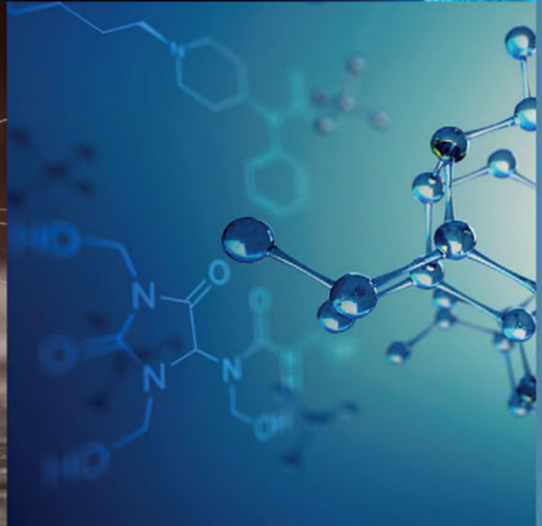
EDITED BY

RAMESH C. GUPTA

SECOND EDITION

BIOMARKERS IN TOXICOLOGY



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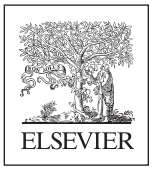

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This book is dedicated to my daughter Rekha, wife Denise,
and parents the late Chandra and Triveni Gupta.

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Foreword

The first edition of *Biomarkers in Toxicology*, edited by Ramesh Gupta, was published in 2014. The whole area of biomarkers, not only in toxicology, is rapidly developing, partly because of the availability of highly sophisticated analytical equipment, and so the second edition of this book is greatly welcomed. The second edition contains 12 new chapters, and most of the rest have been updated.

Merriam Webster defines a biomarker as a distinctive biological or biologically derived indicator (as a metabolite) of a process, event, or condition (as, for example, aging, disease, or oil formation). There are other definitions, for example, in Environmental Health Criteria 222 Biomarkers. In Risk Assessment http://www.inchem.org/documents/ehc/ehc/ehc222.htm#1.0 biomarkers are defined thus "A biomarker is any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease." The subject of the present book is biomarkers in toxicology, but it should be remembered that biomarkers include substances used in the detection of numerous diseases, including the autoimmune diseases, which are not generally thought to be toxicological in origin. However, biomarkers are crucial to toxicology and allied disciplines such as epidemiology and risk assessment.

The earliest toxicological biomarkers of exposure date from before precise analytical techniques were available and include the Kayser−Fleischer ring (described 1902/3), usually indicative of copper accumulation in the cornea in cases of Wilson's disease, as well as lead lines in the gums associated with lead toxicity. The cherry red color noted as a (rather unreliable) clinical sign in carbon monoxide poisoning may also be described as a biomarker.

One of the earliest biomarkers relying on biochemical analytical techniques was measurement of cholinesterase activity, initially whole blood cholinesterase and later plasma pseudocholinesterase (butyrylcholinesterase) and red blood cell acetylcholinesterase. Cholinesterase measurements were introduced at defense laboratories after World War II as a screening test for excessive exposure to organophosphate compounds: a 20% depression in activity was considered to mandate cessation of exposure of individuals to organophosphate nerve agents (the basis of the 20% figure is obscure, but seemed protective). Pseudocholinesterase and red blood cell acetylcholinesterase measurements now have numerous uses in worker protection, clinical diagnosis of poisoning, and human and experimental animal studies (including regulatory ones) in relation to the use of organophosphate and other anticholinesterase pesticides. Since World War II biomarkers of toxicity have ballooned in importance and number in worker and consumer protection and clinical and experimental toxicology and are also widely used in regulation of chemicals in animal and, less commonly, human experimental studies. Toxicological biomarkers are also used in allied disciplines, for example, epidemiology, and may be used to estimate loads of exposure in populations being investigated.

In toxicology, biomarkers are often divided into biomarkers of exposure, of effect, and of susceptibility, and all of these are dealt with in this book, which is extremely wide-ranging. The book has an initial introductory part, including discussion of rodent, nonhuman primate, and zebrafish and *Caenorhabditis elegans* models for toxicological testing. There are two new chapters in this part: firstly, *Drosophila melanogaster, Eisenia fetida,* and *Daphnia magna* for toxicity testing and biomarkers and secondly, adverse outcome pathways and biomarkers.

