The Toxicology of Aflatoxins

Human Health, Veterinary, and Agricultural Significance

Edited by

David L. Eaton
John D. Groopman

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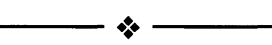

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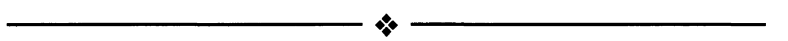
Preface



Over the past thirty years more than 8000 research articles describing the exposure, toxic effects, and mechanisms of action of aflatoxins have been published. The first published reports on the toxicology of aflatoxins pertained primarily to their acute effects, but by the end of the 1960s the carcinogenic potency of these agents was well established and became the focal point of much research. Indeed, the pioneering efforts of George Buchi, who first determined the structural characterization and synthesis of aflatoxins, and Gerald Wogan and Paul Newberne, who individually and collectively pioneered our understanding of the basic biochemistry, toxicology, and carcinogenicity of these agents, are outstanding examples of the application of basic science to a public health problem of global significance. Thus, by the end of the first decade of research on aflatoxins, it was suspected that these compounds were significant human and animal health hazards in various parts of the world. In 1969, Leo A. Goldblatt edited *Aflatoxin: Scientific Background, Control, and Implications,* published by Academic Press. This important book served as a source authority for many years on aflatoxins and provides many insights into the early studies of these agents.

In 1971, aflatoxins were reviewed in Volume 1 of the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. That review was only eleven pages long in the monograph. It was concluded at that time that aflatoxins were possible human carcinogens, but the database was still extremely limited. Twenty years later these mycotoxins

were classified as Group I, known human carcinogens, and the summary of data published in 1993 in Volume 56 of the IARC Monographs is over 150 pages long. This explosion of information reflects the vast increase in information about the mechanisms of action of the aflatoxins over this period of time and reflects the large number of research scientists studying these toxins. The specific knowledge of the chemistry, biochemistry, toxicology, and epidemiology of aflatoxins is far greater than that for any other environmentally occurring chemical carcinogen. Indeed, it is possible to consider the studies of aflatoxin as a template for researching other environmental carcinogens. Toward this end, we have attempted to bring together as comprehensive a group of scientists as possible in assembling this book.

Part I focuses on the acute toxic effects of aflatoxins (Chapters 1 and 2), their biological disposition (Chapters 3–5), and specific aspects of aflatoxin carcinogenicity (Chapters 6–12). Included in these chapters are detailed reviews of the many important mechanistic aspects of aflatoxins that dictate individual and species susceptibility to aflatoxins. The hepatic biotransformation (Chapter 3), pharmacokinetics (Chapter 4), and genotoxin actions (Chapters 7 and 8) of aflatoxins as well as effects on nonhepatic tissues (Chapter 5), nonmammalian organisms (Chapter 6), and modulation by nutritional factors (Chapter 10) are described in detail. Finally, in this section the carcinogenesis of aflatoxin in animal models (Chapter 9) is discussed in the context of the multistage nature of chemical carcinogenesis.

Part II focuses more specifically on our current level of understanding of human exposures and effects of aflatoxins. The current status of the epidemiology of human aflatoxin exposures is detailed in Chapter 11, while Chapter 12 focuses on recent advances in the application of molecular biomarkers to the study of human cancer incidence in aflatoxin-exposed populations. Chapter 13 concludes with an enlightening review and discussion of potential avenues for human therapeutic and/or dietary interventions aimed at reducing liver cancer incidence in high risk populations, derived from our mechanistic understanding of aflatoxin carcinogenesis.

Part III examines agricultural and veterinary aspects of aflatoxin contamination of food and feed, including reviews on the fungal processes and factors that influence aflatoxin production by *Aspergillus* (Chapters 14 and 15), specific veterinary problems associated with aflatoxin contamination of feeds (Chapter 16), and the unique issues and concerns that arise from the excretion of aflatoxin M_1 in milk of dairy cows (Chapter 17). Lastly, current approaches for reducing the presence of aflatoxin contamination in animal feed and human food crops are discussed in detail (Chapter 18).

Part IV focuses on the complicated and difficult, yet extremely important, aspect of analysis of aflatoxins in food, feed, and biological samples. Chapter 19 reviews current approaches to the analytical determination of aflatoxins in complex matrices; Chapter 20 discusses strategies and problems in accurate sampling, preparation, and analysis of aflatoxins in food and feed; and Chapter 21

discusses the recent development of specific antibodies toward aflatoxin—methods that have found widespread use both in biomonitoring human populations and for analytical detection of aflatoxins in food and feed.

Part V concludes the book with a discussion of the important and sometimes controversial aspect of "quantitative risk assessment" of aflatoxins, which have profound regulatory implications, using either or both animal and human data (Chapter 22), and a discussion of the economic impacts of aflatoxin contamination that impact us all (Chapter 23).

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Acknowledgments

We are grateful to all of the contributors for taking the time and effort to complete these chapters in a thorough yet timely manner. In addition to the individual contributions of each of our chapter authors, who are recognized leaders in their respective areas of specialization, many other scientists from around the world have contributed extensively to our understanding of aflatoxin biochemistry and toxicology. The lifelong contribution of Gerald Wogan to the study of aflatoxins should be especially noted, not only for his extensive and continuing publications in this area, but also for his role in training many of the top researchers in the field today. Indeed, many of the chapter authors in this book trained in Dr. Wogan's laboratory.

Many of us who are involved in the investigation of aflatoxins and other natural products find this work fascinating and compelling; however, we are also drawn to these compounds because of their real public health significance. Worldwide variations in daily exposure to aflatoxins are at least 5000-fold and, in some underdeveloped countries, human exposure can exceed 1 mg per day at certain times of the year. In other parts of the developed world, human exposure is much lower, less than 50 ng per day, but the veterinary and other economic consequences of aflatoxin exposure are still great. Given this situation it is hoped that the understanding of basic mechanisms of action of aflatoxins will lead to the design of effective prevention strategies for both the developed and developing world. Fortunately, the past support of many governments and their agencies

have provided the finances necessary to do this research and train the scientists with the skills to tackle these problems. In the future, as new environmental contaminates are discovered, the studies on aflatoxins will provide an important model for how mechanistically driven research can be used to devise and implement appropriate safety regulations to protect the public's health.

Finally, in addition to the many scientists who have provided the scientific substance for this book, we thank Azure Skye for her extensive and excellent administrative support in the development of this book from its inception. We are also grateful to the many people at Academic Press for their assistance, patience, and understanding in working with us to complete this book in a timely manner. We would be remiss without specifically acknowledging the research support provided by the National Institutes of Health, specifically the NCI and NIEHS, for research and training grants that have fostered our own interest in completing this book.

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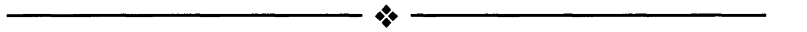
Part I



Experimental Toxicology of Aflatoxins

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