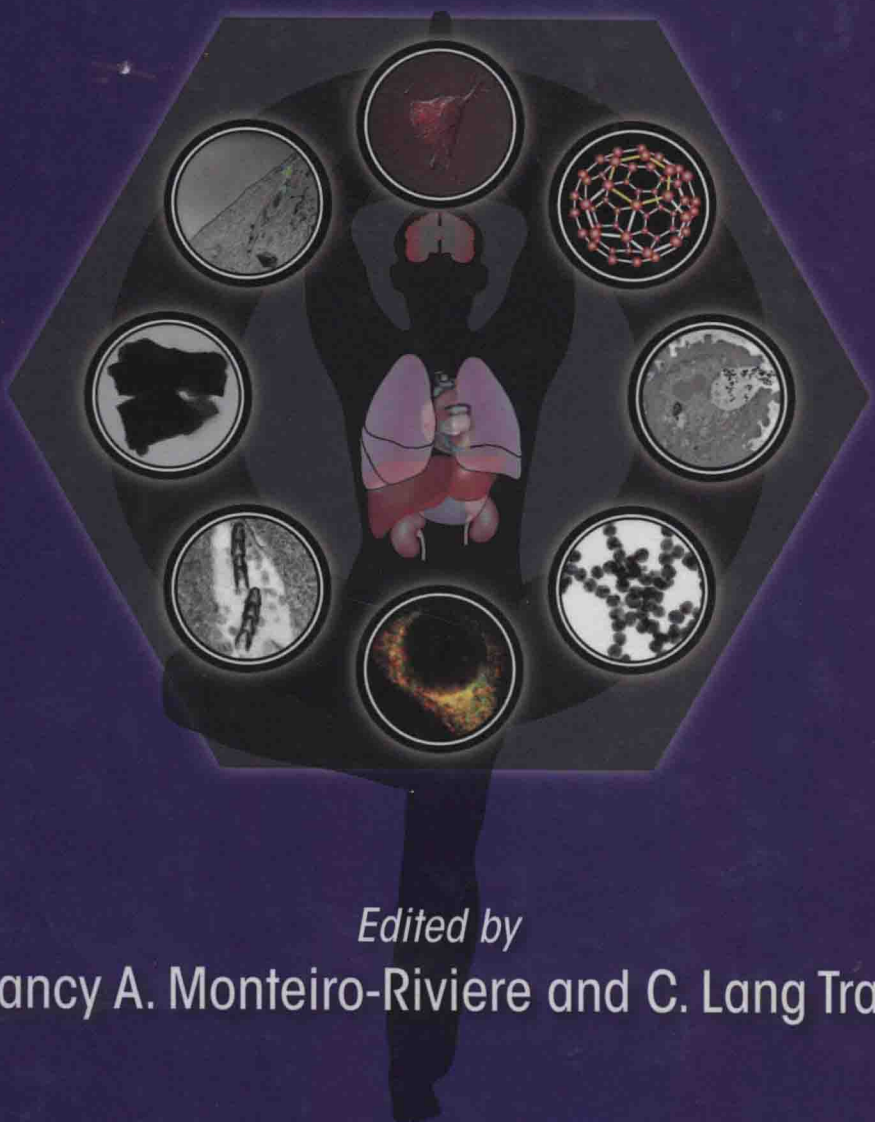
Second Edition

Nanotoxicology

Progress toward Nanomedicine



Edited by
Nancy A. Monteiro-Riviere and C. Lang Tran

CRC Press
Taylor & Francis Group

Second Edition

Nanotoxicology

Progress toward Nanomedicine

Edited by

Nancy A. Monteiro-Riviere and C. Lang Tran

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20130923

International Standard Book Number-13: 978-1-4822-0387-5 (Hardback)

Library of Congress Cataloging-in-Publication Data

Nanotoxicology (Monteiro-Riviere)
Nanotoxicology : progress toward nanomedicine / [edited by] Nancy A. Monteiro-Riviere and C. Lang Tran. -- Second edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4822-0387-5 (alk. paper)
I. Monteiro-Riviere, Nancy A., editor of compilation. II. Tran, C. L., editor of compilation. III. Title.
[DNLM: 1. Nanotechnology--methods. 2. Nanostructures--therapeutic use. 3. Nanostructures--toxicity. QT 36.5]

