· SIXTH EDITION ·

HAMILTON & HARDY'S INDUSTRIAL TOXICOLOGY

Edited by

RAYMOND D. HARBISON
MARIE M. BOURGEOIS · GIFFE T. JOHNSON

WILEY

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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

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.

SECTION I

INTRODUCTION

SECTION EDITOR: RAYMOND D. HARBISON

1

THE MODERN APPROACH TO THE DIAGNOSIS OF OCCUPATIONAL DISEASE

RAYMOND D. HARBISON AND JEFFREY H. MANDEL

BACKGROUND

An understanding of the health effects that may occur from occupational exposures is critical in terms of the potential human toll and an industry's success and sustainability. The diagnosis of workplace-induced diseases is necessary if the disease in question is to be prevented. In the context of modern medicine, the diagnosis of an occupational disease is a multidisciplinary process and includes input from professionals in occupational medicine, nursing, industrial hygiene, toxicology, epidemiology, engineering, and others. Though physicians are primarily responsible for making an individual diagnosis, the remaining disciplines are critical parts of the process for establishing the nature and cause of the disease(s). It is the collective group that has become paramount to the understanding and control of occupational disease within modern societies. The diagnosis of an occupational disease may be understood in the context of a public health model, which incorporates the interplay between the agent, the host, and the disease. With this approach, the agent may be physical, chemical, or biological and has the potential to cause harm depending on its characteristics (e.g., corrosive, pathogenic, and carcinogenic), the exposure concentration and duration, and the ability to target organs in exposed individuals. The host is the individual or population exposed to the agent. The disease results from the interaction of these two factors. The host in this model includes healthy individuals as well as susceptible individuals (e.g., genetic predisposition and life stage). With acute or chronic high-level exposures, host susceptibility generally increases, due to a variety of mechanisms, including saturation of detoxification reactions and increased bioactivation. Manufacturing facilities control exposures through engineering controls, personal protective equipment, chemical substitution, area monitoring, personal monitoring, hazard communication, and employee training and education.

Despite the vast number of professionals involved, the diagnosis of an occupational disease is complicated by important factors. First, many diseases that occur as a result of workplace exposures (e.g., asthma from isocyanates) may also occur from non-workplace exposures to the same compounds or may be caused by other agents (nonspecificity). Second, disease manifestation is often idiopathic and may be attributed to the workplace purely on the basis of the disease postceding employment. Third, the majority of chemicals in commerce either have not been tested in experimental animals or have been tested but lack data on the mode of action and human relevance of adverse effects. The absence of this type of information complicates extrapolations from animal studies to workers. Finally, many tests used in clinical medicine are not specific for identifying exposures to an agent of interest. For example, a blood test that reveals high carboxyhemoglobin (COHb) levels only confirms an internal dose of carbon monoxide. It does not confirm whether the source exposure was to carbon monoxide, methylene chloride, or some other causative agent. Similarly, chest radiograph findings that suggest interstitial lung disease do not confirm exposures to a specific causative agent (e.g., wood dust). Testing of workers is subject to each test's sensitivity, specificity, and positive and negative predictive value. To complicate matters, many tests do not have established "gold standards" to which they may be compared. All of these issues may potentially compromise the accuracy of diagnoses.

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As alluded to in the above examples, a multilevel assessment is needed in the diagnosis of an occupational disease. The exposure in question must be assessed in terms of what is known about it, whether the worker's complaints are consistent with this exposure, and insights into the actual work environment are the initial necessary perspectives needed. These are followed by a detailed account of the individual's illness, the person's medical history, occupational history, physical findings, laboratory findings, and a review of the epidemiological literature involving this person's exposure–disease relationship. Finally, some type of assessment of causation is necessary to determine whether there is adequate information to suggest that an exposure could produce the disease in question. This assessment typically involves a comprehensive review of the existing epidemiological literature on the topic. All this is theoretically needed before an occupational disease can be considered. Each of these will be considered in greater detail in the subsequent paragraphs.

COMPONENTS OF THE DIAGNOSIS

The History of Illness

The worker's disease history is often the only information available to the team of professionals assigned to determine the etiology of the disease. In some cases, associations with the workplace are based entirely upon this history, hence its importance. Accordingly, the trained interviewer attempts to have as much of this as possible iterated directly in the worker's own words. A description of the worker's symptoms is the basis of this history, but there needs to also be a focus on the occupational aspects of the illness. Identification of the illness occurring temporally with the workplace is helpful since exposure–disease associations may become worse during the workday, the workweek, often with improvement after work, or on weekends away from the job. It is also important to clarify the duration of the exposure and whether coworkers with similar jobs have had health problems. Since some illnesses have long latencies, the examiner must determine the prior work history of an individual. The practitioner may also use other sources of information, including the employer, incident reports, the state or federal Occupational Safety and Health Administration (OSHA), and an industrial hygienist familiar with the workplace controls, practices, and safety data sheets (SDSs). The history should include the following:

1. *Occupational Factors.* Occupational factors must be assessed and understood. These include insights into the agent (exposure) in question as well as the involved work area. Part of this understanding is obtained through an evaluation of processes, engineering controls, personal protective equipment, employee training and compliance, and the identification of potential causative agents (e.g., which materials or chemicals are used?) and opportunities for exposure. The chemicals used must be understood in terms of the potential routes of exposure (e.g., inhalation of volatile organics), toxicokinetics (i.e., absorption, distribution, metabolism, and elimination), and toxicity.
2. *Nonoccupational Factors.* Many diseases that may originate from exposures to a causative agent in the workplace may also occur outside of the workplace. Asthma, for example, may be triggered by occupational or consumer exposure to certain isocyanates, but it may also be triggered by exposure to cat dander. Lung cancer may be related to asbestos exposure, smoking, or both. Few diseases have only an occupational basis. In fact, estimates of 5–10% of all cancers have been attributed to exposures in the occupational setting (Doll, 1984). The vast majority of cancers are not associated with occupational exposures and are thought to be multifactorial in origin (e.g., environmental exposures, lifestyle choices/hobbies, and genetic predisposition). In particular, attention must be given to these factors in the assessment of occupational disease. Especially important are exposures that occur to individuals with preexisting diseases, since these may complicate an illness resulting from an exposure. For example, an individual with underlying chronic bronchitis may have a reduced capacity for pulmonary clearance, which may predispose this individual to an adverse outcome following exposure to specific types of agents (e.g., fibers or insoluble particles).

The Physical and Laboratory Examinations

The physical and laboratory examinations are regarded as means of verifying what is already suspected following the history of illness. A skilled examiner is able to combine these two areas with a high likelihood of an accurate diagnosis, without any additional evaluation. The occupational physical examination, such as the history of illness, needs to focus on the organ where known toxicity occurs. If the worker has breathing difficulties and has exposure to a lung irritant, the examination will need to focus on the respiratory system. Other organ systems are evaluated for the sake of being thorough and to identify additional potential areas of abnormality.

Following the physical examination, the examiner may need to verify the disease suspected with the use of specific tests. In the above case, it would be appropriate to perform a pulmonary function test (e.g., spirometry) to evaluate the worker's inhalation and exhalation during normal breathing