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卡萨瑞特·道尔

6th  
EDITION

毒理学

*Casarett & Doull's*

TOXICOLOGY

THE BASIC SCIENCE OF POISONS

Curtis D. Klaassen



人民卫生出版社



McGraw-Hill

# CASARETT AND DOULL'S TOXICOLOGY

## THE BASIC SCIENCE OF POISONS

Sixth Edition

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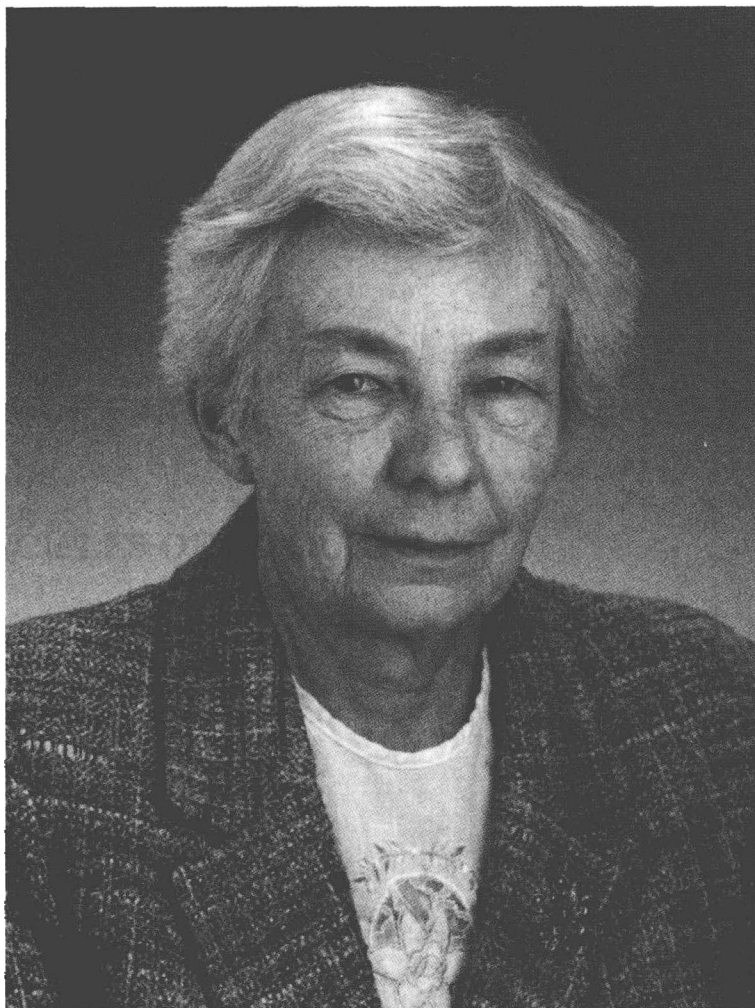
# CASARETT AND DOULL'S TOXICOLOGY

## THE BASIC SCIENCE OF POISONS

What is there that is not poison?  
All things are poison and nothing (is)  
without poison. Solely the dose  
determines that a thing is not a poison.  
*Paracelsus*  
(1493–1541)

### NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The author and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the author nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.



This edition of the textbook is dedicated to the memory of Dr. Mary Amdur, who was a coeditor on editions two through four.

Mary Amdur received her B.S. in Chemistry from the University of Pittsburgh in 1943, and, in just three years, was awarded the Ph.D. in Biochemistry from Cornell. She spent her academic career at the Harvard School of Public Health (1949–1977), Massachusetts Institute of Technology (1977–1989), and the Institute of Environmental Medicine of New York University in Tuxedo Park, New York (1989–1996). She died in February 1998 while flying home from a vacation in Hawaii.

Dr. Amdur was a distinguished toxicologist in the area of air pollution. Her research accomplishments provided seminal contributions to our understanding of the effects of gases and particles on human and animal lungs. She contributed to our knowledge of the adverse effects of sulfuric acid mists and mixtures of gases and particles in the lung. This work had a major role in the establishment of national and international air pollution standards. Her career in toxicology was uniquely distinguished and profound in its impact on public policy and public health.

Dr. Amdur made these accomplishments at a time in which science was strongly male-dominated. Her research career was impaired by a number of barriers, because of this environment (Costa and Gordon, *Toxicol Sci*, 56: 5–7, 2000). In fact, she never was awarded a tenure position at any of the three academic positions where she did her outstanding research.

Dr. Amdur received a number of awards throughout her career. These included the 1974 Donald E. Cummings Memorial Award from the American Industrial Hygiene Association, the 1984 Henry F. Smyth Award from the American Academy of Industrial Hygiene, the 1986 Career Achievement Award from the Inhalation Section of the Society of Toxicology, and the 1989 Herbert E. Stockinger Award from the American Conference of Governmental Industrial Hygienists. In 1997, she became the first woman to receive the Merit Award from the Society of Toxicology.

