Seventh Edition

Lu's Basic Toxicology

Fundamentals, Target Organs, and Risk Assessment

Edited by

Byung-Mu Lee • Sam Kacew

Hyung Sik Kim

CRC Press

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Preface

Toxicology is an important life science. It is valuable in the protection of public health hazards associated with toxic substances in food, air, and water. It also provides a sound basis for formulating measures to protect the health of workers against toxicants in factories, farms, mines, and other occupational environments. Toxicology has played and will continue to play a significant role in the health and welfare of the world. Cognizant of the importance of toxicology, the World Health Organization (WHO) organized a toxicology training course in China in 1982, as part of the ongoing China–WHO collaborative program on medical sciences. The founding author (FCL) was invited to lectures on basic toxicology. The first edition of this book originated from those lecture notes.

Over the years, a number of important developments have occurred in toxicology. Furthermore, some readers of the book have suggested that discussions on a few groups of important chemicals and toxicants would not only provide some general knowledge of these substances, but also facilitate a deeper appreciation of the various aspects of toxicology. The book has received worldwide acceptance, as evidenced by its repeated editions and reprintings, and by the appearance of six foreign language versions (Chinese, French, Indonesian, Italian, Spanish, and Taiwan Chinese).

This new edition, prepared by invited scientists, has been further updated and expanded to include new chapters on clinical toxicology, chemicals and children, reproductive toxicology, and systems toxicology. There are chapters on lactation and occupational toxicology, as well as a chapter section describing the symptomatology of Gulf War syndrome and the probable toxicants implicated. The other chapters have been updated and expanded, notably those on the history of toxicology, carcinogenesis, mutagenesis, toxicology of organ systems—skin, liver, kidney, immune, and nanoparticle, endocrine, and safety/risk assessment. However, details of some toxicity tests have been abbreviated to keep the size of the book within bounds; the retained material is intended to portray more clearly the effects of toxicants.

It is hoped that these additions and updates will enhance the usefulness of the book. In making these changes, the authors have kept in mind the broad aim of the first edition, namely, a relatively comprehensive coverage of the subjects and brevity, thereby continuing to serve as an updated introductory text for toxicology students and for those involved in allied sciences who require a background in toxicology. Further, since toxicology is a vast and rapidly expanding subject, the book is likely to be useful to those who have become specialized in one or a few areas in toxicology, but wish to become more familiar in other areas. The extensive chemical index and subject index will facilitate the retrieval of specific topics.

Byung-Mu Lee
Sam Kacew
Hyung Sik Kim

Editors

Byung-Mu Lee, BS, MS, MSPH, Dr PH, Division of Toxicology, College of Pharmacy, Sungkyunkwan University, South Korea, is associate editor of the *Journal of Toxicology and Environmental Health, Part A*; associate editor of *Food and Chemical Toxicology*; editorial board member of *Environmental Health Perspectives*; and advisory editor of *Archives of Toxicology*. He is currently the vice president of the International Association of Environmental Mutagenesis and Genomics Society (IAEMGS). He is the author of 230 papers and reviews, the *Encyclopedia of Environmental Health*, and 11 book chapters, as well as the coauthor of *Lu's Basic Toxicology*, Sixth Edition (Informa, 2013).

Prof. Lee has also been a research advisor of the Ministry of Food and Drug Safety, a committee advisor for the Ministry of Science, ICT, and Future Planning, the Ministry of Environment, and the Ministry of Human Health and Welfare in South Korea. He has been the president of the 13th International Congress of Toxicology (ICT XIII), the Korea Society of Toxicology (KSOT), and the Korea Environmental Mutagen Society (KEMS). He has been the vice president of the Asia Society of Toxicology (ASIATOX). He has organized eight workshops and three international symposia about toxicology, carcinogenesis, chemoprevention, endocrine disruption, and risk assessment. He has been a nominating committee member of the International Union of Toxicology (IUTOX) and deputy member of the Korean Pharmaceutical Society.

