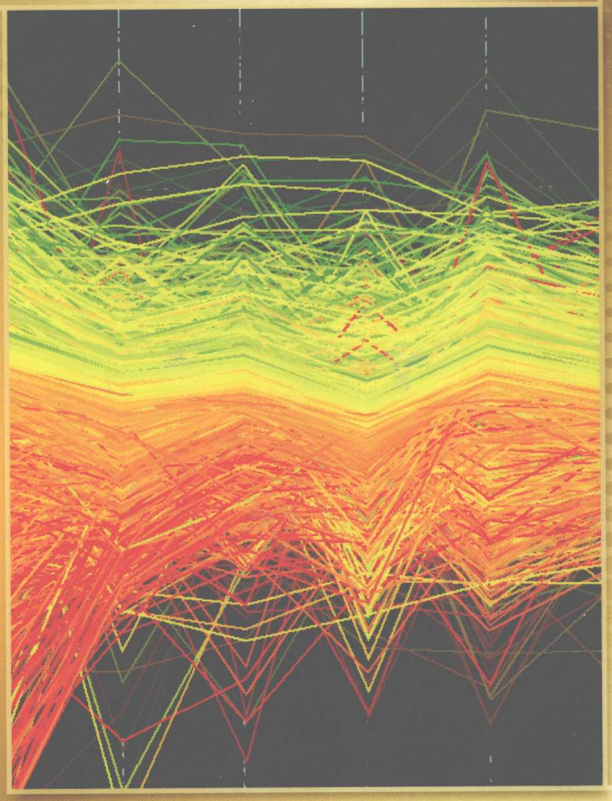
2

Handbook of Systems Toxicology

Editors Daniel A. Casciano and Saura C. Sahu



WILEY

Handbook of Systems Toxicology

Editors

Daniel A. Casciano

University of Arkansas at Little Rock, Little Rock, AR, USA

Saura C. Sahu

US Food and Drug Administration, Laurel, MD, USA

VOLUME 2

WILEY

This edition first published 2011

Registered office

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

Library of Congress Cataloging-in-Publication Data

Handbook of systems toxicology / [edited by] Daniel A. Casciano, Saura C. Sahu.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-470-68401-6 (hardback)
1. Toxicology. I. Casciano, Daniel A. II. Sahu, Saura C.
RA1190.H36 2011
615.9–dc22

2010043281

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN-13 978-0-470-68401-6 (HB)

Typeset in 10/12pt Times by Thomson Digital, Noida, India
Printed and bound by Grafos SA, Barcelona, Spain

This book is printed on acid-free paper responsibly manufactured from sustainable forestry, in which at least two trees are planted for each one used for paper production

Handbook of Systems Toxicology

Contributors

Andrea Adamcakova-Dodd *Department of Occupational and Environmental Health, University of Iowa, Iowa City, IA, USA*

Jiri Adamec *Bindley Biological Sciences Center, Purdue University, West Lafayette, IN, USA*

Md. Altaf-Ul-Amin *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Ioannis P. Androulakis *Department of Biomedical Engineering, Rutgers University, Piscataway, NJ, USA, Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA* and *Environmental Bioinformatics and Computational Toxicology Center, Piscataway, NJ, USA*

Hiroko Asahi *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Jiri Aubrecht *Pfizer Global Research and Development, Groton, CT, USA*

Armelle Baeza-Squiban *Functional and Adaptive Biology Group, Laboratory of Molecular and Cellular Responses to Xenobiotics, University of Paris 7 Diderot-Paris, Paris, France*

Kirsten A. Baken *Department of Health Risk Analysis and Toxicology, Maastricht University, Maastricht, The Netherlands*

Stephanie D. Baker *GEI Consultants Inc., Denver, CO, USA*

Mayukh Banerjee *Molecular and Human Genetics Division, Indian Institute of Chemical Biology, Kolkata, India*

Nivedita Banerjee *Interdisciplinary Program of Toxicology, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA*

Richard D. Beger *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Frederick A. Beland *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Giovanni Bernardini *Department of Biotechnology and Molecular Sciences, University of Insubria, Varese, Italy,* and *Centre for Interuniversity Research, Polytechnic University of Milan, Milan, Italy*