Part II, systems toxicity biomarkers, comprises chapters on biomarkers of toxicity in relation to all important organs and organ systems. There is an additional chapter on reproductive and developmental toxicity biomarkers, and another on ototoxicity biomarkers. Part III, renamed chemical agents, solvents, and gases toxicity biomarkers, deals with biomarkers in relation to the toxicity of specific groups of compounds and comprises chapters on pesticides, as well as polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), brominated flame retardants, polycyclic aromatic hydrocarbons (PAHs), bisphenol A, melamine and cyanuric acid, and metals; there is a very useful chapter on biomarkers of chemical mixture toxicity. Part IV (biotoxins biomarkers) has three chapters on, respectively, freshwater cyanotoxins, mycotoxins, and poisonous plants: biomarkers for diagnosis (of poisoning). Part V covers pharmaceuticals and nutraceuticals, with chapters on drug toxicity biomarkers and nutriphenomic biomarkers together with a new chapter on biomarkers of toxicity for dietary ingredients contained in dietary supplements. Part VI covers nanomaterials and radiation, with two chapters, one on biomarkers of exposure and effect of engineered nanomaterials and the other on biomarkers of exposure and effects of radiation.

Part VII is entitled carcinogens biomonitoring and cancer biomarkers and contains six chapters. These are on biomonitoring exposures to carcinogens, genotoxicity biomarkers, epigenetic biomarkers in toxicology, breast cancer biomarkers, pancreatic and ovarian cancer biomarkers, and prostate cancer biomarkers. Part VIII is called disease biomarkers and deals with biomarkers of Alzheimer's disease, biomarkers of Parkinson's disease, biomarkers for drugs of abuse and neuropsychiatric disorders: models and mechanisms, osteoarthritis biomarkers, pathological biomarkers in toxicology and oral pathology biomarkers. Of these, the chapters on osteoarthritis and oral pathology are new. Part IX is called special topics. This part of the book contains chapters on biomarkers of mitochondrial dysfunction and toxicity, biomarkers of blood-brain barrier dysfunction, biomarkers of oxidative/nitrosative stress and neurotoxicity, cytoskeletal disruption as a biomarker of developmental neurotoxicity, membrane transporters and transporter substrates as biomarkers for drug pharmacokinetics, pharmacodynamics, and toxicity/adverse events, and citrulline: pharmacological perspectives and role as a biomarker in diseases and toxicity. Of these chapters, that on the blood-brain barrier dysfunction is new and is particularly welcome as the blood-brain barrier is very important in protecting the central nervous system against toxicants. The last part of the book is on applications of biomarkers. It contains three new chapters: biomarkers detection for toxicity testing using microarray technology, metabolomics, and proteomics. Also there are chapters on transcriptomic biomarkers, percellome toxicogenomics, biomarkers in computational toxicology, biomarkers in biomonitoring of xenobiotics and biomarkers in toxicology, risk assessment, and environmental chemical regulations.

The 67-chapter book has an outstanding array of authors from the United States, Canada, Denmark, Finland, Greece, India, Italy, Japan, Portugal, Romania, and Spain. Professor Gupta deserves our gratitude for assembling such a distinguished group of experts to produce so comprehensive a book on this rapidly growing and very important field.

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CHAPTER

1

Introduction

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Biomarkers can broadly be defined as indicators or signaling events in biological systems or samples of measurable changes at the molecular, biochemical, cellular, physiological, pathological, or behavioral levels in response to xenobiotics. The Biomarkers Definitions Working Group of the National Institutes of Health (NIH) has defined the biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes or pharmacological responses to a therapeutic agent." In the field of toxicology, biomarkers have been classified as markers of exposure, effect, and susceptibility. Measurement of biomarkers reflects the time course of an injury and provides information on the molecular mechanisms of toxicity. These biomarkers provide us the confidence of accurate diagnosis, prognosis, and treatment. The biomarkers of early chemical exposure can occur in concert with biomarkers of early disease detection, and that information aids in avoiding further chemical exposure and in strategic development of a novel treatment, including personalized medicine (i.e., treating the patient, and not the disease). In essence, with the utilization of specific biomarkers, an ounce of prevention can be worth a pound of treatment.

