全国高等学校双语教材

ESSENTIALS OF TOXICOLOGY

毒理学基础

Second Edition
第 2 版

Chief Editors Huang Jiwu Tong Jian
主 编 黄吉武 童 建

人民卫生出版社
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PREFACE
前 言

如果从专业课中挑选一门课程，那么在为预防医学专业开设的课程中，可以说没有哪一门课程能比毒理学与生物基础学科有更加密切的联系，并依赖于其进展；同时也没有哪一门课程能像毒理学这样，为后期的卫生专业课程提供了从微观到宏观多个生物学层次上的广泛深入的理论基础，并促进了这些学科的发展。毒理学就是这样一门少有的具备基础和应用双重特性的学科。而在语言方面，毒理学文献不但涉及生理学、生物化学、遗传学、免疫学等多学科的词汇，同时也提供了阅读各卫生专业文献资料必备的专业术语和表述程式。以上这些特点决定了毒理学这门桥梁课程的专业代表性，因而适合作为突破口来进行双语教学的探讨与实践。

本书初版的编写着力于提供一部能适合当时学生水平和教学要求的，内容适当、语言适宜、难度适中的双语教材。然而其出版已 7 年有余，作为一门新兴学科，毒理学的发展迅速，知识更新很快。为提升其使用价值，保持教材的新颖性、适用性和先进性，与时俱进、适时修订再版显然是非常必要的。

本次修订从教学需求出发，广泛吸取了师生在使用过程中的反馈意见，是在侧重基础理论和基本知识、保持主要内容连贯稳定的基础上进行的。修订编写利用英语编写的便利条件，直接借鉴国外教材编写的先进理念和做法；继续保持本书“讲专业，教英语”的特点，贯彻专业理论与专业英语教学相结合的思路，采用“英语原文为主，汉语译文参照”的形式，提供了大量多种形式的互动资料，拓宽学生自学空间，便于教师备课授课；努力做到阐述便于学生理解，并与疾病预防实践密切结合；其中重点更新充实的章节包括毒作用影响因素、发育、免疫、呼吸、神经、心血管和生殖内分泌毒理学，而生物转化、致突变、致癌和管理毒理学等章节实际上是全文重新编写的。修订参考了新出版的英文原版图书，扩大了检索范围，涵盖了新涌现的学科领域，纳入了最新的发展趋势，着重反映主流学术观点并通过多本标准教科书进行了印证，从而使课文更具科学性，语言更加规范，内容更加充实。

毒理学发展的趋向之一是学科之间的交叉融合。例如管理毒理学近来就强化了人文社会科学的内容。考虑到存在国情的差别，本拟介绍国内管理技巧和法规制定的情况。然而这方面可供参照的相关英文公开资料极少，难以组织成文，最终还是放弃了这种想法。不过，我国建立的体系是与国际接轨的，其科学原理应该是普遍适用的，技术方法也是共通的。特别是通过后续专业课程的学习，学生的知识结构更可以得到完善充实。实际上，国际上的方法也并非完全统一，故本教材仅选择介绍当今流行的国际主流管理体系。

本书由 16 所重点医学院校的 18 位教授参与编写。编者们付出了艰苦的创造性劳动，主要体现在从浩如烟海的文献中筛选出适合的素材，去伪存真、去粗取精，重新组织编排成通顺的英语课文。在参照原著时，除陈述的内容是成熟公认的原理和惯例外，尽可能地更换角度，采用不同的文字来表达，避免原封不动地照搬。尽管如此，由于英语作为外语的限制，仍较多引用了原著作(主要是教科书)的语句文字，而课文中又难以逐一标注出处，在此一并加以说明，并对原著作者付出的劳动致以谢意。

黄吉武　童　建

2016 年 1 月

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GENERAL TOXICOLOGY

第一部分　普通毒理学

CHAPTER 1

INTRODUCTION TO TOXICOLOGY

CHAPTER OUTLINE

DEFINITION OF TOXICOLOGY

Toxicology is the study of the adverse effects of chemicals on living organisms. It is a multidisciplinary subject which comprises many different areas. Regardless of the specialization within toxicology, a toxicologist is trained to perform one or both of the two basic functions of toxicology, which are to (1) examine the nature of the adverse effects produced by a chemical and (2) assess the probability of these hazards/toxicities occurring under specific conditions of exposure. Ultimately, the goal and basic purpose of toxicology is to provide a basis for appropriate controlling measures so that these adverse effects can be prevented.

