

# An Introduction to Toxicology



Philip C. Burcham

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*For my wonderful parents*



## About the Author

After undergraduate majors in chemistry and pharmacology, Phil Burcham completed a Ph.D. in biochemical toxicology in 1990 under the supervision of Dr. Andrew W Harman at the University of Western Australia. He then completed post-doctoral training in molecular toxicology under Lawrence J Marnett at Vanderbilt University. After teaching pharmacology and toxicology at the University of Adelaide for 12 years, he returned to Perth to establish a research group focused on studying noxious smoke constituents. His research efforts have led to 55 scientific publications. He has over 20 years of experience in teaching toxicology, pharmacology and drug metabolism to science, medicine, pharmacy, podiatry and dentistry students. His popular team-taught freshers course, *Drugs that Changed the World*, attracts over 400 enrolments. He currently serves on the Editorial Advisory Board of *Chemical Research in Toxicology* and the Editorial Board of *Toxicological Sciences*. He is also a member of the toxicology subsection of the *Faculty of 1,000 (Biology)*.





# Preface

Some five or six decades ago, the normal perils of childbirth were shockingly escalated for an unsuspecting generation of mothers in Germany, Canada, Australia and the UK. In a ghastly epidemic that unfolded over several years beginning in the late 1950s, distraught parents were confronted by the birth of babies with severely disfigured upper and lower limbs. By the time the sedative drug thalidomide was identified as the culprit, some 10,000 infants were affected – assailed within the womb by a poison that condemned its victims to lives of struggle and significantly reduced horizons.

The thalidomide disaster was a jarring wake-up call to a generation of scientists, regulators and physicians, a sharp lesson concerning the need for extreme diligence when testing new drugs for safety and unexpected harmful effects. Inspired by the scope of the disaster, a whole branch of science blossomed into existence – *modern toxicology*. New scientific societies dedicated to studying the harmful effects of drugs and industrial chemicals promptly emerged. New journals appeared for toxicologists wishing to publish their research findings. Innovative scientific institutions as well as university departments offering toxicology training programmes were established all around the world.

In today's fast-moving research enterprise, five decades is a very long time, yet recent history suggests the societal need for toxicology expertise remains as strong as ever. Many significant toxicity-related episodes rocked the global community during the first decade of the new millennium. These included the withdrawal of the arthritis drug Vioxx due to cardiotoxicity concerns; the adulteration of infant formula with the protein-mimic melamine; the contamination of children's toys with lead-containing paints or the solvent 1,4-butanediol; the finding of high acrylamide levels in potato chips; and many deaths in Bangladesh and Nigeria due to respective outbreaks of arsenic and lead poisoning. In the USA, ongoing controversies over the human and environmental impact of the 2010 Deepwater Horizon oil spill as well as chronic exposure to high-volume synthetic chemicals such as the plasticiser Bisphenol A or the herbicide atrazine show that toxicological issues still arouse great public concern. In an era shaped by social media in which immediate, emotive reactions govern public responses to many issues, the need for rigorous, science-based investigation of chemically induced disease remains high.

This book seeks to provide a basic overview of modern toxicology. Due to its introductory scope, it does not endeavour to summarise the entire toxicological enterprise. For example, coverage of topics pertaining to chemical regulation and risk assessment is limited; hence, an apology is offered to any readers seeking to expand their knowledge of these vital topics.

A primary aim is to convey a basic appreciation of contemporary understandings of the *mechanisms* underlying chemically induced disease. This emphasis reflects the dramatic advancements over recent times to understand *how* chemicals inflict harm on cells and body organs. Special stress is placed on the main ‘big idea’ in modern toxicology – namely *bioactivation* – the ubiquitous phenomenon whereby many relatively harmless chemicals are converted to noxious metabolites within the body. We will see how this process helps explain a wide variety of chemically induced toxic syndromes. Since one can complete an entire undergraduate or graduate programme of biological chemistry, biochemistry or cell biology without ever meeting this key concept, bioactivation-dependent toxicity was made a conceptual centrepiece of this volume.

Our journey begins with a potted history of the emergence of modern toxicology (Chap. 1) before exploring some basic concepts relevant to chemically mediated disease (Chap. 2). The various toxicokinetic processes that control the behaviour of chemicals within the body receive attention in Chap. 3 before laying the foundations of a basic understanding of chemical bioactivation in Chap. 4. Various adaptive responses that occur in mammalian systems to counteract the harmful effects of foreign chemicals are introduced in Chap. 5. Separate chapters then explore the relevance of bioactivation to major toxic phenomena such as organ injury, birth defects and cancer (Chaps. 6, 7 and 8). Next, to show how toxicological paradigms can enrich medical understandings of major human diseases, the book closes with explorations of the mechanistic basis for the main disorders plaguing heavy users of two widely consumed ‘chemical mixtures’ – alcoholic beverages (Chap. 9) and tobacco smoke (Chap. 10).

This book attempts to convey some of the adventure and excitement that accompanied the growth of modern toxicology. Readers will also gain appreciation for the achievements of the thousands of researchers who have to date prevented repetition of poisoning episodes that mimic the appalling thalidomide disaster. If my efforts are in any way instrumental in inspiring some budding scientists to embark on a toxicology career, this writing project will have been worthwhile.

In addition to the many individuals who contributed to my own education as a toxicologist, I thank my humanities colleagues at UWA for helping to broaden my awareness of the long-standing interactions between humans and chemicals. I am especially indebted to Dr Philippa Martyr for her insights into the social and historical aspects surrounding alcohol use (Chap. 9). Any limitations in my brief surveys of either scientific or historical issues are certainly my own.

Perth, Western Australia, Australia  
July 2013

Philip C. Burcham

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