· SIXTH EDITION ·

HAMILTON & HARDY'S

INDUSTRIAL TOXICOLOGY

Edited by

RAYMOND D. HARBISON

MARIE M. BOURGEOIS · GIFFE T. JOHNSON

WILEY

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CONTRIBUTORS

Alison J. Abritis, MPH, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Mayowa Amosu, Laboratory Manager, Smith Lab Environmental Health Sciences, University of Georgia, Athens, GA, USA

Lisa A. Bailey, PhD, Gradient Corporation, Cambridge, MA, USA

James C. Ball, PhD, Research Scientist, Integrated Risk Information System (IRIS), U.S. Environmental Protection Agency, Washington, DC, USA

Marek Banasik, MD, PhD, Institute of Public Health and Environmental Protection, Warsaw, Poland

Charles Barton, PhD, DABT, Senior Toxicologist & Toxicology Program Manager, Oak Ridge Institute for Science and Education (ORISE), Oak Ridge Associated Universities (ORAU), Oak Ridge, TN, USA

Robert W. Benson, PhD, Toxicologist, Office of Partnerships and Regulatory Assistance, U.S. Environmental Protection Agency, Denver, CO, USA

J. Michael Berg, PhD, Toxicologist, Center for Toxicology and Environmental Health, LLC, Houston, TX, USA

Leslie A. Beyer, MS, DABT, Gradient Corporation, Arlington, MA, USA

Robyn Blain, MS, PhD, Technical Specialist, ICF International, Fairfax, VA, USA

Jacob R. Bourgeois, BS, ChE, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Marie M. Bourgeois, PhD, MPH, Research Assistant Professor, Center for Environmental/Occupational Risk Analysis and Management, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

K. Paul Boyev, MD, Associate Professor, Director, Division of Otology-Neurotology, Residency Program Director, Department of Otolaryngology-Head and Neck Surgery, College of Medicine, University of South Florida, Tampa, FL, USA

Michael A. Cardinale, MS, CIH, Environmental Health Officer John F. Kennedy Space Center National Aeronautics and Space Administration NASA-Kennedy Space Center, FL, USA

Vincent Castranova, PhD, National Institute for Occupational Safety and Health, Morgantown, WV, USA

Clara Y. Chan, MSc, DABT, Senior Toxicologist, Veritox, Inc., Redmond, WA, USA

Juhi K. Chandalia, Data Scientist, Zettics, Concord, MA, USA

John Christie, RD, CSSD, CSCS, Performance Nutritionist, Phoenix, AZ, USA

C. Clifford Conaway, PhD, DABT, Department of Pharmacology New, York Medical College, Valhalla, NY, USA

Jayme P. Coyle, MSPH, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Ghazi A. Dannan, PhD, Office of Research and Development, National Center for Environmental Assessment,

U.S. Environmental Protection Agency, Washington, DC, USA

Ushang Desai, MBBS, MPH, Research Assistant, Center of Environmental & Occupational Risk Analysis, Department of Environmental & Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

David G. Dodge, MS, DABT, Senior Toxicologist, Gradient, Cambridge, MA, USA

Anna M. Fan, PhD, Chief, Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland/Sacramento, CA, USA

Nikolay M. Filipov, PhD, Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, GA, USA

M. Rony Francois, MD, MSPH, PhD, Director for Public Health Services, Supervisory Occupational Medicine Physician, Public Health Emergency Officer, Naval Health Clinic, Corpus Christi, TX, USA

Jason M. Fritz, PhD, Toxicologist, Office of Research and Development, National Center for Environmental Assessment/Integrated Risk Information System, U.S. Environmental Protection Agency, Washington, DC, USA

Jason S. Garcia, MPH, CPH, College of Public Health, University of South Florida, Tampa, FL, USA

Phillip T. Goad, PhD, Toxicologist, Center for Toxicology and Environmental Health, LLC, North Little Rock, AR, USA

James Godin, DPT, CSCS, Director of Tactical Performance Rehabilitation, EXOS, Inc., Tampa, FL, USA

Julie E. Goodman, PhD, DABT, Gradient Corporation, Cambridge, MA, USA

Joseph M. Greco, CHP, CLSO, VP, Imaging Physics, Upstate Medical Physics – A Landauer Medical Physics Partner, Victor, NY, USA

Maureen R. Gwinn, PhD, DABT, Associate National Program Director, Community Health, Sustainable and Healthy Communities, National Center for Environmental Assessment, Washington, DC, USA

