field setting.

1. *Clinical toxicology* is the diagnosis and treatment of human poisoning.
2. *Veterinary toxicology* is the diagnosis and treatment of poisoning in animals other than humans, particularly livestock and companion animals, but not excluding feral species. Other important concerns of veterinary toxicology are the possible transmission of toxins to the human population in meat, fish, milk, and other foodstuffs, and the care and ethical treatment of experimental animals.
3. *Forensic toxicology* concerns the medicolegal aspects, including detection of poisons in clinical and other samples.
4. *Environmental toxicology* is concerned with the movement of toxicants and their metabolites and degradation products in the environment and in food chains, and with the effect of such contaminants on individuals and, especially, populations. Because of the large number of industrial chemicals and possibilities for exposure, as well as the mosaic of overlapping laws that govern such exposure, this area of applied toxicology is well developed.
5. *Industrial toxicology* is a specific area of environmental toxicology that deals with the work environment and constitutes a significant part of *industrial hygiene*.

E. Chemical Use Classes. This includes the toxicology aspects of the development of new chemicals for commercial use. In some of these use classes, toxicity, at least to some organisms, is a desirable trait; in others, it is an undesirable side effect. Use classes are not composed entirely of synthetic chemicals; many natural products are isolated and are used for commercial and other purposes and must be subjected to the same toxicity testing as that required for synthetic chemicals. Examples of such natural products include the insecticide, pyrethrin, the clinical drug, digitalis, and the drug of abuse, cocaine.

1. *Agricultural chemicals* include many compounds, such as insecticides, herbicides, fungicides, and rodenticides, in which toxicity to the target organism is a desired quality whereas toxicity to "nontarget species" is to be avoided. Development of such selectively toxic chemicals is one of the applied roles of comparative toxicology.
2. *Clinical drugs* are properly the province of pharmaceutical chemistry and pharmacology. However, toxic side effects and testing for them clearly fall within the science of toxicology.
3. *Drugs of abuse* are chemicals taken for psychological or other effects and may cause dependence and toxicity. Many of these are illegal but some are of clinical significance when used correctly.

4. *Food additives* are of concern to toxicologists only when they are toxic or being tested for possible toxicity.
5. *Industrial chemicals* are so numerous that testing them for toxicity or controlling exposure to those known to be toxic is a large area of toxicological activity.
6. *Naturally occurring substances* include many phytotoxins, mycotoxins, minerals, and so on, all occurring in the environment. The recently expanded and now extensive use of herbal "remedies" and dietary supplements has become a cause of concern for toxicologists and regulators. Not only is their efficacy frequently dubious, but their potential toxicity is also largely unknown.
7. *Combustion products* are not properly a use class but are a large and important class of toxicants, generated primarily from fuels and other industrial chemicals.

F. Regulatory Toxicology. These aspects, concerned with the formulation of laws, and regulations authorized by laws, are intended to minimize the effect of toxic chemicals on human health and the environment.
   1. *Legal aspects* are the formulation of laws and regulations and their enforcement. In the United States, enforcement falls under such government agencies as the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the Occupational Safety and Health Administration (OSHA). Similar government agencies exist in many other countries.
   2. *Risk assessment* is the definition of risks, potential risks, and the risk–benefit equations necessary for the regulation of toxic substances. Risk assessment is logically followed by *risk communication* and *risk management.* Risk assessment, risk communication, and risk management are frequently referred to as *risk analysis*.

## 1.2 RELATIONSHIP TO OTHER SCIENCES

Toxicology is a highly eclectic science and human activity drawing from, and contributing to, a broad spectrum of other sciences and human activities. At one end of the spectrum are those sciences that contribute their methods and philosophical concepts to serve the needs of toxicologists, either in research or in the application of toxicology to human affairs. At the other end of the spectrum are those sciences to which toxicology contributes.

In the first group, chemistry, biochemistry, pathology, physiology, epidemiology, immunology, ecology, and biomathematics have long been important while molecular biology has, in the last two or three decades, contributed to dramatic advances in toxicology.

In the group of sciences to which toxicology contributes significantly are such aspects of medicine as forensic medicine, clinical toxicology, pharmacy, and pharmacology, public health, and industrial hygiene. Toxicology also contributes in an important way to veterinary medicine, and to such aspects of agriculture as the development and safe use of agricultural chemicals. The contributions of toxicology to environmental studies have become increasingly important in recent years.

Clearly, toxicology is preeminently an applied science, dedicated to the enhancement of the quality of life and the protection of the environment. It is also much more. Frequently, the perturbation of normal life processes by toxic chemicals enables us to learn more about the life processes themselves. The use of dinitrophenol and other uncoupling agents to study oxidative phosphorylation and the use of α-amanitin to study RNA polymerases are but two of many examples. The field of toxicology has expanded enormously in recent decades, both in numbers of toxicologists and in accumulated knowledge. This expansion has brought a change from a primarily descriptive science to one which utilizes an extensive range of methodology to study the mechanisms involved in toxic events.

