# Preface

In the past decade, nanotoxicology has emerged as a specific domain within the toxicological sciences. In fact, there has been an exponential rise in the number of scientific articles on the subject; however, nanotoxicology as a discipline is still struggling with the fundamental question: are there specific environmental safety and health concerns associated with nanomaterials as a function of their particular or novel properties, and does this call for specific regulations to be applied for nanoenabled products and technologies? Furthermore, while considerable progress has been made during the last 10 years, and important lessons have been learned, such as the realization that a thorough physicochemical characterization is needed to properly evaluate the toxicological results, nanotoxicology still faces a number of challenges related to standardization and validation of test methods, and the implementation of reference materials, to allow for comparability of results across different studies; there is also a need for more realistic test scenarios, including low-dose, long-term exposures to nanomaterials. Notwithstanding, we have already made significant progress in terms of teasing out the properties that make some nanomaterials harmful and others essentially inert.

Indeed, in the 5 years that have passed since the first edition of the present volume, a vast number of new studies have been published that are of relevance for potential human health effects of nanomaterials. In this new and updated edition, several new chapters have been added, including a comprehensive chapter on risk assessment of nanomaterials, and all the chapters in the present volume have been updated to encompass new research findings regarding hazard, exposure, and risk of nanomaterials. The overall objective remains: to assess the potential of engineered nanomaterials to cause human disease, by systematically examining their possible effects on different organs and systems.

The first section of the book comprises eight chapters, aimed at providing sufficient background on nanomaterial exposure assessment and biomonitoring, as well as hazard assessment and risk assessment, to enable the reader to properly evaluate the subsequent chapters on potential human health effects. More specifically, the first chapter of the book gives an overview of the biological interactions of nanoparticles, focusing on the emerging concept of the biocorona, essentially the adsorption of proteins and other biomolecules onto the surface of nanoparticles, thus endowing the particles with a new, biological "identity." The following chapter provides a detailed description of the physicochemical characterization of the intrinsic properties of nanomaterials (or, the synthetic "identity"), with a discussion on the parameters measured as well as the methods used for these measurements. The authors also discuss the definition of a nanomaterial, which is important not least from a regulatory point of view. The third and fourth chapter deal with hazard assessment of nanomaterials and they describe two different, yet complementary approaches to the problem: on the one hand, the selection of the most appropriate in vitro (cell culture)

and/or in vivo (animal) tests, and on the other, the use of computational approaches and the development of predictive models. These chapters are followed by two chapters on exposure assessment and biomonitoring, respectively; focusing in particular on the occupational setting in which inadvertent exposure may occur (as opposed to the intentional administration of nanoparticles in the clinical setting). The chapter on exposure also discusses the most appropriate health surveillance programs, based on the current knowledge of the biological effects of nanomaterials. The chapter on biomonitoring includes a discussion on the emerging topic of systems toxicology and the application of global "omics" approaches with which to assess effect or exposure to nanomaterials. The first section of this volume closes with two chapters on regulation and legislation, and risk assessment and risk management, respectively. The former chapter is coauthored by experts from the European Union, United States, and Japan/Korea, and provides a unique view on international regulations applicable to nanomaterials. In the chapter on risk assessment, the authors discuss the concept of grouping or categorization of nanomaterials and how this may inform modern risk assessment approaches.

The second section of this volume includes 10 chapters addressing the pathogenic potential of engineered nanomaterials for specific organs and tissues. The first and second chapters in this section describe the possible adverse effects of nanomaterials on the respiratory system, one of the most important routes of exposure to engineered nanomaterials; the first one is focused on basic mechanisms of pulmonary effects of nanomaterials, with a special view to inflammation, fibrosis, and carcinogenicity, while the second one discusses allergic reactions and asthma, focusing on carbon nanotubes, which have been extensively studied from the point of view of pulmonary exposure (in animals). The subsequent chapters each deal with the effects of nanomaterials on specific organ systems, including the cardiovascular system, the neurological system/central nervous system, the immune system, the endocrine system, the gastrointestinal tract, and the skin. The body of evidence for the disease potential of nanomaterials is substantial: the possibility of pulmonary fibrosis, malignant mesothelioma, and atherosclerotic disease thus needs to be considered, at least for some nanomaterials. In other cases, the link with human diseases is much more tenuous, such as for neurodegenerative disorders, or inflammatory bowel disease, or for diseases or imbalances of the endocrine system. It should be considered, however, that the amount of research on the possible pulmonary and cardiovascular effects is much higher than for nanomaterial effects on neurological, gastrointestinal, or other organ systems. The skin seems the most impervious organ to the injurious action of nanomaterials, although, as pointed out by the authors, more long-term studies are needed to ascertain the potential for adverse effects. The skin is the principal, physical barrier protecting us from the outside world, while the immune system provides a first line of defense against foreign intrusion. Particular attention to the interactions of nanomaterials with the immune system are therefore warranted; indeed, assessment of immune effects may be viewed as a "sentinel" form of hazard assessment of nanomaterials. As noted by the authors, model systems that reflect vulnerable conditions, like chronic obstructive pulmonary disease, are needed; the majority of studies have been conducted using models of the healthy organism. The second section ends with a chapter on fertility and reproduction, and a chapter specifically devoted to genotoxicity (DNA damage) and cancer. Detrimental effects of

nanomaterials on embryonic development have been reported and this remains an area of great concern. Similarly, the potential for certain engineered nanomaterials to elicit genotoxicity is well documented, and recently, some nanomaterials were classified as being potentially carcinogenic in humans.

This book gives a state-of-the-art presentation of relevant research on adverse effects of engineered nanomaterials on human health. We are indebted to all the colleagues from around the globe who have contributed. We hope that this volume will serve as a useful guide for students and researchers in the field and for clinicians, policymakers, and regulators with an interest in nanosafety and human health.

*Bengt Fadeel*
*Karolinska Institutet*

*Antonio Pietroiusti*
*University of Rome Tor Vergata*

*Anna A. Shvedova*
*National Institute for Occupational and Safety Health*