R857.N34
610.28--dc23 2013036688

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Second Edition

Nanotoxicology

Progress toward Nanomedicine

Preface

Nanotechnology promises new materials for industrial applications by having new or enhanced physicochemical properties that are different in comparison to their micrometer-sized counterparts. The market size for nanotechnology is expected to grow to over $3 trillion by 2015. As in all industrial applications, the potential exposure of humans and the environment to these materials is inevitable. As these new materials go through their life cycle—from development, to manufacture, to consumer usage, to final disposal—different human groups (e.g., workers, bystanders, or consumers), environmental compartments (e.g., air, soil, sediment, or water), and species (e.g., worm, fish, or human) will be exposed to these materials. Emerging data have shown a range of toxic (hazardous) effects from engineered nanoparticles, suggesting that combined with the potential exposure these nanoparticles may result in a risk (product of hazard and exposure) to human health or the environment. Although standard methods exist for hazard and risk analysis of conventional chemicals, these tools need to be modified and verified before being applied to nanomaterials. In a similar way, presently used standard approaches to risk management, control, and reduction need to be rendered relevant for nanomaterials. Thus, the development of nanotechnology-based products must be complemented with appropriate validated methods to assess, monitor, manage, and reduce the potential risks of engineered nanomaterials (ENMs) to human health and the environment. Not only good management tools are important but public awareness is also important for industrial development and acceptance. Public mistrust of any new technology is often high, and demonstrating *safe* products of nanotechnology will enhance the confidence of consumers, workers, and other stakeholders. Hence, efficient communication strategies to the public and stakeholders of significant progress are of high importance.

Many concerns have been expressed as to the safety of ENMs. There has been a concerted effort among government agencies, industrial sponsors, academicians, scientists, and the public to try to identify the potential hazards of nanotechnology. The first edition of this book provided the basic knowledge of nanomaterials safety and discussed the proper use for characterization, nomenclature standards, and physicochemical characteristics of nanoparticles that determined their toxicity in biological and environmental systems. Since the first publication of this book in 2007, the field of nanoscience and nanomedicine continues to grow substantially.

This second edition of *Nanotoxicology: Progress toward Nanomedicine* has been greatly expanded and includes many new authors who offer suggestions on how to conduct nanomaterial toxicology studies and stress the need for proper characterization. The need for developing and ascertaining the tools used for risk assessment and management of ENMs is paramount. In the second publication of this book, our aim is to document the continuing development of the essential tools used for ENM characterization and in vitro and in vivo toxicology testing. Of importance is the contribution of nanosafety research to nanomedicine. The interplay between these

two disciplines is going to deliver in the near future the most startling insights into the interaction between ENMs and the biological milieu.

Section I deals with the impacts of nanotechnology on biomedicine. Nanomedicine development has improved over traditional approaches as new ENMs emerge at the nanoscale. There is a great need for appropriate functionalization for tissue-specific targeting or drug delivery to tissues that can be tuned with nanomaterials. Many nanomaterials may degrade once in the body and the toxicity and clearance pathways may be altered. The biointeractions of multifunctional nanoparticle-based therapy are discussed. It was once thought that the primary applications of nanomedicine were for diagnosis and cancer treatment but due to functionalization the treatment of many diseases can now be investigated. The ability to control some of the specific physicochemical properties of nanoparticles such as size, surface area, and shape has allowed for control over the nanoparticle functions so that they can be used for treatment of different diseases.