Alexandru S. Biris *Nanotechnology Center, University of Arkansas at Little Rock, Little Rock, AR, USA*

Fabian Blank *Division of Pulmonary Medicine, Department of Clinical Research, University of Bern, Bern, Switzerland*

Margaret Bogle *Obesity Prevention Research Unit, Agricultural Research Service, US Department of Agriculture, Little Rock, AR, USA*

Sonja Boland *Functional and Adaptive Biology Group, Laboratory of Molecular and Cellular Responses to Xenobiotics, University of Paris 7 Diderot-Paris, Paris, France*

Maribel Bruno *National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC, USA*

Jason P. Burgess *Discovery and Analytical Sciences, RTI International, Research Triangle Park, NC, USA*

Lyle D. Burgoon *Center for Integrative Toxicology, Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI, USA*

Anna Giulia Cattaneo *Department of Biotechnology and Molecular Sciences, University of Insubria, Varese, Italy*

Raghothama Chaerkady *McKusick-Nathans Institute of Genetic Medicine and Departments of Biological Chemistry, Pathology and Oncology, Johns Hopkins University, Baltimore, MD, USA*

Ching-Wei Chang *Division of Personalized Medicine and Nutrition, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

James J. Chen *Division of Personalized Medicine and Nutrition, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Minjun Chen *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Maurizio Chiriva-Internati *Division of Hematology and Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA*

Myung-Haing Cho *Laboratory of Toxicology, College of Veterinary Medicine, and Department of Nanofusion Technology, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea*

Wan-Seob Cho *ELEGI/Colt Laboratory, Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK* and *Nutrition and Functional Food Research Team, National Institute of Food and Drug Safety Evaluation, Seoul, Korea*

Mona I. Churchwell *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Martin J. D. Clift *Division of Histology, Institute of Anatomy, University of Bern, Bern, Switzerland*

Ludmila Danilova *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA*

Varsha G. Desai *Center for Functional Genomics, Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Rob DeWoskin *National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, USA*

Naomi Diaz *Department of Chemistry, Purdue University, West Lafayette, IN, USA*

Robert J. Edwards *Experimental Medicine and Toxicology, Hammersmith Hospital Campus, Imperial College London, London, UK*

Heidrun Ellinger-Ziegelbauer *Investigational Toxicology, Bayer Schering Pharma AG, Wuppertal, Germany*

Hong Fang *Z-Tech, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Timothy R. Fennell *Discovery and Analytical Sciences, RTI International, Research Triangle Park, NC, USA*

Mark Fielden *Comparative Biology and Safety Sciences, Amgen Inc., South San Francisco, CA, USA*

Heidi Foth *Institute of Environmental Toxicology, Martin Luther University, Halle, Germany*

James C. Fuscoe *Division of Systems Biology, National Center for Toxicological Research, FDA, Jefferson, AR, USA*

P. Fu *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Prashant Gabani *Division of Biological and Health Sciences, University of Pittsburgh, Bradford, PA, USA*

Yuan Gao *Center for Proteomics, Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Yue Ge *National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC, USA*

Peter Gehr *Division of Histology, Institute of Anatomy, University of Bern, Bern, Switzerland*

Anna Georgieva *Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Panos G. Georgopoulos *Department of Environmental and Occupational Medicine, RW Johnson Medical School, UMDNJ, Piscataway, NJ, USA, Department of Biomedical Engineering, Rutgers University, Piscataway, NJ, USA, Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA* and *Environmental Bioinformatics and Computational Toxicology Center, Piscataway, NJ, USA*

Mario Di Gioacchino *Centre for Aging Sciences, G D'Annunzio University Chieti-Pescara, Chieti, Italy* and *Department of Medicine and the Sciences of Aging, Faculty of Medicine and Surgery, G D'Annunzio University Chieti-Pescara, Chieti, Italy*

Ashok K. Giri *Molecular and Human Genetics Division, Indian Institute of Chemical Biology, Kolkata, India*