Prof. Lee has received numerous awards, including the Young Scientist Award, Brookhaven Symposium (U.S.); the Yun Ho Lee Award of Scientific Merit (International Aloe Science Council (U.S.); and the Merit Award from the Minister, Ministry of Food Drug Safety (Republic of Korea).

Prof. Lee's research areas include: carcinogenesis, chemoprevention, endocrine disruption, molecular epidemiology, biomarkers, systems toxicology, and risk assessment/management.

Sam Kacew, PhD, ATS, is an associate director of Toxicology, McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa; professor of pharmacology, University of Ottawa; and scientist, Institute for Population Health, University of Ottawa.

Prof. Kacew is a visiting professor at the following institutions: the University of Guildford in Surrey, England; a Colgate-Palmolive visiting professor at the University of New Mexico; the Institute of Toxicology at National Taiwan University in Taipei, Taiwan; the Joszef Fodor National Center of Public Health in Budapest, Hungary; the Department of Occupational Health, Shanghai Medical University in Shanghai, China; the Zhehjiang University in Hangzhou, China; Nanjing Medical University, Nanjing, China; and the Division of Toxicology at Sungkyunkwan University in Suwon City, Korea.

Prof. Kacew is currently the editor-in-chief of the *Journal of Toxicology and Environmental Health, Part A, Current Issue*; editor-in-chief, *Journal of Toxicology and Environmental Health, Part B, Critical Reviews*; North American editor, *Toxicological and Environmental Chemistry*; associate editor of *Toxicology and Applied Pharmacology*; editor, *Encyclopedia of Environmental Health*; editor, *Lu's Basic Toxicology* (Fourth and Fifth editions); and guest editor of a special issue of *Toxicology and Applied Pharmacology* entitled "Toxicological Reviews in Fetal Childhood Development." He has edited several texts on pediatric toxicology and serves on several editorial boards. He has been a peer reviewer for the Environmental Protection Agency (EPA) on the Integrated Risk Information System (IRIS) documents, on the U.S. EPA Health Effects Assessment Summary Table (HEAST) chemicals, on the chemical-specific issue papers for the Superfund Technical Support Center (STSC) for the U.S. EPA, and has served on National Institutes of Health (NIH) grant study sections.

Prof. Kacew is a member of the Board on Environmental Studies and Toxicology (BEST) of the National Academy of Sciences (U.S.) and is a member of the Science Advisory Council (SAC) of the National American Flame Retardant Association (NAFRA).

Prof. Kacew has been a member of the board of trustees of Toxicology Excellence for Risk Assessment (TERA) and a member of the board of Review for Siloxane D5 appointed by the Minister of Environment of Canada. He has also been a member of the Committee on Toxicology of the National Academy of Sciences (NAS) of the United States and served as a chairman on the NAS Subcommittee on Iodotrifluoromethane; chairman on the NAS Subcommittee on Tetrachloroethylene; and a member of the NAS Subcommittees including Flame Retardants, Jet Propulsion Fuel-8, and Toxicologic and Radiologic Effects from Exposure to Depleted Uranium during and after Combat; and a member of the Advisory Expert Committee of the Canadian Network of Toxicology Centers. He served as a chairman of a U.S. EPA Panel on Peer Review Assessment of Toxicity

Values for Total Petroleum Hydrocarbons, member of the Panel on the Beryllium Lymphocyte Proliferation Screening Test, an expert panel member on the Breast Milk Monitoring for Environmental Chemicals in the United States, a core panel member of the Voluntary Children's Chemical Evaluation Program (VCCEP), part of a U.S. EPA initiative, expert panel member on the Pest Management Regulatory Agency of Health Canada on Citronella Science Review, expert panel member on drug-induced phospholipidosis to several pharmaceutical companies, expert panel member of the Council of Canadian Academies on Integrated Testing of Pesticides, and member of the Institute of Medicine (IOM) Committee on Blue Water Navy Vietnam Veterans and Agent Orange Exposure.