In the world, more than 80,000 commercial and industrial chemicals are now in use and 500-

1,000 new chemicals are added each year. Because of this escalation in the numbers of chemicals to which humans may potentially expose, toxicology has become increasingly important in the area of quantitative estimates of the potential effects on human health and environmental significance of various types of chemical exposures (e.g., pesticide residues on food, contaminants in drinking water, and airborne dusts in the workplace).

SCOPE OF TOXICOLOGY

Three Main Specialized Areas

The professional activities of all toxicologists fall into three main areas: descriptive, mechanistic, and regulatory.

Descriptive Toxicology

A descriptive toxicologist is concerned directly with toxicity testing, which provides information for safety evaluation and regulatory requirements. The concern may be limited to effects on humans, as in the case of drugs and food additives, or to potential effects on fish, birds, and plants, as well as other factors that might disturb the balance of the ecosystem.

Mechanistic Toxicology

A mechanistic toxicologist is concerned with identifying and understanding the mechanisms by which chemicals exert toxic effects on living organisms. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome observed in laboratory animals is or is not directly relevant to humans. Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease. An understanding of the mechanisms of toxic action contributes to the knowledge of basic physiology, pharmacology, cell biology, and biochemistry.

Regulatory Toxicology

A regulatory toxicologist has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or another chemical poses a sufficiently low risk to be marketed for a stated purpose. Regulatory toxicologists also assist in the establishment of standards for the amount of chemicals permitted in ambient air, industrial atmospheres, and drinking water, often integrating scientific information from basic descriptive and mechanistic toxicology studies with the principles and approaches used for risk assessment.

Other Specialized Areas of Toxicology

In addition to the above categories, there are other divisions of toxicology which may be based on the classes of chemicals dealt with or application of knowledge from toxicology for a specific field:

- Forensic toxicology is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on humans and animals, in establishing causes of death, and in determining their circumstances in a postmortem investigation.

- Clinical toxicology is concerned with disease caused by or uniquely associated with toxic substances. Efforts are directed at treating patients poisoned with drugs or other chemicals and at the development of new techniques to treat those intoxications.
- Environmental toxicology focuses on the impact of chemical pollutants in the environment on biological organisms, most commonly on nonhuman organisms such as fish, birds, and terrestrial animals.
- Drug toxicology plays a major role in the preclinical safety assessment of chemicals intended for use as drugs, and studies potential effects of drugs after high doses. Drug toxicology also elucidates the mechanisms of side effects observed during clinical application.
- Occupational toxicology is the subdiscipline concerned with the chemical exposures and diseases found in the workplace. Both acute and chronic occupational poisonings have exerted a major influence on the development of toxicology in general. Occupational toxicology also helps in the development of safety procedures to prevent intoxications in the workplace and assists in the definition of exposure limits.

MULTIDISCIPLINARY NATURE OF TOXICOLOGY

Relationship to Other Sciences

Although generally accepted as a specific scientific field during last century, the practice of toxicology is not a discipline in its own right but comprises many different disciplines at present. Toxicology is highly eclectic interdisciplinary science with contribution from and to a broad spectrum of other sciences. At one end of the spectrum are those sciences who 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, physiology, immunology, pathology, epidemiology, biomathematics, and ecology 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 public health, occupational health, internal medicine, forensic medicine, and pharmacy. 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.