## 1.3 A BRIEF HISTORY OF TOXICOLOGY

Much of the early history of toxicology has been lost, and in much that has survived, toxicology is of almost incidental importance in manuscripts dealing primarily with medicine. Some, however, deal more specifically with toxic action or with the use of poisons for judicial execution, suicide, or political assassination. Regardless of the paucity of the early record, and given the need for people to avoid toxic animals and plants, toxicology must be one of the oldest practical sciences.

The Egyptian papyrus, *Ebers*, dating from about 1500 BC, must rank as the earliest surviving pharmacopeia, and the surviving medical works of Hippocrates, Aristotle, and Theophrastus, published during the period 400–250 BC, all include some mention of poisons. The early Greek poet Nicander treats, in two poetic works, animal toxins (Therica) and antidotes to plant and animal toxins (Alexipharmica). The earliest surviving attempt to classify plants according to their toxic and therapeutic effects is that of Dioscorides, a Greek employed by the Roman emperor Nero about 50 AD.

There appear to have been few advances in either medicine or toxicology between the time of Galen (131–200 AD) and that of Paracelsus (1493–1541). It was the latter who, despite frequent confusion between fact and mysticism, laid the groundwork for the later development of modern toxicology by recognizing the importance of the dose–response relationship. His famous statement "All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy" succinctly summarizes that concept. His belief in the value of experimentation was also a break with earlier tradition.

There were some important developments during the eighteenth century. Probably the best known is the publication of Ramazini's *Diseases of Workers* in 1700 which led to his recognition as the father of occupational medicine. The correlation between the occupation of chimney sweeps and scrotal cancer by Percival Pott in 1775 is almost as well-known although it was foreshadowed by Hill's correlation of nasal cancer and snuff use in 1761.

Orfila, a Spaniard working at the University of Paris in the early nineteenth century, is generally regarded as the father of modern toxicology. He clearly identified toxicology as a separate science and, in 1815, published the first book devoted exclusively to toxicology. An English translation in 1817 was entitled *A General System of Toxicology or, A Treatise on Poisons, Found in the Mineral, Vegetable* *and Animal Kingdoms, Considered in Their Relations with Physiology, Pathology and Medical Jurisprudence.* Workers of the late nineteenth century who produced treatises on toxicology include Christian, Kobert, and Lewin. The recognition of the site of action of curare by Claude Bernard (1813–1878) began the modern study of the mechanisms of toxic action. Since then, advances have been numerous—too numerous to list in detail. They have increased our knowledge of the chemistry of poisons, the treatment of poisoning, the analysis of toxicants and toxicity, as well as modes of toxic action and detoxication processes, and specific molecular events in the poisoning process.

With the publication of her controversial book, *The Silent Spring*, in 1962, Rachel Carson became an important influence in initiating the modern era of environmental toxicology. Her book emphasized stopping the widespread, indiscriminate use of pesticides and other chemicals and advocated use patterns based on sound ecology. Although sometimes inaccurate and with arguments often based on frankly anecdotal evidence, her book is often credited as the catalyst leading to the establishment of the U.S. EPA and she is regarded by many as the mother of the environmental movement.

It is clear, however, that since the 1960s, toxicology has entered a phase of rapid development and has changed from a science that was largely descriptive to one in which the importance of mechanisms of toxic action is generally recognized. Since the 1970s, with increased emphasis on the use of the techniques of molecular biology, the pace of change has increased even further, and significant advances have been made in many areas, including chemical carcinogenesis and xenobiotic metabolism, among many others.

## 1.4 DOSE–RESPONSE RELATIONSHIPS

As mentioned previously, toxicity is a relative event that depends not only on the toxic properties of the chemical and the dose administered but also on individual and interspecific variation in the metabolic processing of the chemical. The first recognition of the relationship between the dose of a compound and the response elicited has been attributed to Paracelsus (see Section 1.3). It is noteworthy that his statement includes not only that all substances can be toxic at some dose, but that "the right dose differentiates a poison from a remedy," a concept that is the basis for pharmaceutical therapy.

A typical dose–response curve is shown in Figure 1.2, in which the percentage of organisms or systems responding to a chemical is plotted against the dose. For many chemicals and effects, there will be a dose below where no effect or response is observed. This is known as the *threshold dose*. This concept is of significance because it implies that a *no observed effect level* (NOEL) can be determined and that this value can be used to determine the safe intake for food additives and contaminants such as pesticides. Although this is generally accepted for most types of chemicals and toxic effects, for chemical carcinogens acting by a genotoxic mechanism, the shape of the curve is controversial, and for regulatory purposes, their effect is assumed to be a no-threshold phenomenon. Dose–response relationships are discussed in more detail in Chapter 10—Acute Toxicity and Chapter 20—Toxicity Testing.

