

Pan Stanford Series on
Biomedical
Nanotechnology

Volume 5

— Handbook of —
**Safety Assessment of
Nanomaterials**

From Toxicological Testing to Personalized Medicine



edited by
Bengt Fadeel



Handbook of Safety Assessment of Nanomaterials

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Published by

Pan Stanford Publishing Pte. Ltd.
Penthouse Level, Suntec Tower 3
8 Temasek Boulevard
Singapore 038988

Email: editorial@panstanford.com

Web: www.panstanford.com

British Library Cataloguing-in-Publication Data

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

**Handbook of Safety Assessment of Nanomaterials:
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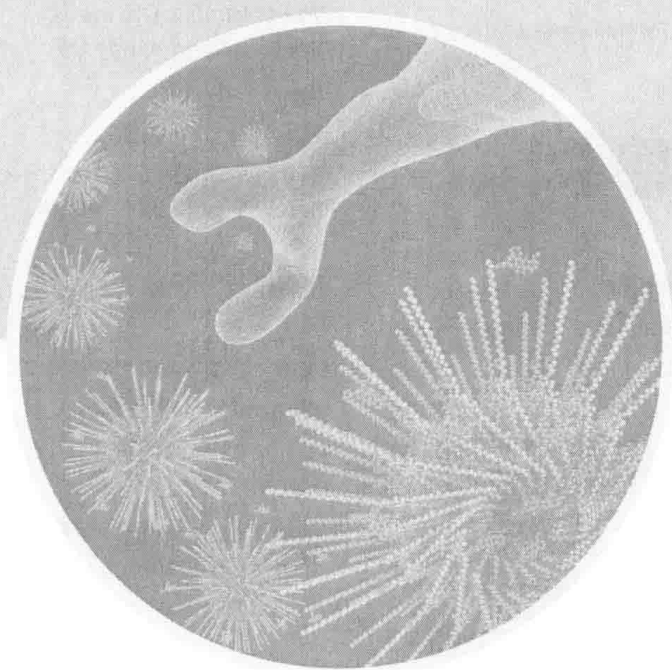
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ISBN 978-981-4463-36-2 (Hardcover)

ISBN 978-981-4463-37-9 (eBook)

Printed in the USA

— Handbook of —
**Safety Assessment of
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Pan Stanford Series on Biomedical Nanotechnology

Series Editors

Vladimir Torchilin and Mansoor Amiji

Titles in the Series

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Vladimir Torchilin and Mansoor Amiji,
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Handbook of Safety Assessment of Nanomaterials: From Toxicological Testing to Personalized Medicine

Bengt Fadeel, ed.

2014

978-981-4463-36-2 (Hardcover)

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Preface

"...for I was never so small as this before, never!"

Lewis Carroll, *Alice's Adventures in Wonderland* (1865)

Nanomedicine is the application of nanobiotechnology in clinical medicine. For instance, nanotechnologies offer exciting opportunities for targeted drug delivery, thus bringing to life the concept of a "magic bullet" imagined by Paul Ehrlich a century ago. Nevertheless, understanding whether such nanoscale objects per se exert adverse effects in a biological system is of critical importance. Nanotoxicology, in turn, may be viewed as the study of the undesirable interference between man-made nanomaterials and cellular nanostructures. In this handbook, included in the Pan Stanford series on *biomedical nanotechnology*, we attempt to bridge nanotoxicology and nanomedicine by applying the lessons learned from toxicological testing of manufactured nanomaterials to the field of nanomedicine.

The present volume opens with a historical perspective on the development of nanomedicine, written by Dr. Duncan, a pioneer in the field. Dr. Duncan points out that a balanced discussion of the risks and benefits of nanotechnologies is critically important to ensure the speedy and safe realization of the promises of nanomedicine. Indeed, this is the underlying motivation for the entire volume. Then, Dr. Stone et al. discuss the basic principles of nanotoxicology, highlighting progress in the field in recent years; the authors also provide recommendations for the proper design of experiments to assess nanomaterial hazards. Drs. Warheit and Sayes touch on the need for robust physicochemical characterization of nanomaterials for toxicity testing, and Drs. Fadeel and Parak discuss the biological "identity" of nanomaterials.