The field most closely related to toxicology is pharmacology. In many countries, toxicology as a discipline has developed from pharmacology. Pharmacology and toxicology both study the effect of chemicals on living organisms and have often used identical methods. However, fundamental differences have developed with advances in these sciences. Pharmacology focused on chemicals with beneficial effects (drugs) at lower doses whereas toxicology studied the adverse health effects occurring with the same chemicals at high doses. Today, the main interest of research in toxicology

has shifted to studies on the long-term effects of chemicals after low-dose exposure, such as cancer or other irreversible diseases, moreover, most chemicals of interest to toxicologists are not used as drugs.

Toxicology is a recognized scientific discipline encompassing both basic and applied issues. Few disciplines can point to both basic sciences and direct applications at the same time. Toxicology may be unique in this regard.

Toxicology Is Both A Science and An Art

Toxicology, like medicine, is both a science and an art. The science of toxicology is defined as the observational and data-gathering phase, whereas the art of toxicology consists of the utilization of the data to predict outcomes of exposure in human and animal populations. In most cases, these phases are linked because the facts generated by the science of toxicology are used to develop extrapolations and hypotheses to explain the adverse effects of chemical agents in situations where there is little or no information. For example, the observation that the administration of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) to female Sprague-Dawley rats induces hepatocellular carcinoma is a fact. However, the conclusion that it will also do so in humans is a prediction or hypothesis. It is important to distinguish facts from predictions. When we fail to distinguish the science form the art, we confuse facts with predictions and argue that they have equal validity, which they clearly do not. In toxicology, as in all science theories have a higher level of certainty than do hypotheses, which in turn are more certain than speculations, opinions, conjectures, and guesses.

HISTORICAL ASPECTS OF TOXICOLOGY

Antiquity and Middle Ages

Toxicology dates back to the earliest humans, who used animal venoms and plant extracts for hunting, warfare, and assassination. Primitive man was aware of natural poisons from animals and plants and indeed used these on his weapons. The word toxicology is derived from *toxicon* - a poisonous substance into which arrow heads were dipped and *toxikos* - a bow. The Ebers papyrus (circa 1500 BC) contains information pertaining to many recognized poisons. Hippocrates (circa 400 BC) in his writings showed that the ancient Greeks had a professional awareness of poisons and of the principles of toxicology, particularly with regard to the treatment of poisoning by influencing absorption. He also mentioned clinical toxicology principles pertaining to bioavailability in therapy and overdosage.

Using poisons for murder, suicide and political assassination was quite common. It is well known for example that Socrates (circa 470-399 BC) committed suicide by taking hemlock as state method of execution. King Mithridates Ⅵ (132-63 BC) of Pontus did numerous acute toxicity experiments on unfortunate criminals to search for antidotes to poisonous substances and regularly protected himself with a mixture of 50 different antidotes.

Dioscorides (40-90 AD), a Greek physician in the court of the Roman emperor Nero, made the first attempt at a classification of poisons, which was accompanied by descriptions and drawings. His classification into plant, animal, and mineral poisons not only remained a standard for 16 centuries but is still a convenient classification.

In the Middle Ages, especially in Italy, the art of poisoning for political ends developed into a cult. The Borgias were infamous among the families engaged in poisoning during the fifteenth and sixteenth centuries.

Age of Enlightenment

A significant figure in the history of science and medicine in the late Middle Ages was the renaissance man Philippus Aureoles Theophrastus Bombastus von Hohenheim-Paracelsus (1493-1541) Paracelsus (Figure 1-1). Between the time of Aristotle and the age of, there was little substantial change in the biomedical sciences. A view initiated by Paracelsus that became a lasting contribution held as corollaries that (1) experimentation is essential in the examination of responses to chemicals; (2) one should make a distinction between the therapeutic and toxic properties of chemicals; (3) these properties are sometimes but not always indistinguishable except by dose; and (4) one can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects. Paracelsus summarized his views in the following famous phrase: "All substances are poisons; there is none that is not a poison. The right dose differentiates a poison from a remedy." This statement is properly regarded as a landmark in the development of the science (Figure 1-2).

Figure 1-1 P. A. Paracelsus (1493-1541)

This Swiss physician and scientist questioned and rejected the irrational medicine of his time. He realized especially the crucial importance of dose in relation to both the adverse and the beneficial. effects of chemicals.