Kambria K. Haire, MPH, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Kelly W. Hall, MPH, PhD, Associate Director, Toxicology, Global Product Safety and Toxicology, Merck Consumer Care, Memphis, TN, USA

Ali K. Hamade, PhD, DABT, Environmental Public Health Program Manager, Alaska Section of Epidemiology, Division of Public Health, Department of Health and Social Services, Anchorage, AK, USA

Yehia Y. Hammad, DSc, Professor, College of Public Health University of South Florida, Tampa, FL, USA

Raymond D. Harbison, PhD, ATS, Professor, Center for Environmental/Occupational Risk Analysis and Management, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Stephen C. Harbison, PhD, MPH, Southwestern Energy Company, Conway, AR, USA

Jerry F. Hardisty, DVM, Experimental Pathology Laboratories, Inc., Research Triangle Park, NC, USA

Judith W. Henck, PhD, DABT, Research Advisor, Nonclinical Safety Assessment, Eli Lilly and Company, Greenfield, Indiana, USA

Thomas W. Hesterberg, PhD, MBA, Senior Toxicologist, Center for Toxicology and Environmental Health, LLC, Denver, CO, USA

David J. Hewitt, MD, MPH, DABT, Resources for Environmental and Occupational Health (REOH), Missoula, MT, USA

James V. Hillman, MD, FAAP, FACEP, FACMT, Clinical Professor of Pediatrics, University of South Florida College of Medicine, Tampa, FL, USA

R. Timothy Hitchcock, CIH, CLSO, LightRay Consulting, Inc., Cary, NC, USA

Ching-Hung Hsu, PhD, DABT, HEC Pharm Group, China

Kathleen T. Jenkins, MD, MPH, Florida Association of Occupational and Environmental Medicine, Tampa, FL, USA

David R. Johnson, MD, MS, MHA, FACOEM, DABT, Professor Center for Environmental/Occupational Risk Analysis and Management, Department of Environmental and Occupational Health, University of South Florida College of Public Health, Tampa, FL, USA

Giffe T. Johnson, PhD, MPH, Research Assistant Professor, Center for Environmental/Occupational Risk Analysis and Management, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Paul Jonmaire, PhD, Director, Health & Safety/Toxicology, Ecology and Environment, Inc., Lancaster, NY, USA

Sharon S. Kelley, MS, PhD, Chief Executive officer, Associates in Emergency Medical Education, Inc., Tampa, FL, USA

Bruce J. Kelman, PhD, DABT, FATS, European Registered Toxicologist, United Kingdom and EUROTOX Registries, University of Edinburgh, Edinburgh, UK

Laura E. Kerper, PhD, Gradient Corporation, Cambridge, MA, USA

Robert A. Klocke, MD, Emeritus Professor and Chair, Department of Medicine, University at Buffalo, Buffalo, NY, USA

David Y. Lai, PhD, DABT, Senior Toxicologist, Risk Assessment Division, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, DC, USA

Alex LeBeau, PhD, MPH, Toxicologist/Environmental Scientist, Conestoga-Rovers & Associates, Inc., Dallas, TX, USA

Janice S. Lee, MHS, PhD, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA

Richard V. Lee, Professor, Department of Medicine, School of Medicine, University of Buffalo, The State University of New York, Buffalo, NY, USA

Thomas A. Lewandowski, PhD, DABT, ERT, Toxicologist, Gradient Corporation, Seattle, WA, USA

Haixia Lin, Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Jefferson, AR, USA

Christopher M. Long, ScD, DABT, Principal Scientist, Gradient Corporation, Cambridge, MA, USA

April M. Luke, MS, Toxicologist, Office of Research and Development, National Center for Environmental Assessment/Integrated Risk Information System, U.S. Environmental Protection Agency, Washington, DC, USA

Ann Lurati, ARNP, ACNP-BC, DNP, MPH, COHN-S, Occupational Health Nurse Practitioner, University of South Florida, Tampa, FL, USA

Michael H. Lumpkin, PhD, DABT, Senior Toxicologist, Center for Toxicology and Environmental Health, LLC, Little Rock, AR, USA

Jeffrey H. Mandel, MD, MPH, Associate Professor, Division of Environmental Health Sciences, University of Minnesota School of Public Health, Minneapolis, MN, USA

Kathleen MacMahon, DVM, MS, Education and Information Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention Cincinnati, OH, USA

Mugimane G. Manjanatha, Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Jefferson, AR, USA