These introductory chapters are followed by a series of chapters on different approaches to nanomaterial testing: Dr. Hartung makes the case for in vitro tests, while Drs. Lai and Warheit argue that short-term in vivo (animal) studies are needed. Dr. Burello adds an important perspective on mathematical modeling of quantitative

structure–activity relationships (QSARs) for nanomaterials, pointing toward a predictive nanotoxicology. Finally, Dr. Riviere explores the use of physiologically based nanomaterial pharmacokinetic models, or PBNPKs, with which to describe nanomaterial distribution and fate *in vivo*.

Our immune system serves as the first line of defense against foreign intrusion, and it is therefore of key importance to understand nanomaterial interactions with the immune system, not only from a toxicological point of view, but also if we are to develop nanocarriers for targeted drug delivery or imaging. Three chapters are devoted to immune interactions of nanomaterials: Dr. Moghimi et al. discuss factors that regulate nanomaterial interactions with the innate and adaptive immune system, leading to immunostimulation or immunosuppression, while Dr. Szebeni focuses on complement activation by nanomaterials. Dr. Kostarelos et al. discuss a special case of immune cell interactions with nanomaterials, namely, the biodegradation of carbon-based nanomaterials by enzymes expressed in innate immune cells (or in plants).

Next, we find a comprehensive chapter devoted to genotoxicity and carcinogenicity of nanomaterials (Dr. Woei Ng et al.) and a series of chapters on nanomaterial toxicity affecting specific organs, including chapters on pulmonary and cardiovascular toxicity (Drs. Cassee and Castranova), neurotoxicity (Drs. Sharma and Sharma), dermatotoxicity (Drs. Monteiro-Riviere and Riviere), and reproductive toxicity (Dr. Saunders et al.). The chapter on pulmonary and cardiovascular toxicity focuses on two commercially relevant nanomaterials, titanium dioxide and carbon nanotubes, and on the inhalation route of exposure of particular relevance for occupational exposure. These findings may nevertheless inform us on mechanisms of relevance for nanomedicine. Similarly, the chapter on neurotoxicity takes as its starting point accidental exposure to various types of nanoparticles, but the authors add an exciting perspective on the use of nanomaterials for neuroprotection. The chapter on dermal effects of nanoparticles offers an overview of current literature, and the discussion is of equal relevance from pharmacological (i.e., topical application of drugs, vaccines) and toxicological points of view. The potential for nanoparticles to exert adverse effects on the male or female reproductive systems remains poorly understood, but this is of particular importance not only to understand occupational/environmental exposure but also in the

context of the deliberate administration of nanoscale objects in patients.

Finally, a perspective on ethical aspects of nanomedicine is provided. Here, Dr. Kuiken argues that there may be nothing new in terms of the ethical questions that arise as we are confronted with nanomedicines; the question is how much risk we are willing to accept with a new technology before it is proven effective and “safe.” This will become even more evident as personalized medicine is enabled, in part, through nanomedicine. This, then, brings us full circle: medicine, and nanomedicine, is essentially the art and science of risk-benefit assessment. Nanotoxicology provides the tools to deal with the “risk.”

The book closes with a personal view of the future of (nano) medicine, written by Dr. Hunziker, president of the European Society of Nanomedicine (ESNAM).

I wish to thank the authors who contributed their valuable time and expertise toward the preparation of this book. I hope that the present volume will serve as a useful manual for students and scientists interested in the safe development of nanomedicines.