Rosalba Gornati *Department of Biotechnology and Molecular Sciences, University of Insubria, Varese, Italy,* and *Center for Interuniversity Research, Polytechnic University of Milan, Milan, Italy*

Vicki H. Grassian *Interdisciplinary Graduate Program in Human Toxicology, University of Iowa, Iowa City, IA, USA* and *Department of Chemistry and Department of Chemical and Biochemical Engineering, University of Iowa, Iowa City, IA, USA*

Hans Peter Grimm *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Lei Guo *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Subramanian Gurunathan *Department of Bioinformatics, SRM University, Chennai, India*

Gabriel Helmlinger *Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Ralf Herwig *Bioinformatics Group, Department of Vertebrate Genomics, Max-Planck-Institute for Molecular Genetics, Berlin, Germany*

Philip G. Hewitt *eTox, Institute of Toxicology, Merck Serono Research, Merck KGaA, Darmstadt, Germany*

Yoko Hirabayashi *National Center for Biology and Safety Research, National Institute of Health Sciences, Tokyo, Japan*

Aki Hirai *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Huixiao Hong *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Amber Hopf-Jannasch *Bindley Biological Sciences Center, Purdue University, West Lafayette, IN, USA*

Salik Hussain *Functional and Adaptive Biology Group, Laboratory of Molecular and Cellular Responses to Xenobiotics, University of Paris 7 Diderot-Paris, Paris, France*

Marianthi G. Ierapetritou *Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA* and *Environmental Bioinformatics and Computational Toxicology Center, Piscataway, NJ, USA*

Taisen Iguchi *Okazaki Institute for Integrative Bioscience, National Institute for Basic Biology, National Institutes of Natural Sciences, and Department of Basic Biology, The Graduate University for Advanced Studies, Myodaiji, Okazaki, Japan*

Tohru Inoue *National Center for Biology and Safety Research, National Institute of Health Sciences, Tokyo, Japan*

Sastry Isukapalli *Department of Environmental and Occupational Medicine, RW Johnson Medical School, UMDNJ, Piscataway, NJ, USA, Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA* and *Environmental Bioinformatics and Computational Toxicology Center, Piscataway, NJ, USA*

Marc Jacobsen *Department of Immunology, Bernhard-Nocht Institute for Tropical Medicine, Hamburg, Germany*

Sang-Hee Jeong *GLP Research Center, College of Natural Science, Hoseo University, Asan City, Korea*

Pius Joseph *Molecular Carcinogenesis Laboratory, Toxicology and Molecular Biology Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV, USA*

Shigehiko Kanaya *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Jim Kaput *Division of Personalized Nutrition and Medicine, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Yasuhiko Kato *Okazaki Institute for Integrative Bioscience, National Institute for Basic Biology, National Institutes of Natural Sciences, and Department of Basic Biology, The Graduate University for Advanced Studies, Myodaiji, Okazaki, Japan*

Ji-Eun Kim *Laboratory of Toxicology, College of Veterinary Medicine, and Department of Nanofusion Technology, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea*

Thomas B. Knudsen *National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, USA*

Rohan Kulkarni *Division of Genetic and Reproductive Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Thierry Lave *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Weisheng Lin *Frontage Laboratory, Great Valley Corporate Center, Malvern, PA, USA*

Dalia Lovera *Obesity Prevention Research Unit, Agricultural Research Service, US Department of Agriculture, Little Rock, AR, USA*

Henk van Loveren *Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands* and *Department of Health Risk Analysis and Toxicology, Maastricht University, Maastricht, The Netherlands*

Yinfa Ma *Department of Chemistry, University of Science and Technology Rolla, MO, USA*

Meena Mahmood *Nanotechnology Center, University of Arkansas at Little Rock, Little Rock, AR, USA*

Francelyne Marano *Functional and Adaptive Biology Group, Laboratory of Molecular and Cellular Responses to Xenobiotics, University of Paris 7 Diderot-Paris, Paris, France*

Kaori Matsuda *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Beverly McCabe-Sellers *Obesity Prevention Research Unit, Agricultural Research Service, US Department of Agriculture, Little Rock, AR, USA*