Prof. Kacew has received the Achievement Award of the Society of Toxicology of Canada in 1983, the Achievement Award of the Society of Toxicology in 1986, the ICI (Zeneca) Traveling Lectureship Award in 1991, the U.S.–China Foundation Award in 1995, the Colgate-Palmolive Visiting Professorship Award in 1997, and the Public Communications Award.

Hyung Sik Kim, MS, PhD, is a professor of the Division of Toxicology, College of Pharmacy, Sungkyunkwan University, South Korea.

Prof. Kim earned a PhD performing research on chemical carcinogenesis and chemoprevention at the College of Pharmacy, after which he joined the Korea Food and Drug Administration, serving as a senior researcher, where he was involved in reproductive and developmental toxicology and endocrine toxicology. He spent 2 years at the National Institutes of Health (NIH) in Bethesda, Maryland carrying out cancer and radiopharmaceutical research. Since 2003, he has been an assistant professor in the Division of Toxicology, College of Pharmacy at Pusan National University in South Korea.

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Prof. Kim has served as an advisory committee member of government (National Food and Drug Safety, Ministry of Environment, Ministry of Health and Welfare) and has served as the vice chairman of the National Scientific Committee for the 13th International Congress of Toxicology (ICT) held in Seoul, Korea. He has also served as the vice chairman of

the National Scientific Committee of the 8th International Congress of the Asian Society of Toxicology, held in Jeju, South Korea in 2015.

His primary research areas of interest are the identification of new cancer biomarkers, mechanisms of new anticancer agents, and cancer chemoprevention.

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section one

General principles of toxicology

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chapter one

History of toxicology

Byung-Mu Lee

Contents

What is toxicology?

Toxicology (*toxicos*; poisonous + *logy*; science) also called *toxicological science* is the fusion of sciences based on biology, chemistry, physics, anatomy, physiology, pathology, psychology, zoology, pharmacology, genetics, biochemistry, statistics, and mathematics. Toxicology is traditionally defined as the science of poisons which are also termed as toxicants, toxic substances, toxins, xenobiotics, or stressors. A more descriptive definition of toxicology is the study of the nature and mechanisms underlying toxic effects exerted directly or indirectly by substances such as biological, chemical, physical, genetic, or psychological agents on living organisms and other biological systems. Toxicology also deals with quantitative or qualitative assessment of the adverse effects in relation to the concentration or dosage, duration, and frequency of exposure of the organisms.

The assessment of health hazards of industrial chemicals, environmental pollutants, and other substances represents an important element in the protection of the health of workers and members of communities.

In-depth studies of the nature and mechanism of the effects of toxicants are invaluable in the development of specific antidotes and other ameliorative measures. Along with other sciences, toxicology contributes to the development of safer chemicals used as drugs, food additives, and pesticides, as well as many useful industrial chemicals used for the fabrication of computers, cellular phones, televisions, and electronic equipment. Even the adverse effects per se are exploited in the pursuit of more effective insecticides, anthelmintics, antimicrobials, antivirals, and warfare agents. The purpose of toxicology is to protect humans or ecosystems from exposure to hazardous substances. Therefore, to ensure human safety, risk assessment which evaluates human safety based upon toxicological data and human exposure levels, in order to set human safe limits, may be considered one of the most important goals of toxicology (Song et al., 2013).

Mutiple fields of toxicology and applications

Toxicology is a fusion science composed of multiple fields and has a broad scope. It deals with toxicity studies of substances used

1. In medicine for diagnostic, preventive, and therapeutic purposes.
2. In the food industry as direct and indirect additives.
3. In agriculture as pesticides, growth regulators, artificial pollinators, and animal feed additives.
4. In the chemical industry as solvents, components, and intermediates of plastics, components of electronic devices and many other types of chemicals. It is also concerned with the health effects of metals (as in mines and smelters), radiation, petroleum products, paper and pulp, flame retardants, toxic plants, and animal toxins. Overall, toxicology covers general safety issues in our lives and ecosystem.