Robert R. Maronpot, DVM, MS, MPH, DACVP, DABT, FIATP, Maronpot Consulting, LLC, Raleigh, NC, USA

M.E. (Bette) Meek, Institute of Population Health, University of Ottawa, Ottawa, Canada

Matthew Mifsud, MD, Department of Otolaryngology-Head and Neck Surgery, University of South Florida, Tampa, FL, USA

Steven Morris, MD, RN, Assistant Professor, Basic Sciences, College of Nursing, University of South Florida, Tampa, FL, USA

Carlos A. Muro-Cacho, MD, Professor, Pathology and Cell Biology, University of South Florida; Chief, Anatomic Pathology, James A. Haley Veterans' Hospital, Tampa, FL, USA

Nicole Nation, University of Georgia, Athens, GA, USA.

Daniel A. Newfang, MS, CIH, CSP, Center for Environmental/Occupational Risk Analysis and Management, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL, USA

Dorian S. Olivera MS, PhD, CLAD, Inhalation Toxicology Program Manager, Technology Solutions Group, Life Sciences Division, Alion Science and Technology Corporation, Durham, NC, USA

Michael K. Peterson, MEM, DABT, Senior Toxicologist, Gradient Corporation, Cambridge, MA, USA

Michael W. Perkins, PhD, Research Physical Scientist, Analytical Toxicology Division, U.S. Army Medical Research, Institute of Chemical Defense, MD, USA

David M. Polanic, JD, College of Law, Michigan State University, East Lansing, MI, USA

Debra J. Price, PhD, MSPH, MEd, Director of Education, Health Services Advisory Group. Inc., Tampa, FL, USA

Joseph A. Puccio, MD, FAAP, Medical Director, Student Health Center, College of Medicine, University of South Florida, Tampa, FL, USA

Erin L. Pulster, MSMS, Senior Chemist and Laboratory Manager, Environmental Laboratory of Forensics, Mote Marine Laboratory, Sarasota, FL, USA

Humairat H. Rahman, MBBS, MPH, Department of Environmental and Occupational Health, University of South Florida College of Public Health, Tampa, FL, USA

Santhini Ramasamy, PhD, MPH, DABT, Senior Toxicologist, Office of Water, Office of Science and Technology, U.S. Environmental Protection Agency, Washington, DC, USA

Lorenz R. Rhomberg, PhD, ATS, Gradient Corporation, Cambridge, MA, USA

Keith D. Salazar, PhD, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA

Philip J. Scarpa, Jr, MD, MS, FAsMA, Deputy Chief Medical Officer, John F. Kennedy Space Center, National Aeronautics and Space Administration, NASA-Kennedy Space Center, FL, USA

Alfred M. Sciuto, PhD, Fellow, Academy of the Toxicological Society, Research Physiologist, Medical Toxicology Branch, Analytical Toxicology Division, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD, USA

Davinderjit Singh MBBS, MPH, Toxicology and Risk Assessment, Environmental and Occupational Health College of Public Heath, University of South Florida, Tampa, FL, USA

Mary Alice Smith, PhD, Associate Professor, Environmental Health Science Department, University of Georgia, Athens, GA, USA

Thomas J. Steinbach, DVM, DACVP, DABT, Experimental Pathology Laboratories, Inc., Sterling, VA, USA

Frank D. Stephen, PhD, Assistant Professor of Biology, Department of Math & Natural Sciences, D'Youville College, Buffalo, New York, USA

Daniel L. Sudakin, MD, MPH, FACMT, FACOEM, Associate Professor, Oregon State University, Department of Environmental and Molecular Toxicology, Corvallis, OR, USA

James R. Taffer, MSPH, CIH, Manager, Environmental Health Services, InoMedic Health Applications, Inc. John F. Kennedy Space Center, FL, USA

Thomas Truncale, DO, MPH, Associate Professor of Medicine, Program Director, Occupational Medicine Residency, University of South Florida, James A. Haley Veterans' Hospital, Tampa, FL, USA

Peter A. Valberg, PhD, Principal, Environmental Health, Gradient Corporation, Cambridge, MA, USA

Marco Vinceti, MD, PhD, Dipartimento di Medicina Diagnostica, Clinica e di Sanità Pubblica, Università di Modena e Reggio Emilia, Modena, Italy

Qingli Wang, Center for Drug Evaluation, Chinese Food and Drug Administration (CFDA), Beijing, China

Donald E. Wasserman, MSEE, MBA, Independent Occupational Vibration Consultant, D.E. Wasserman, Inc., Frederick, MD, USA