Bengt Fadeel

Stockholm, July 2014

Contents

<i>Preface</i>	xvii
----------------	------

1. Nanomedicine(s) and Their Regulation	1
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Ruth Duncan

1.1	Background: A Decade of “Nano”; Where Are We Now?	1
1.1.1	Convergence of Scientific Disciplines: Old Ideas, New Terminology?	3
1.1.2	Medicine Regulation: Evolution, Not Revolution	4
1.1.3	Lessons Learned from >40 Years of Clinical Experience with Nanomedicines	10
	1.1.3.1 Products in routine use and clinical development	10
	1.1.3.2 Clinically documented adverse reactions	15
1.2	Emerging Nanotechnologies: New Medicines or Nice Publications?	19
1.3	Nanomedicine Safety-Nanotoxicology: Lessons to Share	21
1.3.1	General Areas of Overlapping Interest	21
1.3.2	Manufacture, Characterization, and Formulation: Quality by Design	22
1.3.3	Definition of the Toxicity of a Nanomaterial/Nanomedicine	24
1.3.4	Pharmacokinetics, Body Distribution, and Passage across Biological Barriers	26
1.3.5	Endocytosis and Intracellular Trafficking	28
1.4	Conclusions	30
1.5	Update 2012–2014	30

2. Nanotoxicology: Focus on Nanomedicine	43
<i>Helinor Johnston, Ali Kermanizadeh, and Vicki Stone</i>	
2.1 Introduction	43
2.2 Nanomedicine and Nanotoxicology	44
2.3 Nanomaterial Physicochemical Properties	47
2.3.1 Size	47
2.3.2 Morphology	49
2.3.3 Composition	50
2.3.4 Surface Properties	51
2.3.5 Dissolution	53
2.3.6 Agglomeration	54
2.3.7 Charge	55
2.4 Assessment of Nanomaterial Toxicity	55
2.5 Nanomaterial Physicochemical Characterization	58
2.6 Relationship between Exposure Route and Toxicity	59
2.7 Conclusions	61
3. Nanomaterial Characterization for Toxicity Testing	69
<i>David B. Warheit and Christie M. Sayes</i>	
3.1 Introduction	69
3.1.1 Nanoparticles Used in the Industry	70
3.1.2 Nanoparticles Used in Medicine	70
3.2 Characterization of Particles Used in the Industry	71
3.2.1 Titanium Dioxide	71
3.2.2 Amorphous Silica	73
3.2.2.1 Production of synthetic amorphous silica	74
3.2.2.2 Silica production based on the "wet process"	75
3.2.2.3 Production of pyrogenic silica	75
3.2.2.4 Surface-modified synthetic amorphous silica	76
3.2.3 Health Risks	76
3.3 Characterization of Particles Used in Medicine	76
3.3.1 Polymeric Materials	77
3.3.2 Metal Colloids	78

3.4	Nanomaterial Characterization Methods	79
3.4.1	Transmission Electron Microscopy and Energy-Dispersive Spectroscopy	79
3.4.2	Emission and Absorption Spectroscopy	80
3.4.3	Dynamic Light Scattering and Zeta Potential	81
3.5	Conclusions	82
4.	The Synthetic and Biological Identities of Nanomaterials	85
	<i>Bengt Fadeel and Wolfgang J. Parak</i>	
4.1	Safety Assessment of Nanomaterials	85
4.2	Understanding Nanomaterial Properties	86
4.2.1	Linking Physicochemical Properties to Toxicity	87
4.2.2	Predictive Modeling of Nanomaterial Toxicity	91
4.3	The Nanomaterial Biocorona	93
4.3.1	The Biocorona Concept	93
4.3.2	Pathophysiological Impact of the Biocorona	95
4.3.3	Implications of the Biocorona for Targeting	97
4.3.4	Nanoparticles vs. Molecules: The Case of Dendrimers	99
4.4	Future Perspectives	100
5.	Nanotoxicology: The Case for in vitro Tests	113
	<i>Thomas Hartung</i>	
5.1	Introduction	113
5.2	Alternative or Advanced Methods in Toxicology	115
5.2.1	Do We Need Special Methods for Nanotoxicology?	116
5.2.2	Do We Need a Traditional or an Alternative Toxicology for NPs?	118
5.2.3	Special Problems for in vitro Nanotoxicology	124
	5.2.3.1 Agglomeration	124
	5.2.3.2 Stability	124

