Third Edition

Practical Toxicology

Evaluation, Prediction, and Risk

David Woolley
Adam Woolley

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For Sandy, David, Stewart, and Kate.

APAHW

For Mairi, Ben and Cara, and for my Mother and Father.

DRW

All things are poison and nothing without poison;
only the dose determines that a thing is not poison.

Philippus Theophrastus Aureolus Bombastus von Hohenheim
(Paracelsus, 1493–1541), alchemist, physician, and astrologer

If a man will begin with certainties, he shall end in doubts;
but if he will be content to begin with doubts,
he shall end in certainties.

Francis Bacon
Philosopher, statesman, scientist, jurist, orator, and author,
from *The Advancement Of Learning* (1605);
Bacon has been considered to be the father
of the empirical approach and of critical scientific thought.

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Preface

Toxicology is a dynamic subject with unique relevance to the public and, as a result, places heavy responsibility on the people who practice it, those who register or accredit toxicologists, and those who regulate or manage it. As a consequence, toxicologists and toxicology are inherently conservative, and the practice of the discipline reflects this. In this case, practice includes both the conduct of the experiments and their interpretation by regulatory authorities or the toxicological community. Whatever its purpose, good-quality toxicological evaluation is essential. Although there is a wide-ranging bibliography in toxicology, the textbooks do not necessarily tell the reader how to conduct a toxicological evaluation and then to extend that process to risk assessment. In addition, the procedures with which toxicity studies are designed and conducted are not easily accessible to the reader who wishes to learn more about the subject and, perhaps, to understand the processes of evaluation and risk assessment, and their application in the real world.

The first and second editions of this book arose out of our perception that there was a need for a practical, user-friendly introductory text for those coming to toxicology from related fields or professions, and who need some insight into how toxicity studies and investigations are carried out. We thought that the book should be informative but readable and should also act as a gateway to the subject, indicating where further information can be found, including the use of websites for literature searches and other areas, such as regulations and guidelines.

The book is set out as a guide on how to evaluate toxicity and then how to handle and use the data that are generated. After an introduction to the concepts of toxicology, the book takes the reader through the processes of toxicity testing and interpretation before looking at the concepts of hazard prediction and risk assessment and management. Two final chapters look at the evaluation of different chemical classes and at the future of toxicity testing and risk assessment.

The audience for this book includes new graduates starting careers in toxicology, those coming to the subject from different fields, and specialists in particular areas of toxicology who need some background on the other areas.

Toxicology has been evolving especially quickly since the second edition was published, and this new edition includes several new chapters or sections that address *in silico* toxicology, nanotoxicology, immunotoxicity of biological products, and risk assessment of extractables, leachables, and other impurities in drug substances and products. All the existing chapters have been thoroughly reviewed and revised to bring them up to date with current practice, including comment on add-ons to conventional studies (e.g., safety pharmacology and bone marrow micronucleus tests) and new test designs (e.g., OECD 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test).

Toxicological evaluation of chemicals is conducted within a number of overlapping regulatory frameworks, covering chemical or product classes such as agrochemicals or plant protection products, industrial chemicals, medical devices, cosmetics and consumer products, and pharmaceuticals. However, the basic principles of toxicology

are common to all areas, whether you are evaluating pharmaceuticals or industrial chemicals. The differing frameworks result in slightly different study designs and durations, while the objectives are subtly oriented toward the product class. Broadly, there are two types of chemical exposure: unintentional (e.g., agrochemicals) and intentional (primarily pharmaceuticals). These two categories drive the objectives and regulatory frameworks for evaluation. We are largely pharmaceutical toxicologists, so there is some bias toward this area of toxicology, but the principles outlined here are applicable to all areas of toxicological investigation.

Much toxicology is conducted for safety evaluation; however, it should be remembered that safety is a negative and, as such, cannot be proven. As stated in the front pages, Paracelsus realized the basic principle of toxicology that the elusive concept of safety is solely dependent on dose; water is toxic, if taken to excess.

Throughout the book, words like "may," "could," and "however" appear frequently; this is tacit recognition that there are few certainties in life beyond the single gold standard that wherever a statement is made, there will be someone to disagree with it. As with any walk of life, if a situation is seen as black and white, it simply means that the intervening shades of gray have not been discovered or are not understood. This is particularly true for any aspect of judgment or interpretation; differing opinions between toxicologists, especially toxicological pathologists, can be extremely frustrating for anyone needing a definitive answer to a question of safety. Getting a decision wrong in toxicology can be associated with far-reaching adverse effects and with consequent litigation or (politically far worse) loss of votes. For this reason, toxicologists (especially those in regulatory agencies) tend to be conservative in their opinions; this is not necessarily a bad thing. However, conservatism is made more likely by poor, incomplete, or poorly understood data or results, which may lead to imposition of inappropriately restrictive exposure limits.

The intention of this book is to provide a basis of knowledge—a series of pointers—which can be expanded through use of the references given. There are many different ways of achieving an objective in toxicological study and evaluation, and this book cannot pretend to address them all or to be absolutely definitive in any one area.

The future of toxicology is assured; the means of its future investigation is changing, and it behooves us to think about what we are doing or what we are asking toxicologists to do (or, more importantly, not to do). As toxicologists, we should do nothing without thought, without considering the impact of our actions on the animals we use, the public, or a host of other stakeholders. In many ways, if we cause the reader to think more about toxicology and its importance and impact on this world, we will have achieved one of our unwritten objectives.

Acknowledgments

Such a wide-ranging text could not be prepared in isolation. Many thanks go to those who assisted with the first and second editions, whose contributions are still valid and provided valuable guidance and comment. In addition, Annette Dalrymple provided assistance with the overview of the Pig-a assay and other tobacco-related texts. Having said that, all the opinions expressed are our own, as is responsibility for any errors that may still lurk in the text.

We also would like to thank Sandy Woolley, for obtaining the necessary permissions. Finally, I would like to thank Barbara Norwitz, who initiated this third edition, and Steve Zollo for taking up the baton when Barbara retired.

About the Authors

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David Woolley, PhD BScBioMedSci (Pharmacology) CBiol MRSB ERT, has been a consultant and director of *In Silico* Toxicology at ForthTox since 2008 following the completion of his PhD in neuropharmacology. He has extensive experience with the use of Derek Nexus, Meteor, Leadscope, ToxTree, Vega, and TEST and has prepared reports for submission to regulatory authorities, particularly on the potential mutagenicity and genotoxicity of pharmaceutical impurities, leachates, and degradants. He has also prepared nonclinical overviews on behalf of major pharmaceutical companies and prepared numerous toxicological overview reports and biological evaluations for medical devices. David is a European Registered Toxicologist and a Chartered Biologist. He is a member of the British Toxicology Society, the British Pharmacology Society, the Royal Society of Biology, the Society of Toxicology, and the American College of Toxicology.