Joan M. Watkins, DO, MPH, Affiliate Faculty, Occupational and Environmental Medicine Residency, College of Public Health and College of Medicine, University of South Florida, Tampa, FL, USA

Benjamin Wong, BS PhD, Research Physical Scientist, MTB, ATD, United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD, USA

Carol S. Wood, PhD, DABT, Oak Ridge National Laboratory, Oak Ridge, TN, USA

Daniel Woodard, MD, Aerospace Physician Innomedic Health Applications, Kennedy Space Center, FL, USA

Yin-tak Woo, PhD, DABT, Senior Toxicologist, Risk Assessment Division, Office of Chemical Safety Pollution Prevention, U.S. Environmental Protection Agency Washington, DC, USA

ABBREVIATIONS

5-HT	5-Hydroxytryptamine
AAS	Anabolic androgenic steroids
ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
ARDS	Acute respiratory distress syndrome
ASSE	American Society of Safety Engineers
ATA	Atmospheres absolute pressure
ATP	Adenosine triphosphate
ATSDR	Agency for Toxic Substances Disease Registry
BEI	Biological exposure indices
BZE	Benzoylecgonine
CaO	Calcium oxide
CASRN	Chemical Abstract Service Registry Number
CB	Control banding
CDC	Center for Disease Control and Prevention
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CIH	Certified Industrial Hygienist
CN^-	Cyanide anion
CNS	Central nervous system
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhemoglobin
CONSB	Carbon Monoxide Neuropsychological Screening Battery
CS_2	Carbon disulfide
CSA	Controlled Substances Act
CSP	Certified Safety Professional
CWA	Chemical warfare agent
DEA	Drug Enforcement Agency
DNEL	Derived no effect level
DNS	Delayed neuropsychiatric syndrome
DPE	Delayed postanoxic encephalopathy
ECG	Electrocardiography
EME	Ecgonine methyl ester
EPA	Environmental Protection Agency
EU	European Union
FEV_1	1-Minute forced expiratory volume
FVC	Forced vital capacity
GABA	Gamma-aminobutyric acid
GBL	Gamma-butyrolactone
GC	Gas chromatography
GC–MS	Gas chromatography/mass spectrometry
GHB	Gamma-hydroxybutyric acid
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HCl	Hydrochloric acid
HCN	Hydrogen cyanide
HDL_c	High-density lipoprotein concentration
HOCl	Hypochlorous acid
H_2S	Hydrogen sulfide
HSE	Health Safety Executive
IDLH	Immediately Dangerous to Life and Health
IHD	Ischemic heart disease
ILO	International Labour Organization
IRIS	Integrated Risk Information System
LC–MS	Liquid chromatography/mass spectrometry
LC–MS/MS	Liquid chromatography/tandem mass spectrometry
LDL_c	Low-density lipoprotein concentration
LOD	Limit of detection
MAPK	Mitogen-activated protein kinase
MGP	Manufactured gas plants
MMF	Midmaximal flow
MRLs	Minimal risk levels
MS	Mass spectrometry
NaCN	Sodium cyanide

NGOs	Non-governmental organizations
NIOSH	National Institute of Occupational Safety and Health
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NRC	Nuclear Regulatory Commission
OEB	Occupational exposure band
OEHS	Occupational and Environmental Health and Safety
OEL	Occupational exposure limit
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbon
PEL	Permissible exposure limit
PPE	Personal protective equipment
$PM_{2.5}$	Particulate matter
PtD	Prevention through design
RADS	Reactive airways dysfunction syndrome
RBC	Red blood cell
REL	Recommended exposure limit
ROS	Reactive oxygen species
SDS	Safety data sheet
SEG	Similar exposure group
SLs	Screening levels
SMR	Standardized mortality ratio
STEL	Short-term exposure limit
THC	Delta-9-tetrahydrocannabinoid
TLV	Threshold limit value
UK	United Kingdom
U.S.	United States
WHO	World Health Organization

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THE HERITAGE OF ALICE HAMILTON, M.D. AND HARRIET HARDY, M.D.

It has been over a century since Alice Hamilton graduated medical school, and almost a century since Harvard appointed her as the first female associate professor. It has only been just under three-quarters of a century since the first female full professor at Harvard, Harriet Hardy, was appointed. Few working people entering the fields of occupational and environmental health and hygiene are old enough to appreciate the incredible strides made in these fields to protect workers, families, flora, and fauna. Even fewer still are old enough to understand the personal and professional battles fought by Dr. Hamilton and Dr. Hardy in just trying to attend college, gain employment in their field, and establish the credibility automatically and generously granted to men with lesser education and experience.