Biomarkers are used in drug development, during preclinical and clinical trials, for efficacy and safety assessment. Biomarkers can reveal valuable information regarding diagnosis, prognosis, and predict treatment efficacy or toxicity; serve as markers of disease progression; and serve as auxiliary endpoints for clinical trials (Stern et al., 2018), with the ultimate goal of delivering safe and effective medicines to patients (Lavezzari and Womack, 2016: Gerlach et al., 2018). In addition, a biomarker in drug development should be ethically acceptable (Hey, 2017). Safety biomarkers can be used to predict, detect, and monitor drug-induced toxicity during both preclinical studies and human clinical trials. Developing and validating highly sensitive methods for measurement of biomarkers and understanding the resultant data are complex processes that require a great deal of time, effort, and intellectual input. Furthermore, understanding drug metabolism seems essential in some cases, as the metabolite of a drug can be used as a biomarker, and the drug and/or its metabolite has to be patented by the United States Patent Office and by a similar governmental office/agency in other countries. In the past, many drugs were developed with biomarker assays that guided their use, and this trend is likely to continue in the future for drug discovery and development. With the judicious use of biomarkers, as in evidence-based medicine, patients are most likely to benefit from select treatments and least likely to suffer from their adverse effects. On the contrary, utilization of a bad biomarker can be as harmful to a patient as a bad drug. Therefore, biomarkers need to be validated and evaluated by an accredited laboratory, which participates in a proficiency testing program, to provide a high level of confidence to both clinicians and patients.

In the toxicology field, biomarkers should be specific, accurate, sensitive, validated, biologically or clinically relevant, and easy and fast to perform to be useful as predictive tools for toxicity testing and surveillance and for improving quantitative estimates of exposure and dose. Therefore, biomarkers are utilized for biomonitoring data that are useful in a variety of applications, from exposure assessment to risk assessment, management, and regulations (Ganzleben et al., 2017).

In the early 1990s, Dr. Maria Cristina Fossi from the University of Siena, Italy, emphasized the approach for the development and validation of nondestructive biomarkers over destructive biomarkers in the field of toxicology. She described the ideal biomarker as being measurable in readily available tissues or biological products and obtainable in a noninvasive way; related

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to exposure and/or degree of harm to the organism; directly related to the mechanism of action of the contaminants; highly sensitive with techniques that require minimal quantities of sample and are easy to perform and cost-effective; and suitable for different species.

The development and validation of new techniques in the laboratory may provide the basis for a valuable field method. But, before a new biomarker's application, some basic information is required, such as dose–response relationships, and biological and environmental factors, which can influence the baseline values of responses. It is important to mention that, when dealing with a biochemical or metabolic biomarker, species differences can be the biggest challenge for any toxicologist.

Biomarkers have applications in all areas of toxicology, especially in the fields of pesticides, metals, mycotoxins, and drugs. In the case of veterinary toxicology, biomarkers of plant toxins deserve equal attention. Farmers, pesticide application workers, and greenhouse workers are exposed to pesticides by direct contact and their family members can be exposed via secondhand exposure. Measurement of residues of pesticides, and their metabolites and metals in urine, serves as the most accurate and reliable biomarkers of exposure in agriculture, industrial, and occupational safety and health settings. Recent evidence suggests that in utero or early life exposure to certain pesticides, metals, and other environmental contaminants may cause neurodegenerative (Alzheimer's, Parkinson's, schizophrenia, Huntington's, ALS, and others) and cardiovascular diseases, diabetes, and cancer later in life. In these diseases and many others, specific and sensitive biomarkers play important roles in early diagnosis, and this can serve as the cornerstone for timely therapeutic intervention.

Mycotoxin-related toxicity, carcinogenesis, and other health ailments are encountered in man and animals around the world. In developing countries, where regulatory guidelines are not strictly followed, adverse health effects (especially reproductive and developmental effects) are devastating. In these scenarios, early biomarkers of exposure play a pivotal role in avoiding further exposure to the contaminated food/feed and thus safeguard human and animal health.