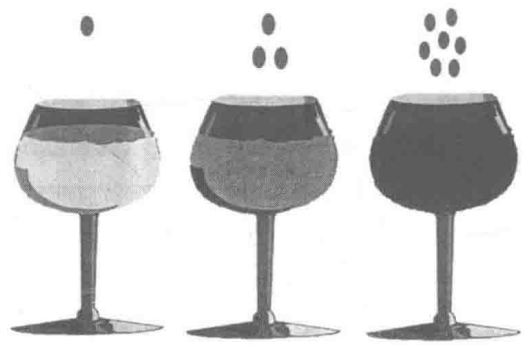

Figure 1-2 Effects of amount on response

The greater the dose, the greater the effect. Fill three large glasses with approximately 3/4 water. This represents the approximate water content of an individual. Put one drop of blue food color in the first glass, three in the second glass, and then seven in the last glass. Stir with a pen and look at the change in color as a response to increased dose of food color in each glass. Think how some chemicals, caffeine being one, distribute throughout total body water.

The development of the industrial revolution stimulated a rise in many occupational diseases. During this period of time, occupational toxicology was established and advanced by the work of Bernardino Ramazzini. His classic, published in 1700 and entitled *Discourse on the Diseases of Workers*, set the standard for occupational medicine. Percival Pott's (1795) recognition of the role of soot in scrotal cancer among chimney sweeps was the first reported example of polyaromatic hydrocarbon carcinogenicity.

The nineteenth century dawned in a climate of industrial and political revolution. Organic chemistry was in its infancy in 1800, but by 1825 phosgene and mustard gas had been synthesized. These two agents were used in World War Ⅰ as war gases.

Another significant figure in toxicology was Mathieu Joseph Bonaventure Orfila (1787-1853), a Spaniard working at the University of Paris in the early nineteenth century, who is said to be the father of modern toxicology (Figure 1-3). He clearly identified toxicology as a separate science. He conducted numerous quantitative toxicological studies on experimental animals, relating the dose of a toxic agent to the biological effects that ensued. Orfila also made major contributions to the special area of forensic toxicology. He applied the methods of analytical chemistry to tissues from autopsy material and exhumed bodies to detect the presence of poisons as proof of poisoning. Orfila also critically examined the procedures used at this time in the treatment of poisoning, many of which were ineffective. Many of his recommendations concerning the elimination of poisons from the body and the use of artificial respiration remain valid today.

Figure 1-3 M. J. B. Orfila (1787-1853)
A Spanish chemist and physician, he can properly be called "the father of modern toxicology". His two-volume work, published as an English translation in 1817, was the first textbook of toxicology.

Many German scientists contributed greatly to the growth of toxicology in the late nineteenth and early twentieth centuries. Among the giants of the field are Oswald Schmiedeberg (1838-1921) and Louis Lewin (1850-1929). Schmiedeberg's research focused on the synthesis of hippuric acid in the liver and the detoxification mechanisms of the liver in several animal species. Lewin made contributions to the chronic toxicity of narcotics and other alkaloids.

Modern Age

Toxicology has evolved rapidly during the twentieth century. The exponential growth of the discipline can be traced to the World War Ⅱ era with its marked increase in the production of drugs, pesticides, munitions, synthetic fibers, and industrial chemicals.

Prohibition of alcoholic beverages in the United States opened the door for early studies of neurotoxicology, with the discovery that triorthocresyl phosphate (TOCP), methanol, are neurotoxicants. Mueller's discovery of DDT and several other organohalides such as

hexachlorobenzene and hexachlorocyclohexane, during the late 1920s resulted in wider use of insecticidal agents. The tragic event of sulfanilamide in glycol solution led to the passage of the Copeland bill in 1938, the major bill involving the formation of the U.S. Food and Drug Administration (FDA). The sulfanilamide disaster played a critical role in the further development of toxicology, resulting in work by Eugene Maximillian Geiling in the University of Chicago that elucidated the mechanism of toxicity of both sulfanilamide and ethylene glycol. Studies of the glycols were simultaneously carried out at the U.S. FDA by a group led by Arnold Lehman. The scientists associated with Lehman and Geiling were to become the leaders of toxicology over the next 40 years.