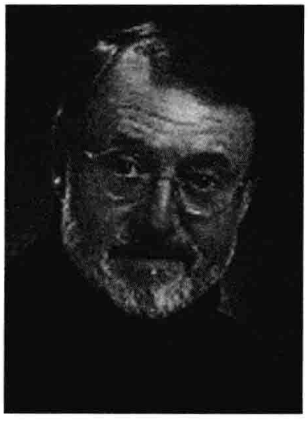
Both women had to limit their choices of educational institutions to those designed or willing to accept women. Both had to withstand accusations of emotionalism and "hysteria" as naysayers sought to discredit them. Dr. Hamilton achieved a notable landmark in being appointed the first woman faculty at Harvard, but her position was without several of the privileges enjoyed by the male faculty, and she retired from Harvard still an associate professor. Dr. Hardy was similarly notable in her appointment as full professor at Harvard, but she suffered from several physical ailments that took a severe toll on her. However, it would be truly shortsighted to view their difficulties and successes only in terms of gender issues. They were scientists, first and foremost, and most of the dissension encountered during their professional lives was primarily due to their challenging the deep-seated socially dismissive attitude toward worker health, the associations between chemicals and illness, and the industries' unwillingness to incur expenses in attending to employee needs.

Certainly, the dimming of memories signifies positive strides in occupational and environmental health goals and gender equality. However, the historical advances in occupational and environmental health are now so much a part of our way of life that we risk losing the appreciation of the sacrifices, and the successes of the people behind these changes. Neither Dr. Hamilton nor Dr. Hardy proffered theories that were gracefully met with acceptance, regardless of the supporting evidence or the number of potential lives at risk. Their strength of character drove them, which in turn propelled the changes they sought.

Industrial Toxicology was first drafted by Dr. Hamilton in 1934. Fifteen years later, she teamed with her colleague Dr. Hardy for the second edition. The subsequent editions maintain their names in the title, not just as courtesy but as a genuine homage to their impressive contributions to the health and welfare of global populations, at times at great expense to their own personal life and health. Perhaps, ultimately, this is the legacy carried forth with these volumes, the reason we need to remember exactly who these women were and what they accomplished—so that we may honor them by our dedication and sacrifice in striving for greater knowledge and safer lives.

IN MEMORY

During the lengthy process of creating this sixth edition, we lost one of our most integral people when, on May 7, 2013, Dr. Richard Vaile Lee passed away. A brilliant physician and educator, Dick Lee was also a valued friend and colleague.



Dr. Lee began his collegiate experience at Yale, where he received both his B.S. and M.D. and gained membership in the Alpha Omega Alpha Honor Medical Society. His internship and residency concentration was internal medicine. Between his residency years, he also squeezed in 2 years of service at the Fort Peck Indian Reservation in Montana for the U.S. Public Health Service, remaining an additional year to assist a colleague in general practice. Upon his return to Yale, he completed his residency and was awarded a fellowship in infectious diseases. While a fellow, he also acted as Director for the medical clinics and emergency room for the Department of Medicine.

In 1976, Dr. Lee left Yale to assume the positions of Professor and Vice Chairman of the Department of Medicine at the State University of New York at Buffalo (UB), and Chief of Medical Services for the Buffalo Veterans Administration Medical Center. In 1979, he took over as Head of the Department of Medicine at Buffalo's Children's Hospital. In 1997, he left Children's Hospital to establish a private practice in obstetrics medicine.

Dr. Lee's practice was not confined to a simple driving radius. He practiced "geographic medicine," bringing much-needed medical care and attention to remote locations. He treated tribal cultures in Northern Kenya and Brazil, and he traveled to Thailand, treating refugees from Laos and Cambodia. He developed an acquaintance with the Dalai Lama through his work with Tibetan refugees and was part of the UB board responsible for Dalai Lama's trip to Buffalo in 2006. He developed the UB's Medical Trek Program, sending students to perform medical care in field expeditions across the world.

The range of scholarship was almost as broad as the countries traveled. In addition to his experience in general practice, infectious diseases, and obstetrics, Dr. Lee also served as Medical Director for Ecology and Environment, Inc., in Lancaster. He taught classes at UB in pediatrics, gynecology, and obstetrics in the School of Medicine and Biomedical Sciences as well as various classes in the Department of Social and Preventive Medicine in the School of Public Health and Health Professions, and in the Department of Anthropology in the College of Arts and Sciences. He also served as a consulting physician to both the Buffalo Zoo and the Bronx Zoo.