Nan Mei *Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

William B. Melchior *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Donna L. Mendrick *Center for Proteomics, Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Cristiano Migliorini *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Yohsuke Minowa *Toxicogenomics-Informatics Project, National Institute of Biomedical Innovation, Ibaraki, Osaka, Japan*

Suzanne M. Morris *Division of Genetic and Reproductive Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Nagathihalli S. Nagaraj *Department of Surgery, Division of Surgical Oncology, Vanderbilt University School of Medicine, Nashville, TN, USA*

Kensuke Nakamura *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Baitang Ning *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Michael F. Ochs *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA*

Yasuo Ohno *Toxicogenomics-Informatics Project, National Institute of Biomedical Innovation, Ibaraki, Osaka, Japan*

Eriko Okochi-Takada *Carcinogenesis Division, National Cancer Center Research Institute, Tokyo, Japan*

Yasushi Okuno *Department of Systems Bioscience for Drug Discovery, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*

Neil J. Parrott *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Aziza Kawsar Parvin *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Wimal Pathmasiri *Discovery and Analytical Sciences, RTI International, Research Triangle Park, NC, USA*

Tucker A. Patterson *National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Robert C. Penland *Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Jeroen L.A. Pennings *Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*

Roger Perkins *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Dayton M. Petibone *Division of Genetic and Reproductive Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Constantinos Pistos *Department of Forensic Medicine and Toxicology, Medical School, University of Athens, Athens, Greece*

James A. Popp *Stratoxon LLC, Lancaster, PA, USA*

T.S. Keshava Prasad *Institute of Bioinformatics, Bangalore, India*

Kimberly J. Ralston-Hooper *Ecosystem Research Division, United States Environmental Protection Agency, Athens, GA, USA*

Axel Rasche *Bioinformatics Group, Department of Vertebrate Genomics, Max-Planck-Institute for Molecular Genetics, Berlin, Germany*

Luke D. Ratnasinghe *Cytonix, Beltsville, MD, USA*

Micaela Reddy *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Dirk Repsilber *Genetics and Biometry/Bioinformatics and Biomathematics Group, Research Institute for the Biology of Farm Animals, Dummerstorf, Germany*

Amelia A. Romoser *Interdisciplinary Program of Toxicology, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA*

Barbara Rothen-Rutishauser *Division of Histology, Institute of Anatomy, University of Bern, Bern, Switzerland*

Enrico Sabbioni *Centre for Aging Sciences, G D'Annunzio University Chieti-Pescara, Chieti, Italy*

Saura C. Sahu *Division of Toxicology, Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Laurel, MD, USA*

William Salminen *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Brian C. Sanchez *Colorado Ecological Services Field Office, US Fish and Wildlife Service, Lakewood, CO, USA*

Christie M. Sayes *Interdisciplinary Program of Toxicology, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA*

Christina S. Schmitt *eTox, Institute of Toxicology, Merck Serono Research, Merck KGaA, Darmstadt, Germany*

Laura K. Schnackenberg *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Maria S. Sepúlveda *Department of Natural Resources, Purdue University, West Lafayette, IN, USA*

Leming Shi *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Qiang Shi *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Masayuki Shojo *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Joseph F. Sina *Safety Assessment, Merck Research Laboratories, West Point, PA, USA*

Om V. Singh *Division of Biological and Health Sciences, University of Pittsburgh, Bradford, PA, USA* and *Advance Academic Programs, Zanvyl Krieger School of Arts and Sciences, The Johns Hopkins University, Washington DC, USA*

Frank D. Sistare *Safety Assessment, Merck Research Laboratories, West Point, PA, USA*

William Slikker *National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Rodney W. Snyder *Discovery and Analytical Sciences, RTI International, Research Triangle Park, NC, USA*

Antoine Soubret *Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Julian E. Spallholz *Nutritional Sciences, College of Human Sciences, Texas Tech University, Lubbock, TX, USA*

Alexandra Sposny *eTox, Institute of Toxicology, Merck Serono Research, Merck KGaA, Darmstadt, Germany*