More recently, in 1945, Sir Rudolph Peters studied the mechanism of action of arsenical war gases and so was able to devise an effective antidote known as British Anti-Lewisite. Another seminal event in toxicology that occurred during the World War Ⅱ era was the discovery of organophosphate cholinesterase inhibitors. The importance of the early research on the organophosphates has taken on special meaning in the years since 1960, when these nonbioaccumulating insecticides were destined to replace DDT and other organochlorine insecticides. Toxicologists today owe a great deal to the researchers of chemical carcinogenesis of the 1940s. Much of today's work can be traced to Elizabeth and James Miller's seminal research on reactive intermediate of chemical carcinogenesis and mixed-function oxidases at Wisconsin.

The 1960 were a tumultuous time for society, and toxicology was swept up in the tide. Starting with the tragic thalidomide incident and the publication of Rachel Carson's *Silent Spring* (1962), the field of toxicology developed at a feverish pitch. The end of the 1960s witnessed the "discovery" of TCDD as a contaminant in the herbicide Agent Orange. The discovery of a high-affinity cellular binding protein designated the "Ah" receptor and work on the genetics of the receptor have revolutionized field of toxicology.

The expansion of legislation, journals, and new societies involved with toxicology was exponential during the 1970s and 1980s and showed no signs of slowing down.

Modern toxicology, which is more than 100 years old, is both an experimental and an applied science. It is predictive science that has evolved remarkably since the time of Orfila, particularly in the past 70 years. Recent additions to the discipline include studies of regulatory toxicology: safety evaluation and risk assessment. In this new century, toxicology will be influenced greatly by expanding knowledge in immunology, genetics and molecular biology.

METHODS AND TYPES OF TOXICOLOGY STUDIES

It is, of course, best to rely on human data that have been generated for the same exposure conditions of interest to assess the potential human hazard of a particular chemical. Unfortunately, such data are rarely available. The human data that are most typically available are generated from human populations in some occupational or clinical setting in which the exposure was believed at least initially, to be safe. The exceptions, of course, are those infrequent, unintended poisonings or environmental releases. Thus, data may come from as many as four or five different categories of

toxicology study information for the safety evaluation of a particular chemical. These categories are: basic animal toxicology tests, the less traditional alternative tests (mainly, *in vitro* methods), epidemiology studies, clinical exposure studies, and accidental acute poisonings.

Each type or category of toxicology study has its own advantages and disadvantages and no single test system is likely to be ideal when it's used to assess the potential human hazard or safety of a particular chemical. Therefore, it is necessary to weigh the strengths and weaknesses of each test system in order to reach a conclusion as to the effectiveness of a particular system. These have been summarized in Table 1-1, which lists some of the advantages and disadvantages of toxicology study by category.

Table 1-1 Some advantages and disadvantages of toxicology studies by category

Type of study	Advantages	Disadvantages
***In vivo* methods**	Easily manipulated and controlled Evaluate effects on intact animals and assess organ system interactions Widest range of potential effects to study The chance to identify and elucidate mechanisms of adverse effects	Test species response is of uncertain human relevance Exposures levels may not be relevant to the human exposure level Structural and biochemical differences between test animals and humans who make extrapolation from one to the other difficult
***In vitro* methods**	Less expensive and quick to perform Easier to control for host factors Conservation of animal resources and ethically more acceptable Possible to use human tissue	Cannot fully approximate the complexities that take place in whole organisms Inability to detect delayed and/or chronic toxic effects
Epidemiological studies	The direct observation of effects in humans Real-life exposure conditions relevant to chemical-induced health effects The full range of human susceptibility may be measurable The chance to study the interactive effects of other chemicals	Often costly and time-consuming Many confounding risk factors are present Exposures may have been poorly documented Determining crude endpoints of exposure such as mortality and morbidity Post facto not necessarily designed to be protective of health
Clinical (human) exposure studies	The conditions of these studies are better defined and controlled Most relevant species (humans) to study Exposure conditions may be altered during the exposure interval in response to the presence or lack of an effect making NOAELs* easier to obtain	May be costly to perform The most sensitive group (e.g., young, elderly, infirm) may often be inappropriate for study Primarily limited to examining safe exposure levels or minimally serious effects Usually limited to shorter exposure intervals
Accidental acute poisonings	Exposure conditions are realistic Require very few individuals to perform Inexpensive than other human studies	Accurate exposure information may be lacking The knowledge gained from these studies may be of limited relevance to other human exposure situations