Depending on the specific areas of toxicological application, toxicology can be subdivided into analytical toxicology, clinical toxicology, forensic toxicology, occupational toxicology, environmental toxicology, regulatory toxicology, and so forth. For example, a person may be exposed, accidentally or otherwise, to excessively large amounts of a toxicant and become severely intoxicated. If the identity of the toxicant is not known, *analytical toxicology* will be called upon to identify the toxicant through analysis of body fluids, stomach contents, suspected containers, and so forth. Those engaged in *clinical toxicology* administer antidotes, if available, to counter some specific toxicity, and take other measures to ameliorate the symptoms and signs and hasten the elimination of the toxicant from the body. There may also be legal implications, which is the task of *forensic toxicology*.

Intoxication may occur as a result of occupational exposure to toxicants. This may result in acute or chronic adverse effects. In either case, the problem is in the domain of *occupational toxicology*. The general public is exposed to a variety of toxicants, via air, water, and soil, or contact with skin as well as from food containing additives, pesticides, and contaminants, often at low levels that may be harmless acutely but may have long-term adverse effects. In pregnancy, the fetus is exposed via the maternal circulation while a lactating infant is exposed via breast milk. The sources of these substances, their transport, degradation, and bioconcentration in the environment, and their effects on humans are dealt with in *environmental toxicology*. *Regulatory toxicology* attempts to protect the public by setting laws, regulations, and standards to limit or suspend the use of toxic chemicals as well as defines use conditions for others. Some of the relevant laws in the United States are listed in Appendix 1.1.

To set meaningful regulations and standards, extensive profiles of the toxic effects are essential. Such profiles can only be established with a great variety of relevant and comprehensive toxicological data derived from *in vitro*, *in vivo*, and human studies, which form the foundation of regulatory toxicology.

The basic part of such studies is referred to as *conventional toxicology*. In addition, knowledge of the mechanism of action, provided by *mechanistic toxicology*, enhances the toxicological evaluation and provides a basis for other branches of toxicology. The knowledge gained is then utilized to assess the risk of adverse effects to the environment and humans and is termed a risk assessment. A health risk assessment constitutes a written document based upon all pertinent scientific information regarding toxicology, human experiences, environmental fate, and exposure scenario. These data are subject to critique and interpretation. The aim of a risk assessment is to estimate the potential of an adverse effect in humans and wildlife ecological systems caused by exposure to a specific amount of toxic substances. Risk assessments include several elements such as

1. Description of the potential adverse health effects based on an evaluation of results of epidemiological, clinical, preclinical, and environmental research.
2. Extrapolation from these results to predict the type and estimate the extent of adverse health effects in humans under given conditions of exposure.
3. Assessments as to the number and characteristics of individuals exposed at various intensities and durations.
4. Summary judgments on the existence and overall magnitude of the public health problem given the information of (1), (2), and (3) (Paustenbach, 2002). Risk characterization represents the final and

the most critical step in the risk assessment process whereby data on the dose–response relationship of a chemical are integrated with estimates of the degree of exposure in a population to estimate the likelihood and severity of human health risk (Williams and Paustenbach, 2002; Song et al., 2013).

History of toxicology in early stage

In ancient times, human poisonings occurred after exposure to a numerous unknown or known poisons from different sources such as animals, plants, soil, air, and water. Some plants and heavy metals used for poisons in the world are listed in Table 1.1.

Ebers Papyrus is probably the oldest document that provides human toxicological information on poisons in BC 1500. It attests to awareness of the toxic effects of a number of substances—such as snake venom, poisonous plants like hemlock and aconite, and the toxic heavy metals arsenic, lead, and antimony. Some of these were actually used (intentionally for their adverse effects) for hunting, warfare, suicide, or homicide. For centuries, homicides with toxic substances were common in Europe, thus stimulating continual efforts toward the discovery and development of preventive and antidotal measures. The following are some famous examples of ancient poisonings in humans.