Zhenqiang Su *Z-Tech, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Susan J. Sumner *Discovery and Analytical Sciences, RTI International, Research Triangle Park, NC, USA*

Jinchun Sun *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Ayako Suzuki *Department of Gastroenterology, Duke University, Durham, NC, USA*

Hiroki Takahashi *Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma, Japan*

Hideyuki Takeshima *Carcinogenesis Division, National Cancer Center Research Institute, Tokyo, Japan*

Stamatios Theocharis *Department of Forensic Medicine and Toxicology, Medical School, University of Athens, Athens, Greece*

Peter S. Thorne *Department of Occupational and Environmental Health* and *Department of Civil and Environmental Engineering, University of Iowa, Iowa City, IA, USA*

William H. Tolleson *Division of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Weida Tong *Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Vetrivel Umashankar *Centre for Bioinformatics, Vision Research Foundation, Sankara Nethralaya, Chennai, India*

Tetsuro Urushidani *Toxicogenomics-Informatics Project, National Institute of Biomedical Innovation, Ibaraki, Osaka, Japan* and *Department of Pathophysiology, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyoto, Japan*

Toshikazu Ushijima *Carcinogenesis Division, National Cancer Center Research Institute, Tokyo, Japan*

Rob J. Vandebriel *Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*

Cheng Wang *National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Hajime Watanabe *Department of Biotechnology, Graduate School of Engineering, Osaka University, Osaka, Japan*

William J. Welsh *Department of Pharmacology, RW Johnson Medical School, UMDNJ, Piscataway, NJ, USA* and *Environmental Bioinformatics and Computational Toxicology Center, Piscataway, NJ, USA*

Anna Williams *Division of Personalized Nutrition and Medicine, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Carolyn Wise *Division of Personalized Nutrition and Medicine, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Yang Xu *Nanotechnology Center, University of Arkansas at Little Rock, Little Rock, AR, USA*

Hiroshi Yamada *Toxicogenomics-Informatics Project, National Institute of Biomedical Innovation, Ibaraki, Osaka, Japan*

Reha Yildirimman *Bioinformatics Group, Department of Vertebrate Genomics, Max-Planck-Institute for Molecular Genetics, Berlin, Germany*

Li-Rong Yu *Center for Proteomics, Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA*

Jinsong Zhang *School of Tea and Food Science, Anhui Agricultural University, Anhui, China*

Zheying Zhu *Experimental Medicine and Toxicology, Hammersmith Hospital Campus, Imperial College London, London, UK*

Athina Zira *Department of Forensic Medicine and Toxicology, Medical School, University of Athens, Athens, Greece*

Klaas P. Zuideveld *F. Hoffmann-La Roche, Ltd., Basel, Switzerland*

Preface

One result of the sequencing of the human genome has been the development of a variety of new and emerging technologies which allow the researcher to determine how a cell, tissue, organ or organism functions at the molecular level. These technologies include genomics, proteomics, metabolomics and bioinformatics. A consequence of this development is the initiation of a systems biology approach to understanding the normal or constitutive function of an organism. Systems biology focuses on understanding gene and protein networks involved in cell signaling communication between cells and cellular metabolic pathways. This new approach requires an integration of several scientific disciplines using talents from multidisciplinary research teams. Systems toxicology, a natural derivative of systems biology, combines classical toxicology with the rapidly developing new "omics" technology providing integrated biological response data that describe molecular pathways that are perturbed by a toxicant much sooner than a toxin-induced phenotype is observed, allowing definition of predictive biomarkers. It integrates molecular expression data sets from transcriptomics, proteomics, metabonomics and conventional toxicology with metabolism, toxicological pathways and gene regulatory network information relevant to human toxicology and disease. Systems toxicology develops new primary data as well as an assessment of available data to understand how the molecular machinery of biological systems execute their biological functions in the presence of chemical and biological stress.