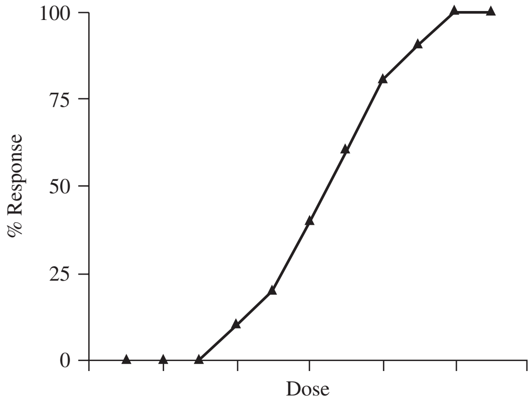


**Figure 1.2** A typical dose–response curve.

## 1.5 SOURCES OF TOXIC COMPOUNDS

Given the enormous number of toxicants, it is difficult to classify them, either chemically, by function, or by mode of action since many of them would fall into several classes. Some are natural products, many are synthetic organic chemicals of use to society, while some are byproducts of industrial processes and waste disposal. It is useful, however, to categorize them according to the expected routes of exposure or according to their uses.

A. Exposure Classes. Exposure classes include toxicants in food, air, water, and soil as well as toxicants characteristic of domestic and occupational settings. Toxicant use classes are described in detail in Chapter 3.
B. Use Classes. Use classes include drugs of abuse, therapeutic drugs, agricultural chemicals, food additives and contaminants, metals, solvents, combustion products, cosmetics, and toxins. Some of these, such as combustion products, are the products of use processes rather than being use classes. All of these groups of chemicals are discussed in detail in Chapter 4.

## 1.6 MOVEMENT OF TOXICANTS IN THE ENVIRONMENT

Chemicals released into the environment rarely remain in the form, or at the location, of release. For example, agricultural chemicals used as sprays may drift from the point of application as air contaminants or enter run-off water as water contaminants. Many of these chemicals are susceptible to fungal or bacterial degradation and are rapidly detoxified, frequently being broken down to products that can enter the carbon, nitrogen, and oxygen cycles. Other agricultural chemicals, particularly halogenated organic compounds, are recalcitrant to a greater or lesser degree to metabolism by microorganisms and persist in soil and water as contaminants; they may enter biologic food chains and move to higher trophic levels or persist in processed crops as food contaminants. This same scenario is applicable to

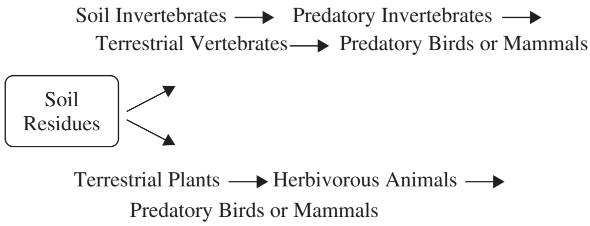


**Figure 1.3** Examples of simplified food chains.

any toxicant released into the environment either for a specific use or as a result of industrial processes, combustion, and so on. Chemicals released into the environment are also susceptible to chemical degradation, a process often stimulated by ultraviolet light.

Although most transport between inanimate phases of the environment results in wider dissemination, but, at the same time, dilution of the toxicant in question, transfer between living creatures may result in increased concentration or bioaccumulation. Lipid-soluble toxicants are readily taken up by organisms following exposure in air, water, or soil. Unless rapidly metabolized, they persist in the tissues long enough to be transferred to the next trophic level. At each level, the lipophilic toxicant tends to be retained while the bulk of the food is digested, utilized, and excreted, thus increasing the toxicant concentration. At some point in the chain, the toxicant can become deleterious, particularly if the organism at that level is more susceptible than those at the level preceding it. Thus, the eggshell thinning in certain raptorial birds was almost certainly due to the uptake of DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane) and DDE (1,1-dichloro-2,2-bis(4-chlorophenyl) ethane) and their particular susceptibility to this type of toxicity. Simplified food chains are shown in Figure 1.3.

It is clear that such transport can occur through both aquatic and terrestrial food chains, although in the former, higher members of the chains, such as fish, can accumulate large amounts of toxicants directly from the medium. This accumulation occurs because of the large area of gill filaments, their intimate contact with the water, and the high flow rate of water over them. Given these characteristics and a toxicant with a high partition coefficient between lipid membranes and water, considerable uptake is inevitable.

These and all other environmental aspects of toxicology are discussed in Part VII.

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## SAMPLE QUESTIONS

**1.** Briefly define the following terms:
   **a.** Toxicology
   **b.** Poison
   **c.** Genomics
   **d.** Proteomics
   **e.** Metabolomics

**2.** Toxicity has been described as a cascade of events initiated by exposure to a harmful chemical. Name the principal steps in this cascade.

**3.** Name and define three important chemical use classes.