Third Edition

Regulatory Toxicology

Edited by **Shayne C. Gad**

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Preface

Regulatory requirements for the toxicologic safety testing assessment of products have become much more globally harmonized and scientifically complex since the second edition of this volume was published in 2001.

While there is clinical (human) testing for safety in some product areas (drugs, medical devices, and cosmetics), testing in animal models is still predominate. However, nonanimals or *in vitro* models time continues to gain importance for reasons of concern about animal welfare, economics, the need for greater sensitivity, and a better understanding of the mechanisms and causes of toxicity.

As the contents of this volume demonstrate, there now exists a broad range of *in vitro* models for use in either identifying or understanding most forms of toxicity. The availability of *in vitro* models spans both the full range of endpoints (irritation, sensitization, lethality, mutagenicity, and developmental toxicity) and the full spectrum of target organ systems (skin, eye, heart, liver, kidney, nervous system, etc.). This volume devotes chapters to each of these specialty areas from a perspective of presenting the principal models and their uses and limitations.

Chapters that overview the principles involved in the general selection and use of models and that address the issues of safety concerns and regulatory acceptance of these methods are also included.

While this volume seeks to achieve an overview of current practices and requirements (particularly in the non-medical areas), as in any such volume, portions will be dated but not obsolete. The authors and I hope this will provide a sound basis for broad understanding and utilization of these models and their continuing improvement.

Shayne C. Gad

Editor

Shayne C. Gad, BS (Whittier College, Chemistry and Biology, 1971) and PhD in Pharmacology/Toxicology (Texas, 1977), DABT, is the principal of Gad Consulting Services, a twenty-five-year-old consulting firm with nine employees and more than 500 clients (including 140 pharmaceutical companies in the US and 50 overseas). Prior to this, he served in director-level and above positions at Searle, Synergen, and Beckton Dickinson. He has published 50 books and more than 350 chapters, articles, and abstracts in the fields of toxicology, statistics, pharmacology, drug development, and safety assessment. He has more than 40 years of broad-based experience in toxicology, drug and device development, statistics, and risk assessment. He has specific expertise in neurotoxicology, *in vitro* methods, cardiovascular toxicology, inhalation toxicology, immunotoxicology, and genotoxicology. Past president of the American College of Toxicology, the Roundtable of Toxicology Consultants, and three of SOT's (Society of Toxicology) specialty sections. He has direct involvement in the preparation of Investigational New Drug applications (INDs, 115 successfully to date), New Drug Application (NDA), Product License Application (PLA), Abbreviated New Drug Application (ANDA), 501(k), Investigational Device Exemption (IDE), Common Technical Document (CTD), clinical data bases for phase 1 and 2 studies, and Premarket Approval Applications (PMAs). He has consulted for the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and National Institutes of Health (NIH), has trained reviewers, and has been an expert witness for the FDA. He has also conducted the triennial toxicology salary survey as a service to the profession for the last 29 years.

Dr. Gad is also a retired Navy officer with more than 26 years in service.

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1 Introduction

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HISTORICAL PERSPECTIVE

Safety and toxicity testing (also called safety assessment or biocompatibility testing in different regulatory venues) is a necessary and vital part of bringing any chemical- or biological-containing and technologically advanced product to market under acceptable conditions of safe use. Stripped of its technical essence, toxicological testing could be described as the process of giving large amounts of commercial products to either large numbers of experimental animals or *in vitro* test systems, which are then exhaustively studied either as a whole or their component materials and measured for evidence of adverse effects. This, of course, oversimplifies the process and understates the purpose of such testing, which brings us to the question, what exactly is the purpose of such testing? Simply put, a great deal of toxicological testing and research is performed to comply with governmental regulations. While there are moral and ethical reasons for testing products prior to human exposure, testing requirements are codified by the law on a global scale. Ours, after all, is a civilized society. Many books and texts on the science of toxicology have been published in the 15 years since the previous edition of this book. It remains an expanding field with conflicting attempts to harmonize regulations globally, while creating precisely defined requirements in the face of an ever evolving technology field. The first edition of *Casarett and Doull's Toxicology* had only 482 pages in 1975, while the eighth edition in 2013 had 1,454 large format pages.