	5.2.3.3 Dosimetry	124
	5.2.3.4 In vitro biokinetics	125
	5.2.3.5 Cell contact of NPs	125
	5.2.3.6 Artifacts	126
5.3	Existing Alternative Methods and Their Suitability for Nanotoxicology	126
5.3.1	Alternative Methods Based on Nanotechnologies	134
5.3.2	Opportunities for in silico Alternatives in Nanotoxicology	134
5.3.3	Are There Reasons to Make Current Alternative Tests Less Applicable to NPs?	135
5.4	Towards a Human Toxome Project	135
5.5	Conclusions	138
6.	Nanotoxicology: The Case for in vivo Studies	153
	<i>David Y. Lai and David B. Warheit</i>	
6.1	Introduction	153
6.2	In vivo Study Design and Methods	155
6.2.1	Inhalation Exposure	155
6.2.2	Other Inhalation Exposure Methods	158
	6.2.2.1 Intratracheal instillation	158
	6.2.2.2 Pharyngeal/laryngeal aspiration	160
	6.2.2.3 Intratracheal inhalation	162
6.2.3	Dermal Exposure	163
6.2.4	Oral Exposure	164
6.2.5	Parenteral Exposure	164
6.3	In vivo Toxicity Studies of Nanomaterials	164
6.3.1	Nanotubes and Nanofibers	165
	6.3.1.1 Pulmonary exposure	166
	6.3.1.2 Effects on the cardiovascular system	175
	6.3.1.3 Effects on the immune system	177
	6.3.1.4 Oral exposure	178
6.3.2	Fullerenes	179
	6.3.2.1 Pulmonary effects	179
	6.3.2.2 Dermal and eye effects	181

6.3.2.3	Systemic effects	181
6.3.2.4	Reproductive and developmental effects	183
6.3.2.5	Genotoxic effects	183
6.3.3	Titanium Dioxide	184
6.3.3.1	Pulmonary effects	184
6.3.3.2	Carcinogenic effects	190
6.3.3.3	Dermal exposure	192
6.3.3.4	Oral exposure	193
6.3.3.5	Systemic effects	193
6.3.4	Nanosilver	195
6.3.4.1	Pulmonary exposure	196
6.3.4.2	Oral exposure	197
6.3.4.3	Dermal exposure	197
6.3.4.4	Genotoxicity	198
6.4	Conclusions	198
7.	Predictive Nanotoxicology: In silico Approaches	221
	<i>Enrico Burello</i>	
7.1	Introduction	221
7.2	QSAR and QSPR Models for Nanomaterials	225
7.3	Density Functional Theory Approaches	230
7.4	Molecular Mechanics Approaches	234
7.5	Mathematical Modeling of Nanomaterial Bioactivity	236
7.6	Multiscale Modelling and Other Coarse-Graining Methods	237
7.7	Conclusions	239
8.	Physiologically Based Nanomaterial Pharmacokinetic Models	243
	<i>Jim E. Riviere</i>	
8.1	Introduction	243
8.2	What Is Unique about Nanoparticle ADME?	244
8.2.1	Absorption	244
8.2.2	Distribution	245
8.2.3	Elimination	248
8.3	Pharmacokinetic Models	249
8.3.1	PBPK Models	250

8.3.2	In vitro Perfused Tissue Biodistribution Studies	251
8.4	Whole-Animal in vivo PBNPK Models	253
8.5	Need for Biological Characterization Indices	255
8.5.1	Biological Surface Adsorption Index	258
8.6	Conclusions	260
9.	Immunotoxicity of Nanomaterials	265
	<i>Barbara Lettiero, Z. Shadi Farhangrazi, and S. Moein Moghimi</i>	
9.1	Introduction	265
9.2	Nanoparticle Clearance by Immune Cells	268
9.3	Nanoparticle Modulation of Immune Responses	271
9.3.1	Immunostimulation	272
	9.3.1.1 Antigenicity	272
	9.3.1.2 Adjuvanticity	273
	9.3.1.3 Allergenicity and hypersensitivity	274
	9.3.2 Immunosuppression	275
9.4	Conclusions	277
10.	Complement Activation by Nanomaterials	289
	<i>Janos Szebeni</i>	
10.1	Introduction	289
10.2	Complement Activation: An Overview	290
10.3	Complement Activation by Nanoparticles	290
10.4	Mechanisms of Complement Activation by Nanoparticles	297
	10.4.1 Complement Activation by Liposomes	297
	10.4.2 Complement Activation by Micelles	299
	10.4.3 Complement Activation by PEG	302
	10.4.4 Complement Activation on Polymer-Coated Nanoparticles	303
	10.4.5 Complement Activation by Dendrimers, Other Polymers	303
	10.4.6 Complement Activation by Carbon Nanotubes	304
10.5	Consequences of Complement Activation	305
	10.5.1 The CARPA Concept	305