With the current knowledge of system biology, proteomics, metabonomics, toxicogenomics, and various mathematical and computational/chemometric modelings, undetectable biomarkers can be discovered and these biomarkers can predict how tissues respond to toxicants and drugs and/or their metabolites, and how the tissue damage and repair processes compromise the tissue's function. Imaging and chemometric biomarkers are of greater sensitivity and carry more information than conventional biomarkers, as they detect (1) low levels of chemical exposure (exposure biomarker) and (2) an early tissue response (endogenous response biomarker). The priority will always be for the development of a noninvasive approach over an invasive approach, and nondestructive biomarkers over destructive biomarkers, but this may not be possible in all cases.

In 2011, the Joint SOT/EUROTOX Debate proposed that "biomarkers from blood and urine will replace traditional histopathological evaluation to determine adverse responses," identifying and comparing the strengths and limitations of histopathology with serum and urine biomarkers. Unlike histopathological techniques, blood and urine biomarkers are noninvasive, quantifiable, and of translational value. Of course, the complete replacement of histopathological biomarkers with blood and urine may not be possible in the near future, as in some instances histopathological biomarkers will still be used because of recent developments in invaluable molecular pathology techniques.

For the quest of developing the most sensitive and reliable biomarkers, integration of novel and existing biomarkers with a multidisciplinary approach appears fruitful. Furthermore, a multibiomarker approach seems more informative and accurate than a single biomarker approach. By now, microRNAs (miRNAs) have been well recognized as reliable and robust biomarkers for early detection of diseases, birth defects, pathological changes, cancer, and toxicities (Quiat and Olson, 2013; Wang et al., 2013; Bailey and Glaab, 2018). Because they are stable in biofluids, such as blood, there is rapidly growing interest in using miRNAs as diagnostic, prognostic, and predictive biomarkers, and the outlook for the clinical application of miRNA discoveries is promising, especially in molecular medicine. Soon, incorporating pharmacological and toxicological targeting of miRNAs into the development of innovative therapeutic strategies will be routine. Still, more innovative biomarkers need to be developed that will be highly sensitive (biotechnology-based techniques), require minimum quantities of sample, and will promise high-throughput screening.

At the recent meetings of the Society of Toxicology, the EUROTOX, and International Congress of Toxicology, a large number of toxicologists emphasized the importance of biomarkers in health, disease, and toxicity. Accordingly, *Biomarkers in Toxicology*, second edition has been prepared to meet the challenges of today's toxicologists, pharmacologists, environmentalists, and physicians in academia, industry, and government. This reference book is of particular interest to those in governmental agencies, such as NIH, USEPA, USFDA, USDA, NIOSH, OSHA, CDC, REACH, EFSA, etc. This is the most comprehensive biomarkers book to date as it covers every possible aspect of exposure, effects, and susceptibility to chemicals. There are many novel topics

in this volume that are not covered in any previous book. This edition identifies and establishes the most sensitive, accurate, unique, and validated biomarkers that can be used as indicators of exposure and effect(s) of chemicals, and chemical-related long-term diseases, such as cardiovascular, metabolic and neurodegenerative diseases, and cancer. Sixty-seven chapters are organized under eight sections with a user-friendly format, and each chapter is enriched with current literature and references for further reading. This book begins with general concepts of toxicity and safety testing and biomarker development using various animal and animal alternative models, adverse outcome pathways, followed by biomarkers of system/organ toxicity, chemicals, solvents, gases, and biotoxins. There are several chapters on biomarkers of pharmaceuticals, nutraceuticals, petroleum products, chemical mixtures, radiation, engineered nanomaterials, epigenetics, genotoxicity, and carcinogens. In the disease section, chapters cover the biomarkers of Alzheimer's, Parkinson's, neuropsychiatric disorders, osteoarthritis, and some other pathological conditions. Under special topics, chapters are included on mitochondrial dysfunction and toxicity, the blood−brain barrier, oxidative/nitrosative stress, developmental neurotoxicity, miRNAs as indicators of tissue injury, and citrulline in diseases and toxicity. Lastly, a large number of chapters are dedicated to the application of biomarkers in toxicology, including the latest strategies and technologies in the development of biomarkers, biomarkers in drug development, safety evaluation, and toxicity testing and integration of biomarkers in biomonitoring of chemical exposure and risk assessment, especially in the context of industrial, environmental, and occupational medicine and toxicology.

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