Other primary texts on the science of toxicology are listed in Table 1.1. In most of these texts, the emphasis is, rightfully, on the science and technology of toxicology. Most include a chapter on regulatory toxicology, yet most students receive at best a perfunctory introduction to regulatory concerns—usually an overview of Good Laboratory Practices (GLPs). For most doctoral students in toxicology, the GLPs are only a distant drone that hampers and confuses real science with meaningless procedures and paperwork. As a result, most contract lab or regulatory toxicologists begin their careers with little basic cognizance of the regulations that will govern the context, if not the content, of the job or product and this is just the beginning of what is to come. As this book seeks to make clear, virtually all commercial products have to meet regulatory toxicology requirements in their approval for market entry, manufacturing, distribution, and disposal. It is the object of this book to address this regulatory gap. This is a scientist's, engineer's, and manager's guide to these globally spanning regulations. We presume that the reader has a toxicological background and is familiar with basic study designs and terminology. The coverage here is neither exhaustive nor

TABLE 1.1
Key Safety Assessment Reference Texts

Text	Edition	Author, Year
Burger's Medicinal Chemistry and Drug Discovery	7th	Abraham (2010)
Documentation of the Threshold Limit Values and Biological Exposure Indices	7th	ACGIH (2012)
Handbook of Pharmaceutical Additives	3rd	Ash and Ash (2007)
Handbook of Food Additives	3rd	Ash and Ash (2008)
General and Applied Toxicology	3rd	Ballantyne et al. (2009)
Patty's Toxicology	6th	Bingham and Cohrssen (2012)
Martindale: The Complete Drug Reference		Brayfield (2014)
Registry of Toxic Effects of Chemical Substances (RTECS)		CDC (2018)
Contact Dermatitis		Cronin (1980)
Medical Toxicology	3rd	Dart (2004)
Toxicology of Drugs and Chemicals		Deichmann and Gerard (1996)
Pharmacotherapy: A Pathophysiologic Approach	9th	Dipiro et al. (2014)
Inactive Ingredient Database		FDA (2018)
Clinical Toxicology		Ford (2001)
Acute Toxicology Testing	2nd	Gad and Chengelis (1998)
Clinical Toxicology of Commercial Products	5th	Gosselin et al. (1984)
Toxicology of the Eye	4th	Grant (1993)
Hamilton and Hardy's Industrial Toxicology	6th	Harbison et al. (2015)
Haye's Principles and Methods of Toxicology	6th	Hayes an Kruger (2014)
Casarett and Doull's Toxicology: The Basic Science of Poisons	8th	Klaassen (2013)
Carcinogenically Active Chemicals: A Reference Guide		Lewis (1991)
Sax's Dangerous Properties of Industrial Materials	12th	Lewis (2012)
Annual Report on Carcinogens	14th	NTP (2016)
The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals	15th	O'Neil (2013)
Physician's Desk Reference	71st	PDR (2017)
Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens	6th	Pohanish (2011)
Chemical Hazards of the Workplace		Proctor and Hughes (1978)
Chemically Induced Birth Defects	3rd	Schardein (2000)
Scientific American Medicine	Monthly	Decker (2018)
Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose	4th	Shannon et al. (2007)
Catalog of Teratogenic Agents	13th	Shepard and Lemire (2010)
Clinical Significance of Particular Matter: A Review of the Literature		Turco and Davis (1973)
Encyclopedia of Toxicology	3rd	Wexler (2014)
Wiley Handbook of Current and Emerging Drug Therapies		Wiley-Interscience (2007)

encyclopaedic, but provides a guide to current global regulations for a toxicologist, health scientist, or other professional who has little legal interest or training. The central focus of this book is on the use of toxicology in a regulatory and legal arena. The science of toxicology is a secondary concern and, in fact, is discussed in only a cursory fashion.

Other than as an instrument of torture, war, and execution, the use of toxicology by government is a relatively new phenomenon. While the appropriate use of chemicals has been a central part of the industrial (technological and biotechnological) revolution that has resulted in a high standard of living, the unrestricted sale, use, and disposal of chemicals has resulted in more than a few problems. For a variety of factors involved in modern technology (as with centralization of the food supply) and urbanization in the nineteenth century, large numbers of people have increasingly come