For those of us who were fortunate to work with Mary Amdur, we will remember not only her scientific accomplishments but also her wit, demeanor, and absolute honesty.

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# PREFACE

The sixth edition of *Casarett and Doull's Toxicology: The Basic Science of Poisons* marks its silver anniversary. The sixth edition, as the previous five, is meant to serve primarily as a text for, or an adjunct to, graduate courses in toxicology. Because the five previous editions have been widely used in courses in environmental health and related areas, an attempt has been made to maintain those characteristics that make it useful to scientists from other disciplines. This edition will again provide information on the many facets of toxicology and especially on the principles, concepts, and modes of thought that are the foundation of the discipline. Mechanisms of toxicity are emphasized. Research toxicologists will find this book an excellent reference source to find updated material in areas of their special or peripheral interests.

The overall framework of the sixth edition is similar to the fifth edition. The seven units are "General Principles of Toxicology" (Unit 1), "Disposition of Toxicants" (Unit 2), "Non-Organ-Directed Toxicity" (carcinogenicity, mutagenicity, and teratogenicity) (Unit 3), "Target Organ Toxicity" (Unit 4), "Toxic Agents" (Unit 5), "Environmental

Toxicology" (Unit 6), and "Applications of Toxicology" (Unit 7).

The sixth edition reflects the marked progress made in toxicology the last few years. For example, the importance of apoptosis, cytokines, growth factors, oncogenes, cell cycling, receptors, gene regulation, transcription factors, signaling pathways, transgenic animals, "knock-out" animals, polymorphisms, microarray technology, genomics, proteonomics, etc., in understanding the mechanisms of toxicity are included in this edition. More information on risk assessment is also included. References in this edition include not only traditional journal and review articles, but, for the first time, internet sites.

The editor is grateful to his colleagues in academia, industry, and government who have made useful suggestions for improving this edition, both as a book and as a reference source. The editor is especially thankful to all the contributors, whose combined expertise has made possible a volume of this breadth. I especially recognize John Doull, the original editor of this book, for his continued support.

# PREFACE TO THE FIRST EDITION

This volume has been designed primarily as a textbook for, or adjunct to, courses in toxicology. However, it should also be of interest to those not directly involved in toxicologic education. For example, the research scientist in toxicology will find sections containing current reports on the status of circumscribed areas of special interest. Those concerned with community health, agriculture, food technology, pharmacy, veterinary medicine, and related disciplines will discover the contents to be most useful as a source of concepts and modes of thought that are applicable to other types of investigative and applied sciences. For those further removed from the field of toxicology or for those who have not entered a specific field of endeavor, this book attempts to present a selectively representative view of the many facets of the subject.

*Toxicology: The Basic Science of Poisons* has been organized to facilitate its use by these different types of users. The first section (Unit I) describes the elements of method and approach that identify toxicology. It includes those principles most frequently invoked in a full understanding of toxicologic events, such as dose-response, and is primarily mechanistically oriented. Mechanisms are also stressed in the subsequent sections of the book, particularly when these are well identified and extend across classic forms of chemicals and systems. However, the major focus in the second section (Unit II) is on the systemic site of action of toxins. The intent therein is to provide answers to two questions: What kinds of injury are produced in specific organs or systems by toxic agents? What are the agents that produce these effects?

A more conventional approach to toxicology has been utilized in the third section (Unit III), in which the toxic

agents are grouped by chemical or use characteristics. In the final section (Unit IV) an attempt has been made to illustrate the ramifications of toxicology into all areas of the health sciences and even beyond. This unit is intended to provide perspective for the nontoxicologist in the application of the results of toxicologic studies and a better understanding of the activities of those engaged in the various aspects of the discipline of toxicology.

It will be obvious to the reader that the contents of this book represent a compromise between the basic, fundamental, mechanistic approach to toxicology and the desire to give a view of the broad horizons presented by the subject. While it is certain that the editors' selectivity might have been more severe, it is equally certain that it could have been less so, and we hope that the balance struck will prove to be appropriate for both toxicologic training and the scientific interest of our colleague.

L.J.C.

J.D.

Although the philosophy and design of this book evolved over a long period of friendship and mutual respect between the editors, the effort needed to convert ideas into reality was undertaken primarily by Louis J. Casarett. Thus, his death at a time when completion of the manuscript was in sight was particularly tragic. With the help and encouragement of his wife, Margaret G. Casarett, and the other contributors, we have finished Lou's task. This volume is a fitting embodiment of Louis J. Casarett's dedication to toxicology and to toxicologic education.

J.D.

# CASARETT AND DOULL'S TOXICOLOGY THE BASIC SCIENCE OF POISONS

What is there that is not poison?  
All things are poison and nothing (is)  
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