*NOAELs: no observed adverse effect levels

In vivo Methods

In vivo studies are those performed using any intact higher organisms (most commonly, mammals) as a model system. Eight different species are usually used in toxicological whole animal studies. These are, in approximate numbers of animals utilized (from most to least), rat, mouse, rabbit, guinea pig, hamster, dog, ferret, and monkey. There are two main principles underlying all animal experiments in toxicology. The first is that the effects produced by a chemical in laboratory animals, when properly qualified, are applicable to humans. The second is that experimental animals are given chemicals in large amounts (high doses) is a necessary and valid to discover possible hazards in humans because the incidence of an effect in a population is greater as the dose increases.

In vitro Methods

In vitro test systems are those that do not employ intact higher organism as models for predicting potential human effects. There is a wide range of such test systems, which include isolated perfused organs, organ culture, tissue slices, cell cultures (primary cell cultures, established cell lines), tissue homogenates, subcellular fractions, purified enzymes, and lower organisms (prokaryotes). The term, *in vitro* system, is frequently used to include all short-term tests for mutagenicity (e.g., Ames assay). *In vitro* systems per se have a number of limitations which can contribute to their not being acceptable models. At the same time there are substantial potential advantages in using *in vitro* systems. The advantages of using cell or tissue culture in toxicological testing are accurate dosing, quantitation of results, and so on.

Box 1: A cautionary tale

A new drug was being tested at a pharmaceutical company. The first tests were carried out in isolated liver cells *in vitro* and the drug was found to be not toxic to these cells. The drug was then given to experimental animals, in which it caused the destruction of the adrenal glands. When cells from the adrenal gland were used instead of liver cells *in vitro* tests, they were, as expected, destroyed. This was because the cells from the adrenal gland were not able to detoxify the drug whereas the liver cells were. If the ability of the liver cells to detoxify the drug were blocked, they too became susceptible to the toxic effect of the drug. Liver cells are the cells most often used *in vitro* because they are the easiest to prepare and use. They are also often the most readily available kinds of human cell. The toxicity illustrated by this example could easily occur in humans if isolated cells alone were used to test new chemicals.

Epidemiological Studies

Epidemiology and toxicology differ in many other ways but principally in that epidemiology is essentially an observational science, in contrast to the experimental nature of toxicology. Despite the many problems inherent to epidemiological studies including various biases, confounding factors, and inadequate quantitation of exposures, these studies offer a major advantage over those

conducted with animals: providing the actual health experiences of human beings subjected to real-life exposures.

Epidemiological data from well conducted human epidemiological studies are the most convincing of a causal association between chemical exposure and disease, and therefore can be very useful for identification of the potential human hazard. Such data are useful in confirming the safety indicated by animal studies after the establishment of NOAEL. The data are also useful in subsequent periodic reviews, and might facilitate a re-evaluation of the safety standard.

Clinical (Human) Exposure Studies

In addition to epidemiological surveys of populations exposed to a toxic chemical under normal conditions of use, clinical experimental exposure studies in human volunteers are also an important source of information for human toxicological data. Although an experiment is defined as observations under controlled conditions of exposure, there is, at times, only a gray area that distinguishes an experiment with human subjects from observations on human subjects under natural conditions. Such investigations are most often restricted for ethical reasons to the examination of mild, temporary effects of short-term exposures in a limited number of subjects.