Section II on exposure demonstrates that there is no consensus on the use of a single metric to characterize exposure to ENMs and that there is no international standard for measuring and characterizing ENMs. This section provides much-needed information on the requirements for proper detection, measurement, and assessment both for workplace exposure and in consumer products. Section III on modeling provides an insight into the development of quantitative endpoints that are useful in predicting the vivo behavior of nanoparticles. Section IV on methodologies and techniques provides the basic tools for assessing nanoparticle toxicity from the early stages of manufacturing to in vivo biodistribution, where size, surface chemistry, and shape play a major role in toxicity in some tissues. Also, an array of detection methods have been implemented for assessing toxicity in in vivo and in vitro systems, as well as at the single cell and tissue levels. Their benefits and limitations will be discussed. Section V on hazards deals with specific organ systems that have been thoroughly investigated by many international experts with different types of ENMs in multiple in vivo and in vitro models. This section assesses not only the toxicity in organ systems but also some of the applications of ENMs for the potential treatment in neuroregeneration and targeted delivery of imaging or therapeutic nanomaterials to tumors. Also, specialized applications have been developed due to the microcidal activity of many nanoparticles for the use in indwelling catheters, orthopedic implants, bandages for diabetic wounds, and tissue engineering. Numerous strategies also exist for additional medical applications ranging from tumor targeting to the treatment of different cancers. Section VI on risk assessment of nanomaterials is complicated due to the limited information obtained on only a few occupational exposures, lack of comprehensive epidemiological studies, and no clear dose metric due to lack of or improper characterization of nanomaterials. Many coordinated research efforts have been implemented to address the potential risks of nanomaterials, and there is even a greater need to address the knowledge gaps especially with long-term studies.

All of these chapters report on exciting science and show great promise for some ENMs to be used in nanomedicine. They reflect a sense of urgency to develop effective targeted nanotheranostics to be used in clinical trials. There is also both a great

need to understand the complexities and issues of toxicology of nanomaterials and a need for continued harmonization for risk management.

In this book, we have solicited some of the most crucial research, illustrating the development of nanosafety and nanomedicine, their interplay, and convergence. We hope the readers will find inspiration through the chapters contributed by leading international experts in both fields and appreciate the continuing development in nanosafety and nanomedicine.

Editors

Nancy A. Monteiro-Riviere is a Regents Distinguished Research Scholar and University Distinguished Professor of Toxicology and Director of the new Nanotechnology Innovation Center of Kansas State. She was a professor of investigative dermatology and toxicology at the Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University (NCSU) for 28 years. She is also a professor in the Joint Department of Biomedical Engineering at the University of North Carolina (UNC) at Chapel Hill/NCSU and research adjunct professor of dermatology at the UNC-Chapel Hill School of Medicine. She earned a BS (cum laude) in biology from Stonehill College, North Easton, Massachusetts, and an MS and a PhD in anatomy and cell biology from Purdue University, West Lafayette, Indiana, and completed a post-doctoral fellowship in toxicology at Chemical Industry Institute of Toxicology (now Hamner Institutes for Health Sciences) in Research Triangle Park, North Carolina. She was past president of both the Dermal Toxicology and In Vitro Toxicology Specialty sections of the National Society of Toxicology. She is a fellow in the Academy of Toxicological Sciences and in the American College of Toxicology. She was the recipient of the Purdue University inaugural Distinguished Women Scholars Award, Kansas State University Woman of Distinction, and elected to attend the National Academy of Sciences special Keck Futures Initiative Conference on "Designing Nanostructures at the Interface between Biomedical and Physical Systems." She serves as an associate editor for *WIREs Nanomedicine and Nanobiotechnology* and for *Materials Science and Engineering C: Materials for Biological Applications*; and serves on the editorial boards of *Nanomedicine*, *Nanotoxicology*, *Journal of Applied Toxicology*, *Cutaneous and Ocular Toxicology*, *Research and Reports in Transdermal Drug Delivery*, and *Toxicology In Vitro*. She has served on several national and international expert review panels, including many in nanotoxicology, such as the National Research Council of the National Academies Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials and the International Council on Nanotechnology. She has served as an invited expert for the National Nanotechnology Initiative on Nanomaterials, and was appointed to the Scientific Committee on Consumer Safety by the European Commission. She has given more than 145 invited presentations and published more than 280 manuscripts in the field of skin toxicology and nanotoxicology and is editor of the books *Nanotoxicology: Characterization, Dosing and Health Effects* and *Toxicology of the Skin—Target Organ Toxicology Series*. Her current research interests involve in vivo and in vitro studies of skin absorption, penetration and toxicity of chemicals, nanoparticles, development of novel scaffolds for tissue engineering, and novel pharmaceutical drug delivery devices.