Humans are exposed to many chemicals every day in the modern industrial world and the evaluation of the risk of these chemicals to human health requires a better understanding of the mechanism(s) of their toxicity. In the last decade the emergence of the new "omics" technologies has generated a vast amount of molecular information on the effects of chemical toxicants in biological systems such as cells, tissues, organs and organisms. As the emerging technologies mature, the National Academy of Sciences Committee on Toxicity Testing and Assessment of Environmental Agents recommended, in 2007, a new approach to toxicity testing embracing the use of these new tools. Advances in systems toxicology will help develop new strategies for mechanistic and predictive toxicology resulting in new predictive biomarkers using a combination of cross-"omics" and classical toxicology endpoints to detect toxicants much earlier in the toxicity process. Another outcome is the identification of more sensitive and predictive biomarkers of toxicity that will aid in the development and approval of safer and more effective drugs, foods and medical devices. Also, the derived data will facilitate the development of better models of species extrapolation allowing a more relevant assessment of human risk. Development and validation of this emerging science should provide toxicologists with greater confidence using the data developed in our present animal models and should ensure the development of newer models that are more mechanistically relevant in their application to human risk assessment. Additionally, these tools can be used to directly assess human toxicity resulting in more accurate animal and mathematical models for the identification of risk to humans.

Prior to assembling this treatise, we found little or no integrated literature describing this new area of toxicology. The main purpose of this handbook then was to assemble up-to-date, state-of-the-art information presented by investigators who are internationally recognized in their particular research areas. It is therefore hoped that the work will become an authoritative source of current knowledge in this particular area of research. The book is designed primarily for the research scientist currently engaged in this field. However, it should be of interest to scientists in a wider set of disciplines

including toxicology, genetics, medicine and pharmacology as well as drug and food sciences. Also, it should be of interest to federal regulators and risk assessors of drugs and foods, and of environment and consumer products. We have included a section on nanotechnology and nanotoxicology because it is a new area of discovery directed to human use that may have a significant impact on how these materials are used and regulated. We feel that the application of tools resulting from a systems toxicology approach to nanoparticles will provide us with a greater level of confidence in their human efficacy and toxicity.

Since the field of systems toxicology is a rapidly developing, emerging branch of modern toxicology it is expected that there will be a requirement for regular updates to this volume. Although the fundamental concepts presented in these volumes are unchanging, the emergence of new experimental models and new bioinformatic tools will dictate regular updating to track the maturation and validation of this extremely exciting area of toxicology.

Daniel A. Casciano
Saura C. Sahu
January 2011

Acknowledgments

Saura C. Sahu would like to express his sincere gratitude to the following individuals who have helped him, directly or indirectly, in the writing of this handbook: all the participating scientists for their excellent contributions in their own areas of expertise; Dr. Daniel A. Casciano, the co-editor of this handbook, for his advice, inspiration and support; Dr. Joseph E. LeClerc, Dr. Thomas A. Cebula and Dr. Philip W. Harvey for their encouragement; Martin Rothlisberger, Kerry Powell and Anne Hunt of John Wiley & Sons, Ltd, for their cooperation and support, and finally his parents, Gopinath and Ichhamoni, for their gift of life, love and living examples, his wife, Jharana, for her life-long friendship, love and support, and his children, Megha, Sudhir and Subir, for their love and care.

Daniel A. Casciano would like to acknowledge Gertrude Tara-Casciano, Dr George E. Moore and Dr Frank H. Gaertner for their encouragement and advice as well as all the authors who have contributed to this treatise.

