Introduction to Food Toxicology

Second Edition

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Food Science and Technology, International Series

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Preface

Food is one of the most essential materials for the survival of living organisms, following perhaps only oxygen and water in importance. People have been learning how to identify and prepare appropriate foods since prehistoric times. However, there was probably a tremendous sacrifice of human lives before people learned to find and prepare safe foods. For thousands of years trial and error was the only method to detect the presence of poisons in the diet. Systematic data on poisons in foods have been recorded for only approximately 200 years or so. Moreover, food toxicology as a classroom discipline taught in universities has a relatively recent origin. The revolution in the last two decades in our knowledge of the sciences of chemistry and molecular biology that are the foundation of modern toxicology have enhanced to previously unimagined levels; our abilities to both detect extremely small amounts of toxic agents and to understand in great detail the mechanisms of action of these toxic substances.

This volume is a classroom reference for students who do not have strong backgrounds in either toxicology or food science, but who would like to be introduced to the exciting field of toxicology and its application to toxins in food and the environment. The format of the book is designed primarily to teach students basic toxicology of food and environmental toxins and to extend this knowledge to consider molecular targets and mechanisms of action of important toxic agents. The chemical identities of the toxicants and their fates in foods and in the human body are discussed, along with historical notes on the discoveries of the toxins and possible use in ancient times.

Student interest in toxicology has continued to grow since the publication of the first edition of this text. Issues related to toxic materials have received increased attention from the scientific community, regulatory agencies and the general public. The issues and potential problems are reported almost daily by the mass media, and are often the focus of attention in nightly newscasts. The major misunderstanding and confusion raised by many of these reports are almost always due to lack of basic knowledge about toxicology among most reporters and consumers. This volume presents basic principles of modern food toxicology and their application to topics of major interest for human health that will allow students of the subject to better identify and understand the significant problems of toxic materials in foods and the environment.

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Table of Contents

CHAPTER 1

Principles of Toxicology

CHAPTER CONTENTS

Toxicology is defined as the study of the adverse effects of chemicals on living organisms. Its origins may be traced to the time when our prehistoric ancestors first attempted to introduce substances into their diets that they had not encountered previously in their environments. By observing which substances could satisfy hunger without producing illness or death, ancient

Food Science and Technology

people developed dietary habits that improved survival and proliferation of the species in their traditional environment and allowed them to adapt to new environments. In its modern context, toxicology draws heavily on knowledge in chemical and biological fields and seeks a detailed understanding of toxic effects and means to prevent or reduce toxicity. In many instances, the original discoveries of toxins that caused devastating human illness and suffering have led to the development of the toxin as a probe of biological function that is used today to study basic mechanisms and to develop cures for human maladies as diverse as postpartum hemorrhage, psychosis, and cancer.

A brief history of documented uses of toxic agents serves to illustrate the importance of these substances since ancient cultures. The Ebers papyrus of about 1500 BCE, one of the oldest preserved medical documents, describes uses of many poisons such as hemlock, aconite arrow poison, opium, lead, and copper. By 399 BCE, death by hemlock poisoning was a well-established means of capital punishment in Greece, most notably in the forced suicide of Socrates. Around this same time, Hippocrates discussed bioavailability and overdosage of toxic agents, and intended poisonings—used mostly by aristocratic women as a means of dispatching unwanted husbands—were of common occurrence in Rome. By about 350 BCE, Theophrastus, a student of Aristotle, made many references to poisonous plants in his first *De Historia Plantarum*.

In about 75 BCE, King Mithridates VI of Pontus (in modern Turkey) was obsessed with poisons and, from a young age, took small amounts of as many as 50 poisons in the hopes of developing resistance to each of them. This practice apparently induced a considerable resistance to poisons, since according to legend, to avoid enemy capture, the standard poisonous mixture was not effective in a suicide attempt by the vanquished king and he had to fall on his sword instead. The term "mithridatic" refers to an antidotal or protective mixture of low but significant doses of toxins and has a firm scientific basis. However, the claim that vanishingly small doses of toxic agents also produce protective effects, which is the claimed basis for homeopathy, does not have scientific support.