Socrates (BC 470–399), a Greek philosopher, died of hemlock poisoning (according to Plato). Hemlock (*Conium maculatum*) contains coniine, one of the active toxic ingredients and other toxic alkaloids (cicutoxin, oenanthotoxin, virol A, virol C, C17–polyacetylenes) that cause nausea, vomiting, diarrhea, tachycardia, cardiac dysrhythmias, mydriasis, renal failure, coma, respiratory impairment, and death (Schep et al., 2009). Cleopatra (BC 69–30), was made Cleopatra VII and became Queen of Egypt when her father Ptolemy XII died. Although her death is still a mystery, three possible scenarios for her death were suggested (Wexler, 2014): (a) committed suicide on August 12, BC 30, by means of an Egyptian serpent, referred to as her asp (Espinoza, 2001); (b) committed suicide by poison (possibly hidden somewhere in her mausoleum); (c) poisoned by Octavian and/or his men (Orland et al., 1990). Nero (AD 37–68) became Roman Emperor after the death of his adopted father, the Emperor Claudius in AD 54 (possibly by being poisoned with a mushroom). Nero was known as one of the most infamous men who used poisons to murder his rivals as well as his brother-in-law.

Mithridates VI (131–63 BC), the King Mithridates VI of Pontus, was known to expose himself and his prisoners to test poisons and antidotes. He would take small amounts of poison, not exceeding the toxic dosage, and gradually increase the doses until successfully acquiring immunity or tolerance. For this reason, the term "mithridatic" was coined meaning

Table 1.1 List of poisonous plants in the world

Plants	Ingredients	Toxic effect	Country	Year	Ref.
Aconite (*Aconitum napellus*)	Aconitine, yunaconitin, mesaconitine, hypaconitine	Cardiotoxicity, neurotoxicity	Europe, North America	–	Chan, 2009
Chinese tallowtree (*Sapium sebiferum*)	Toxalbumin, saponin	Diarrhea, listlessness, weakness, dehydration	China	1700s	Everest et al., 2005; NCSU, 2011
Colchicum (*Colchicum autumnale*)	Alkaloid colchicine	Arrhythmias, liver failure, pancreatitis, alopecia	Europe	–	Jaeger and Flesch, 1990; Brvar et al., 2004
Deadly nightshade (*Atropa belladonna*)	Atropine, hyoscyamine, scopolamine	Dryness of mouth, ileus, tachycardia	Europe, Asia	Roman times	Rajput, 2013
Hellebore (*Helleborus niger*)	Cardiac glycosides, helleborin, hellebrin,	Dermatitis, convulsions, respiratory failure	Europe	1400 BC	Schep et al., 2009; Cornell University, 2015
Hemlock (*Conium maculatum*)	Cicutoxin, virol A, virol C, oenanthotoxin, C17-polyacetylenes	Tachycardia, mydriasis, renal failure, coma	North America, UK	–	
Henbane (*Hyoscyamus nigar*)	Atropine, hyoscyamine, scopolamine	Dry mouth, delirium, hallucinations, blurred vision, tachycardia	Europe, Africa	681 AD	Alizadeh et al., 2014

(*Continued*)

Table 1.1 (Continued) List of poisonous plants in the world

Plants	Ingredients	Toxic effect	Country	Year	Ref.
Mandrake (*Atropa mandragora*)	Solanum alkaloids, tropane alkaloids	Mydriasis, blurred vision, headache, vomiting	Europe	–	Tsiligianni et al., 2009
Mushrooms (*Amonita muscaria*)	Ibotenic acid, muscinol	Confusion, mydriasis, drowsiness	Italy	–	Michelot & Melendez-Howell, 2003
Opium (*Papaver somniferum*)	Codeine, heroin, morphine, urushiol	Stupor, coma, death, liver and kidney toxicity	Eurasia, Korea	1500 BC	Park et al., 2000; NSM, 2016
Thorn apple (*Datura stramonium*)	Atropine, scopolamine, hyosciamine	Mydriasis, tachycardia, hallucinations	U.S., Asia	–	Thabet et al., 1999
Yew (*Taxus accato*)	Taxine, paclitaxel, cephalomannine	Cardiac arrest, respiratory paralysis, ataxia, death	Canada	–	Cope, 2005; Perju-Dumbrava et al., 2013