10.5.2	The Effector Arm of CARPA	306
11.	Biodegradation of Carbon-Based Nanomaterials	319
	<i>Cyrill Bussy, Alberto Bianco, Maurizio Prato, and Kostas Kostarelos</i>	
11.1	Introduction	319
11.2	Carbon-Based Nanomaterials	320
11.3	Oxidation of Carbon-Based Nanomaterials	322
11.4	Ex vivo Biodegradation of CNMs	323
11.4.1	Ex vivo Biodegradation of SWCNTs	326
11.4.2	Ex vivo Biodegradation of MWCNTs	327
11.4.3	Ex vivo Biodegradation of Graphene	329
11.5	Biodegradation of CNMs in Living Systems	330
11.6	Biological Effects of Biodegraded CNMs	333
11.7	Conclusions	334
12.	Genotoxicity and Carcinogenicity of Nanomaterials	341
	<i>Kee Woei Ng, Yun Zhao, Mustafa Hussain Kathwala, Sijing Xiong, Chit Fang Cheok, and Say Chye Joachim Loo</i>	
12.1	DNA Damage and Repair: An Introduction	341
12.1.1	Endogenous DNA Damage	342
12.1.2	Exogenous DNA Damage	344
12.1.3	Repair of Various DNA Lesions by Specific DNA Repair Pathways	346
12.2	Evidence for Nanomaterial-Induced Genotoxicity and Carcinogenicity	350
12.2.1	Carbon-Based Nanomaterials	350
12.2.2	Metal-Based Nanomaterials	354
12.2.3	Polymeric Nanoparticles	358
12.3	Mechanisms of Nanomaterial-Induced Genotoxicity and Carcinogenicity	359
12.3.1	Physicochemical Properties	359
12.3.2	Primary and Secondary Genotoxicity	362
12.3.2.1	Primary genotoxicity	362
12.3.2.2	Secondary genotoxicity	365
12.3.3	Oxidative Stress	366
12.3.4	Carcinogenicity	366
12.4	Methods to Study Nanomaterial-Induced Genotoxicity and Carcinogenicity	367
12.4.1	Ames Bacterial Mutagenesis	367

12.4.2	In vitro and in vivo Genotoxicity Assays	368
12.4.3	DNA Breakage Assays	368
12.5	Conclusions	371
13.	Pulmonary and Cardiovascular Toxicity of Nanomaterials	389
	<i>Flemming R. Cassee and Vincent Castranova</i>	
13.1	Introduction	389
13.2	Respiratory and Cardiovascular Effects of Pulmonary Exposure to Nanoparticles/ Nanotubes	390
13.2.1	Respiratory Response to Pulmonary Exposure to TiO ₂ Nanoparticles	391
13.2.2	Respiratory Response to Pulmonary Exposure to Carbon Nanotubes	392
13.2.3	Cardiovascular Response to Pulmonary Exposure to TiO ₂ Nanoparticles	394
13.2.4	Cardiovascular Response to Pulmonary Exposure to Carbon Nanotubes	395
13.3	Mechanisms by Which Pulmonary Exposure to Nanoparticles/Nanotubes Affects Cardiovascular Function	396
13.4	Conclusions	399
14.	Neurotoxicity of Nanomaterials	407
	<i>Hari Shanker Sharma and Aruna Sharma</i>	
14.1	Human Exposure to Nanoparticles	407
14.1.1	NP Exposure Affects Disease Pathology	408
14.1.2	Military Personnel and NPs Exposure	408
14.2	Neurotoxicity of Nanoparticles	409
14.3	Concepts of Neurotoxicity	410
14.3.1	Blood–Brain Barrier Disruption: A Gateway to Neurotoxicity	410
14.3.2	BBB Breakdown to Proteins: Cause of Brain Edema Formation	413