In 82 BCE, *Lex Cornelia* (Law of Cornelius) was the first law to be enacted in Rome that included provisions against human poisonings. In approximately 60 CE, Dioscorides, a physician in the Roman armies of Emperors Nero, Caligula, and Claudius, authored a six to eight volume treatise that classified poisons on the basis of origin (plant, animal, mineral) and biological activity, while avoiding the common practice of classification based on fanciful theories of action that were considered important at the

time, such as the theory of humors, which posed that body function is regulated by the proper balance of fluids called black bile, yellow bile, phlegm, and blood. This treatise often suggested effective therapies for poisonings such as the use of emetics, and was the standard source of such information for the next 1500 years.

Paracelsus (1493–1541) is considered to be the founder of toxicology as an objective science. Paracelsus, who changed his name from Phillip von Hohenheim, was an energetic, irascible, and iconoclastic thinker (Figure 1.1). He was trained in Switzerland as a physician and traveled widely in Europe and the Middle East to learn alchemy and medicine in other traditions of the day. Although astrology remained an important part of his philosophy, he eschewed magic in his medical practice. His introduction of the practice of keeping wounds clean and allowing them to drain to allow them to heal won him considerable acclaim in Europe. Most notably for toxicology, Paracelsus was the first person who attributed adverse effects of certain substances to the substance itself and not to its association with an evil or angered spirit or god. Paracelsus is accredited with conceiving the basic concept of toxicology, which often is stated as follows:

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

Although this and other concepts developed by Paracelsus were groundbreaking and major advances in thinking about disease for the time, they put him at odds with the major medical practitioners. As a result, he was forced to leave his home medical practice and spent several of his final years traveling. He was 48 when he died, and there are suspicions that his enemies caught up with him and ended his very fruitful life. How ironic it would be if the father of toxicology were murdered by poisoning!

FIGURE 1.1 *Paracelsus (1493–1541).*

It is useful to evaluate the significance of the Paracelsus axiom in our daily lives by considering examples of well-known substances with low and high toxicity. Water might be considered one of the least toxic of the substances that we commonly encounter. Can it be toxic? Indeed, there are many reports of water toxicity in the scientific literature. For example, in 2002 a student at California State University at Chico was undergoing a fraternity initiation ordeal in which he was required to drink up to five gallons

of water while engaged in rigorous calisthenics and being splashed with ice cold water. Consumption of this amount of water in a short span of time resulted in the dilution of the electrolytes in his blood to the point that normal neurological function was lost and tragically the young man died.

Let us now consider the converse concept that exposure to a small amount of a highly toxic agent can be of little consequence. For example, the bacterium that produces botulism, *Clostridium botulinum*, can produce deadly amounts of botulinum toxin in improperly sterilized canned goods. This bacterial toxin is one of the most toxic substances known. The same toxin, however, is used therapeutically, for example, to treat spastic colon and as a cosmetic to reduce wrinkles in skin.

BRANCHES OF TOXICOLOGY

The science of toxicology has flourished from its early origins in myth and superstition, and is of increasing importance to many aspects of modern life. Modern toxicology employs cutting-edge knowledge in chemistry, physiology, biochemistry and molecular biology, often aided by computational technology, to deal with problems of toxic agents in several fields of specialization.

The major traditional specialties of toxicology address several specific societal needs. Each specialty has its unique educational requirements, and employment in some areas may require professional certification. **Clinical toxicology** deals with the prevention, diagnosis, and management of poisoning, usually in a hospital or clinical environment. **Forensic toxicology** is the application of established techniques for the analysis of biological samples for the presence of drugs and other potentially toxic substances, and usually is practiced in association with law enforcement. **Occupational toxicology** seeks to identify the agents of concern in the workplace, define the conditions for their safe use, and prevent absorption of harmful amounts. **Environmental toxicology** deals with the potentially deleterious impact of man-made and natural environmental chemicals on living organisms, including wildlife and humans.

Regulatory toxicology encompasses the collection, processing, and evaluation of epidemiological and experimental toxicology data to permit scientifically based decisions directed toward the protection of humans from the harmful effects of chemical substances. Furthermore, this area of toxicology supports the development of standard protocols and new testing methods to continuously improve the scientific basis for decision-making processes. **Ecotoxicology** is concerned with the environmental distribution and toxic

effects of chemical and physical agents on populations and communities of living organisms within defined ecosystems. Whereas traditional environmental toxicology is concerned with toxic effects on individual organisms, ecotoxicology is concerned with the impact on populations of living organisms or on ecosystems.