C. Lang Tran is the head of toxicology at the Institute of Occupational Medicine, Edinburgh, United Kingdom. He earned his PhD in biological sciences from Napier University, Edinburgh, United Kingdom, and has contributed more than 30 peer-reviewed articles on toxicology and nanotoxicology.

Lang Tran has led many European projects on Nanosafety (FP6 PARTICLE_RISK, FP7 ENPRA) and is currently the coordinator of the large FP7 project, MARINA. He is one of the editors for the journals *Nanotoxicology* and *Particle and Fiber Toxicology*. Since 2012, he was made an Honorary Professor at Heriot-Watt University, Edinburgh, United Kingdom.

Contributors

Matt Basel
Department of Anatomy and Physiology
Kansas State University
Manhattan, Kansas

Dagmar Bilaničová
Department of Environmental Sciences, Informatics and Statistics
Ca'Foscari University of Venice
Venice, Italy

and

Qi technologies
Pomezia, Rome, Italy

Sonja Boland
Unit of Functional and Adaptive Biology
Laboratory of Molecular and Cellular Responses to Xenobiotics
University of Paris Diderot
Paris, France

Diana Boraschi
Laboratory of Innate Immunity and Cytokines
Institute of Protein Biochemistry
National Research Council
Naples, Italy

Stefan Bossman
Department of Chemistry
Kansas State University
Manhattan, Kansas

Derk Brouwer
Netherlands Organisation for Applied Scientific Research (TNO)
Zeist, the Netherlands

Daniel V. Christophersen
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Sara Corradi
Laboratory of Cell Genetics
Department of Biology
Vrije Universiteit Brussel
Brussels, Belgium

Anna L. Costa
Institute of Science and Technology for Ceramics
Department of Chemical Science and Materials Technology
National Research Council
Faenza, Italy

Pernille H. Danielsen
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Heather A. Enright
Biosciences and Biotechnology Division
Lawrence Livermore National Laboratory
Livermore, California

Bengt Fadeel
Division of Molecular Toxicology
Institute of Environmental Medicine
Karolinska Institutet
Stockholm, Sweden

Dorothy Farrell
Office of Cancer Nanotechnology Research
Center for Strategic Scientific Initiatives
National Cancer Institute
Bethesda, Maryland

Teresa Fernandes
School of Life Sciences
Heriot-Watt University
Edinburgh, United Kingdom

Denis Fourches
Laboratory for Molecular Modeling
Division of Chemical Biology and Medicinal Chemistry
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Laetitia Gonzalez
Laboratory of Cell Genetics
Department of Biology
Vrije Universiteit Brussel
Brussels, Belgium

Piotr Grodzinski
Office of Cancer Nanotechnology Research
Center for Strategic Scientific Initiatives
National Cancer Institute
Bethesda, Maryland

Maureen R. Gwinn
Office of Research and Development
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, District of Columbia

George Hinkal
Office of Cancer Nanotechnology Research
Center for Strategic Scientific Initiatives
National Cancer Institute
Bethesda, Maryland

Danail Hristozov
Department of Environmental Sciences, Informatics and Statistics
Ca`Foscari University of Venice
Venice, Italy

Gary R. Hutchison
School of Life, Sport & Social Sciences
Centre for Nano Safety
Edinburgh Napier University
Edinburgh, United Kingdom

Namrata Jain
Department of Clinical Medicine
Institute of Molecular Medicine
Trinity College
Dublin, Ireland

Keld A. Jensen
Danish Nano Safety Centre
National Research Centre for the Working Environment
Copenhagen, Denmark

Araceli Sánchez Jiménez
Centre for Human Exposure Science
Institute of Occupational Medicine
Edinburgh, United Kingdom

Micheline Kirsch-Volders
Laboratory of Cell Genetics
Department of Biology
Vrije Universiteit Brussel
Brussels, Belgium

Henrik Klingberg
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

James F. Leary
Departments of Basic Medical Sciences and Biomedical Engineering
Birck Nanotechnology Center
Purdue University
West Lafayette, Indiana