His marriage in 1961 to Susan Bradley ultimately produced two sons, Benjamin and Matthew. It also unearthed a family secret. When he announced his impending marriage to his family, Dr. Lee learned that his paternal grandfather was Li Yan Phou, one of a select group of Chinese students to attend school in the United States. Because of strong anti-Asian prejudice (at the time there were laws preventing

Chinese and non-Chinese intermarriages in some states), Dr. Lee's parents had opted to hide the Asian heritage. However, Dr. Lee embraced his Chinese heritage, serving as a trustee for the Yale–China Association and participating in a UB delegation to China to renew an academic affiliation with a Beijing university. He also edited and wrote the foreword for the 2004 edition of his grandfather's book, *When I was a Boy in China*, published under the Anglicized name of Yan Phou Lee.

Dr. Lee produced over 70 publications and garnered several awards. In 2002, he was the Laureate Award winner of the American College of Physicians–American Society of Internal Medicine, and in 2007, he was the winner of the C.G. Barnes Award from International Society of Obstetric Medicine. In the same year, the North American Society of Obstetric Medicine established a lecture in his name for their annual meetings.

So we dedicate this edition to Richard V. Lee, M.D., FACP, FPGS: a scholar, a humanitarian, an educator, a leader, a traveler, a guide, a speaker, a listener, and ultimately an inspiration. By his own words: "a professor." By our words, a great man.

PREFACE

The sixth edition of *Hamilton & Hardy's Industrial Toxicology* has been updated and expanded with new chapters on aspects of regulatory toxicology, toxicity testing, physical hazards, high production volume (HPV) chemicals, and workplace drug use. The format has been modified and now includes information on occupational and environmental sources of exposure, mammalian toxicology, industrial hygiene, medical management, and ecotoxicology where appropriate. The book is organized by substance and includes the latest research on industrial toxicants. The goal was to provide a broad range of professionals with an accessible text. We are extremely grateful to our contributors as they provided integral industry, regulatory, and academic perspectives.

The landscape of industrial toxicology has changed considerably since Dr. Alice Hamilton and Dr. Harriet Hardy published the first edition of the text in 1929. It is estimated that there are now more than 70,000 industrial chemicals in common use. In contrast, regulatory agencies have established fewer than 1000 exposure limits. Determination of an appropriate exposure limit is an exhaustive process; as an illustration, the U.S. Occupational Safety and Health Administration (OSHA) has promulgated fewer than 30 standards (new permissible exposure limits (PELs) for 16 agents, and standards without PELs for 13 carcinogens) since 1970. The European Union's REACH (Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals) framework will require several decades to determine the exposure limits for common chemicals.

The assessment backlog is so critical that OSHA recommends that the employers consider using alternative occupational exposure limits established by the National Institute for Occupational Safety and Health (NIOSH) and American Conference of Industrial Hygienists (ACGIH). Traditional toxicological testing is costly, time consuming, reliant on animal models, and fraught with uncertainty stemming from interspecies extrapolation. Tox21, an interagency project between the National Toxicology Program, the U.S. Environmental Protection Agency, the National Institutes of Health, and the Food and Drug Administration, is a high-throughput testing prototype robot created to address both the knowledge gap and problems of traditional toxicity testing. Tox21 will screen thousands of chemicals using advanced *in vitro* and cell-based assays and non-rodent models such as zebrafish in far less time than previously possible.

The evaluation of risk subsequent to exposure is an essential component of industrial toxicology. It is critical that readers remember that exposure only represents the *opportunity* for contact with a chemical. An exposure does not guarantee that an adverse effect will result. A dose is the amount of the chemical entering the body following an exposure. There are both harmful and safe doses of all chemicals. As Paracelsus said, "All things are poisons, for there is nothing without poisonous qualities . . . it is only the dose which makes a thing poison." Exposure and dose both need to be evaluated for an adequate hazard assessment. This edition of the text includes an assessment of risk where possible.

Hamilton & Hardy's Industrial Toxicology was prepared as a concise reference for academics and professionals alike. There is a wealth of information available on industrial exposures and toxicants. Distillation of these resources into something relevant can be daunting. It is our hope that this text will be that something relevant for our readers.

MARIE M. BOURGEOIS, PH.D.

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