Food toxicology focuses on the analysis and toxic effects of bioactive substances as they occur in foods. Food toxicology is a distinct field that evaluates the effects of components of the complex chemical matrix of the diet on the activities of toxic agents that may be natural endogenous products or may be introduced from contaminating organisms, or from food production, processing, and preparation.

DOSE-RESPONSE

Since there are both toxic and nontoxic doses for any substance, we may also inquire about the effects of intermediate doses. In fact, the intensity of a biological response is proportional to the concentration of the substance in the body fluids of the exposed organism. The concentration of the substance in the body fluids, in turn, is usually proportional to the dose of the substance to which the organism is subjected. As the dose of a substance is increased, the severity of the toxic response will increase until at a high enough dose the substance will be lethal. This so-called individual dose-response can be represented as a plot of degree of severity of any quantifiable response, such as an enzyme activity, blood pressure, or respiratory rate, as a function of dose. The resulting plot of response against the $\log_{10}$ of concentration will provide a sigmoidal curve (as illustrated in Figure 1.2) that will be nearly linear within a mid-concentration range and will be asymptotic to the zero response and maximum response levels. This response behavior is called a **graded dose-response** since the severity of the response increases over a range of concentrations of the test substance.

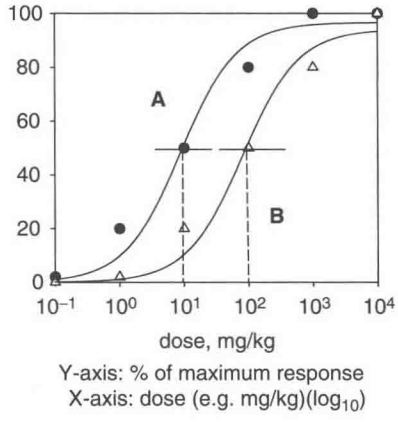

FIGURE 1.2 *Dose-response. The resulting plot of response against the $\log_{10}$ of concentration will provide a sigmoidal curve that will be nearly linear within a mid-concentration range and will be asymptotic to the zero response and maximum response levels.*

Toxicity evaluations with individual test organisms are not used often, however, because individual organisms, even inbred rodent species used in the laboratory, may vary from one another in their sensitivities to toxic agents. Indeed, in studies of groups of test organisms, as the dose is increased, there is not a dose at which all the organisms in the group will suddenly develop the same response.

Instead, there will be a range of doses over which the organisms respond in the same way to the test substance. In contrast to the graded individual dose-response, this type of evaluation of toxicity depends on whether or not the test subjects develop a specified response, and is called an **all-or-none** or **quantal population** response. To specify this group behavior, a plot of percent of individuals that respond in a specified manner against the log of the dose is generated.

Let us consider, for example, the generation of a dose-response curve for a hypothetical hypertensive agent. The test substance would be administered in increasing doses to groups of 10 subjects or test organisms. The percentage of individuals in each group that respond in a specific way to the substance (e.g., with blood pressure 140/100) then is determined. The data then are plotted as percent response in each group versus the log of the dose given to each group. Over a range of low doses, there will be no test subjects that develop the specified blood pressure. As the dose increases, there will be increased percentages of individuals in the groups that develop the required blood pressure, until a dose is reached for which a maximum number of individuals in the group respond with the specified blood pressure. This dose, determined statistically, is the mean dose for eliciting the defined response for the population. As the dose is further increased, the percentages of individuals that respond with the specified blood pressure will decrease, since the individuals that responded to the lower doses are now exhibiting blood pressures in excess of the specified level. Eventually, a dose will be reached at which all the test subjects develop blood pressures in excess of the specified level.

When the response has been properly defined, information from quantal dose-response experiments can be presented in several ways. A frequency-response plot (Figure 1.3) is generated by plotting the percentage of responding individuals in each dose group as a function of the dose.

The curve that is generated by these data has the form of the normal Gaussian distribution and, therefore, the data are subject to the statistical laws for such distributions. In this model, the numbers of individuals on either side of the mean are equal and the area under the curve represents the total population. The area under the curve bounded by the inflection points includes the number of individuals responding to the mean dose, plus or minus one standard deviation (SD) from the mean dose, or 95.5% of the population. This mean value is useful in specifying the dose range over which most individuals respond in the same way.

Frequency-response curves may be generated from any set of toxicological data where a quantifiable response is measured simply by recording the