Guoqiang Li
Department of Mechanical & Industrial Engineering
Louisiana State University
Baton Rouge, Louisiana

Yiyao Li
Neuroscience Program
School of Science and Engineering
Tulane University
New Orleans, Louisiana

Steffen Loft
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Laura MacCalman
Institute of Occupational Medicine
Edinburgh, United Kingdom

Michael A. Malfatti
Biosciences and Biotechnology Division
Lawrence Livermore National Laboratory
Livermore, California

Antonio Marcomini
Department of Environmental Sciences, Informatics and Statistics
Ca`Foscari University of Venice
Venice, Italy

Bashir M. Mohamed
Department of Clinical Medicine
Institute of Molecular Medicine
Trinity College
Dublin, Ireland

Peter Møller
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Nancy A. Monteiro-Riviere
Department of Anatomy and Physiology
Nanotechnology Innovation Center of Kansas State
Kansas State University
Manhattan, Kansas

Jay Nadeau
Department of Biomedical Engineering
McGill University
Montreal, Quebec, Canada

Bernd Nowack
Empa: Swiss Federal Laboratories for Materials Science and Technology
Technology and Society Laboratory
St. Gallen, Switzerland

Adriele Prina-Mello
Department of Clinical Medicine
Institute of Molecular Medicine
Trinity College
Dublin, Ireland

Giulio Pojana
Department of Environmental Sciences, Informatics and Statistics
Ca`Foscari University of Venice
Venice, Italy

Tarl W. Prow
Dermatology Research Centre
School of Medicine
University of Queensland
and
Translational Research Institute
Princess Alexandra Hospital
Woolloongabba, Australia

Kenneth L. Reed
DuPont Haskell Global Centers
Newark, Delaware

Jim E. Riviere
Department of Anatomy and Physiology
Institute of Computational Comparative Medicine
Kansas State University
Manhattan, Kansas

Bryony L. Ross
Institute of Occupational Medicine
Edinburgh, United Kingdom

Martin Roursgaard
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Stefania Sabella
Center for Bio-Molecular Nanotechnology
Italian Institute of Technology
Arnesano, Lecce, Italy

Meghan E. Samberg
Regenerative Medicine/Extremity Trauma
United States Army Institute of Surgical Research
Fort Sam Houston, Texas

Roel Schins
IUF–Leibniz Research Institute for Environmental Medicine
Düsseldorf, Germany

Janeck Scott-Fordsmand
Terrestrial Ecology Section
Department of Bioscience
Aarhus University
Copenhagen, Denmark

Tej Shrestha
Department of Anatomy and Physiology
Kansas State University
Manhattan, Kansas

Tobias Stöger
Comprehensive Pneumology Center
Institute of Lung Biology and Disease
Neuherberg, Germany

Vicki Stone
School of Life Sciences
Heriot-Watt University
Edinburgh, United Kingdom

Fariborz Tavangarian
Department of Mechanical & Industrial Engineering
Louisiana State University
Baton Rouge, Louisiana

Treye A. Thomas
U.S. Consumer Product Safety Commission
Rockville, Maryland

Alexander Tropsha
Laboratory for Molecular Modeling
Division of Chemical Biology and Medicinal Chemistry
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Martie Van Tongeren
Centre for Human Exposure Science
Institute of Occupational Medicine
Edinburgh, United Kingdom

Navin K. Verma
Lee Kong Chian School of Medicine
Nanyang Technological University
Singapore

Lise K. Vesterdal
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Yuri Volkov
Department of Clinical Medicine
Institute of Molecular Medicine
Trinity College
Dublin, Ireland

Sandra Vranic
Unit of Functional and Adaptive Biology
Laboratory of Molecular and Cellular
Responses to Xenobiotics
University of Paris Diderot
Paris, France

Hongwang Wang
Department of Chemistry
Kansas State University
Manhattan, Kansas

David B. Warheit
DuPont Haskell Global Centers
Newark, Delaware

Cao Yi
Section of Environmental Health
Department of Public Health
University of Copenhagen
Copenhagen, Denmark