Certain types of information about the effects of chemicals can only be obtained by direct observations on man. Often, carefully controlled experiments can provide significant information at doses well below those anticipated to be "safe"; measurement of subtle changes of reaction time, behavioral functions, and sensory responses may be examples.

Accidental Acute Poisonings

These studies are typically case reports or a small case series, and so, measures of individual variations in response may be difficult to estimate.

CHALLENGES AND FUTURE PROSPECTS

During the past several decades, toxicology has developed more rapidly than any other science in a comparable period of time. From a discipline largely descriptive of deleterious effects on intact animals, toxicology now embraces all aspects of modern biology from molecular biology to highly sophisticated instrumental analysis. The philosophical basis has shifted from routine risk analysis based primarily on mortality or pathological endpoints to an analysis of mechanisms of toxic action and the development of new paradigms of risk assessment that include mechanistic considerations.

Toxicology's advances are often based on utilizing concepts and techniques developed from basic biomedical research. The field of toxicology has developed a well-characterized set of techniques to assess the behavioral and histopathological consequences of exposure to chemicals using a number of animal models. These techniques are suitable for determining crude endpoints of exposure such as death but not optimal for assessing the more subtle effects of very low level of multi-agent chemical exposure, nor do they offer mechanistic explanations at the molecular level. More recently, *in vitro* techniques using mammalian cell culture, including human cells, have been

developed. These approaches offer high-throughput, inexpensive assays using defined cell types. We now know that gene activity is exquisitely sensitive to environmental perturbations and that genetic regulation is responsive long before the elaboration of long-term pathologies. It is therefore possible to develop a predictive toxicology based on analyses of the genome, proteome and metabolome.

At the beginning of the twenty-first century, the practice of toxicology is undergoing many changes, and still, toxicology faces many challenges. Some of these challenges come from rapid advances in technology, both in biotechnology and bioinformatics. Others are posed by need for continuous review and reappraisal of procedures for evaluating chemical safety. Several recent toxicology issues where progress has been made have drawn attention and are deserving of a review here.

Toxicogenomics: Today's New Technique Revolution in Toxicology

The unprecedented advances in molecular biology during the last two decades have led to a new subdiscipline of toxicology: "toxicogenomics", the application of the functional genomics technologies (transcriptomics, proteomics and metabolomics) in toxicology enables the study of adverse effects of xenobiotic substances in relation to structure and activity of the genome.

In its broadest sense toxicogenomics includes studies of the cellular products controlled by the genome. The new "global" methods of measuring families of cellular molecules, such as RNA, proteins, and intermediary metabolites have been termed "-omic" technologies, based on their ability to characterize all, or most, members of a family of molecules in a single analysis. With these new tools, we can now obtain complete assessments of the functional activity of biochemical pathways, and of the structural genetic (sequence) differences among individuals and species, that were previously unattainable. These powerful new methods of high-throughput and multi-endpoint analysis include gene expression arrays that will soon permit the simultaneous measurement of the expression of all human genes on a single "chip". Likewise, there are powerful new methods for protein analysis and for analysis of cellular small molecules (e.g., metabolites). These new methods have already facilitated significant advances in our understanding of the molecular mechanisms of xenobiotic-induced cell and tissue damage.

It can be anticipate that these new technologies will (1) lead to new families of more sensitive and specific biomarkers of exposure and effect that permit monitoring of subtle gene expression changes; (2) provide an increased understanding of the influence of genetic variation on toxicological outcomes; and (3) allow identification of the most sensitive subgroups that are transformed from an amorphous entity into a clearly defined genetic subset of individuals within the human population.

The biological response to environmental exposure is so complex and involves so many interactive factors and networks that the use of a "systems toxicology" analytical approach is required. Systems toxicology investigates the interaction between xenobiotics and biological systems through monitoring the changes of molecular expression (transcript, protein and metabolite profiling) and conventional toxicological parameters, and then iteratively integrating various response data with bioinformatics and computational techniques. Toxicology is gradually evolving