Abbreviations and Acronyms

1O2	Singlet Oxygen
2-AG	2-Arachidonoylglycerol
2D-DIGE	2D Difference In Gel Electrophoresis
2-DE	Two-Dimensional Electrophoresis
2D-PAGE	Two-Dimensional Polyacrylamide Gel Electrophoresis
2-OG	2-Oxoglutarate
3-NP	3-Nitropropionic Acid
4-NQO	4-Nitroquinoline 1-Oxide
5-FU	5-Fluorouracil
8-OHdG	8-Hydroxydeoxyguanosine
8-OHG	8-Hydroxyguanosine
AA	Arachidonic Acid
AA	Aristolochic Acid
ABC	Ammonium Bicarbonate
ABH6	$\alpha\beta$-Hydrolases 6
Abhd6	Abhydrolase Domain Containing 6
ABM	Agent-Based Modeling
ACAT	Advanced Compartmental Absorption and Transit
ACD	Available Chemical Database
ACD	Available Chemical Directory
ACToR	Aggregated Toxicology Resource
AdFAAH	An Faah-Expressing Adenovirus
AdGFP	GFP-Expressing Control Virus
ADME	Absorption, Distribution, Metabolism, and Elimination
ADMET	Adsorption Distribution, Metabolism, Excretion and Toxicity
AERS	Adverse-Event-Reporting System
AEs	Adverse Events
AF	Attributable Fraction
AFM	Atomic Force Microscopy
AHPS	American Herbal Products Association
AhR	Aryl Hydrocarbon Receptors
AIR	Acute Inflammatory Response
ALA	Amino Levulinic Acid
ALAT	Alanine Aminotransferase
ALD	Alcohol Liver Disease
ALF	Artificial Lysosomal Fluid
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ALT	Alanine Aminotransaminase
AM	Acetoxymethyl
AM	Alveolar Macrophages
AML	Acute Myeloid Leukemia
AMPA	α-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionate Receptors
AMs	Alveolar Macrophages
AMT	Accurate Mass and Time Tags
AMV	Avian Myeloblastoma Virus
ANIT	1-Napthylisothiocyanate
ANOVA	Analysis of Variance

AP	Action Potential
Apaf-1	Apoptotic Protease Activating Factor-1
APAP	Acetaminophen
N-APAP	N-Acetyl-P-Aminophenol
APASE	Alkaline Phosphatase
APD	Action Potential Duration
AR	Aldose Reductase
AR	Androgen Receptor
ARE	Antioxidant Response Elements
ARF	Acute Renal Failure
ARS	Agricultural Research Service
ASAT	Aspartate Aminotransferase
ATHEROMA	Atorvastatin Therapy: Effects on Reduction of Macrophage Activity
ATZ	Atrazine
AUC	Area Under the Curve
AV	Atrioventricular
AXL	Axial
BAL	Bronchoalveolar Lavage
BaP	Benzo[A]Pyrene
BBB	Blood–Brain Barrier
BBDR	Biologically Based Dose–Response
BDL	Bile Duct Ligation
BDPE	Benzo[A]Pyrene Diol Epoxide
BDSM	Birth Defects Systems Manager
BE	Binding Energy
BEAS-2B	Bronchial Epithelial Cells
BED	Biologically Effective Dose
BET	Brunauer, Emmett, and Teller
BMD	Benchmark Dose
BOINC	Berkeley Open Infrastructure for Network Computing
BOSS	Biochemical and Organic Simulation System
BSI	British Standards Institution
B-TOH	Bopidy-α-Tocopherol
BUN	Blood Urea Nitrogen
BW	Body Weight
C/EBP	Ccaat/Enhancer-Binding Protein
CA	Chromosomal Aberration
CADD	Computer Assisted Drug Design
CAM	Caulis Aristolochiae Manshuriensis
CAMD	Computer-Assisted Molecular Design
CAPs	Common Ageing Profiles
CASP	Critical Assessment of Structure Prediction
CAVE	Cave Automatic Virtual Environment
CB	Cannabinoid
CB	Carbon Black
CBD	Cannabidiol
CBPR	Community-Based Participatory Research
CCAT	Chemically-Coded Affinity Tag
CCl_4	Carbon Tetrachloride
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research
CDKs	Cyclin-Dependent Kinases
CEBS	Chemical Effects in Biological Systems
CeO2	Cerium Oxide
CFD	Computational Fluid Dynamics
CFF	Consistent Force Field
CFSAN	Center for Food Safety and Nutrition
CG	Comparative Genometrics
CGAs	Community Genome Arrays
CHCA	α-Cyano-4-Hydroxycinnamic Acid
CHI	Closed Head Injury
CHIC	Community Health Improvement Collaborative
ChIP	Chromatin Immunoprecipitation
CID	Collision-Induced Dissociation
CIM	Cimetidine
CL	Chemiluminescent
cLEL	Categorical Lels
CLH	Hepatic Clearance