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Knowledge gaps between nanotoxicological research and nanomaterial safety

Xiangang Hu [a], Dandan Li [a], Yue Gao [a], Li Mu [b], Qixing Zhou [a,*]

[a] Key Laboratory of Pollution Processes and Environmental Criteria (Ministry of Education), Tianjin Key Laboratory of Environmental Remediation and Pollution Control, College of Environmental Science and Engineering, Nankai University, Tianjin 300071, China

[b] Institute of Agro-Environmental Protection, Ministry of Agriculture, Tianjin 300191, China

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ABSTRACT

With the wide research and application of nanomaterials in various fields, the safety of nanomaterials attracts much attention. An increasing number of reports in the literature have shown the adverse effects of nanomaterials, representing the quick development of nanotoxicology. However, many studies in nanotoxicology have not reflected the real nanomaterial safety, and the knowledge gaps between nanotoxicological research and nanomaterial safety remain large. Considering the remarkable influence of biological or environmental matrices (e.g., biological corona) on nanotoxicity, the situation of performing nanotoxicological experiments should be relevant to the environment and humans. Given the possibility of long-term and low-concentration exposure of nanomaterials, the reversibility of and adaptation to nanotoxicity, and the transgenerational effects should not be ignored. Different from common pollutants, the specific analysis methodology for nanotoxicology need development and exploration furthermore. High-throughput assay integrating with omics was highlighted in the present review to globally investigate nanotoxicity. In addition, the biological responses beyond individual levels, special mechanisms and control of nanotoxicity deserve more attention. The progress of nanotoxicology has been reviewed by previous articles. This review focuses on the blind spots in nanotoxicological research and provides insight into what we should do in future work to support the healthy development of nanotechnology and the evaluation of real nanomaterial safety.

Contents

* Corresponding author at: College of Environmental Science and Engineering, Nankai University, China.
E-mail addresses: huxiangang@nankai.edu.cn (X. Hu), zhouqx@nankai.edu.cn (Q. Zhou).

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1. Introduction

The rapid propagation of nanotechnology into various industries and consumer products is causing exponential growth of nanomaterial production. For example, nanomaterials have been applied in medicine, electronic components, cosmetics, food additives, water treatment and soil remediation (Kotagiri et al., 2015; Chen et al., 2007; Shehada et al., 2015). The number of recent publications about nanotechnology or nanomaterials has increased dramatically. The numbers of published paper were approximately 96,502 and 375,535 in 2005 and 2015, respectively, based on Web of Science (search date was 28th-April-2016; search topic was "nano*"; years published were set as 2005 and 2015, respectively). The use of nanomaterials has raised safety concerns, as their small size facilitates accumulation in and interaction with biological tissues (Nel et al., 2006; Linkov et al., 2011). In addition, these nanomaterials or products containing nanomaterials are likely to be released into the air, water, and soil in the natural environment. Biological responses to nanomaterials are relevant to human health and ecological safety (Balas et al., 2010; Oomen et al., 2014). "Nanotoxicology" is an important topic of nanomaterial safety, and the number of publications linking to nanomaterials has increased quickly over recent decades. The numbers of published paper were 695 and 22,647 in 2005 and 2015, respectively, based on Web of Science (search date was 28th-April-2016; search topics were "nano*" and "toxic*"; years published were set as 2005 and 2015, respectively). To date, researchers from chemical, biological, medical and environmental fields have paid much attention to the investigation and control of adverse effects of nanomaterials.

In the past twenty years, some knowledge of nanotoxicology has been achieved. Some nanoparticles are able to cross cell membranes and then induce significant biological responses (Treuel et al., 2014; Wang et al., 2015a). These biological responses at least include growth inhibition, structural damage, oxidative stress, genotoxicity, protein modification and metabolic disturbance (Paget et al., 2015; Watson et al., 2014). Although many relevant studies have been conducted, debatable results and conclusions are frequently reported; for example, both positive and negative biological responses have been reported for carbon nanomaterials (Hu and Zhou, 2013). These arguments show that some unclear issues remain in nanotoxicology. Compared with nanotoxicology, nanosafety is widely considered by people. However, nanosafety is not nanotoxicology. Nanotoxicology focuses on the physiology, pathology and biomolecular mechanisms of nanomaterials. Nanosafety focuses on the evaluation of nanomaterial risks in natural environments and biology. The main results and conclusions of nanotoxicology are from a lab, while the main results and conclusions of nanosafety should match the actual environment and real organisms where the field studies are important. Nanotoxicology serves for nanosafety, and nanosafety serves for the management of nanomaterials. Currently, there are knowledge gaps between nanotoxicological research and nanomaterial safety. For example, high-dose and short-term studies in distilled water, phosphate-buffered saline and culture medium are common in nanotoxicology, whereas nanomaterial exposures in real environments or biology are low-dose and long-term in complex matrices (Xu et al., 2015b; Adeleye et al., 2014). The results and conclusions from the above two conditions are remarkably different. In addition, thousands of nanomaterials are reported and applied in various fields; traditional toxicological assays cannot provide global insight into biological responses to all nanomaterials (George et al., 2011; Jung et al., 2015). Importantly, organisms–organisms and the around environments exist together and correlate ecologically, and nanotoxicological studies limited to cells or individual levels cannot reflect the real nanomaterial risks (Ma et al., 2015; Khodakovskaya et al., 2013).

To solve the above problems, some key issues and major challenges should be clarified. Reviews of nanomaterial toxicity and biological responses have been published in some journals; most of the contents are simple lists of reports from the literature, and knowledge gaps between nanotoxicological research and nanomaterial safety are rarely explored. Herein, we neither list the global literature nor show all knowledge involving biological responses to nanomaterials. The key issues are highlighted and the major challenges are discussed to reduce the scientific "blind spots" and knowledge gaps as well as identify future directions in which this field is likely to develop. Biologically and environmentally relevant exposure conditions and matrices are highlighted with respect to testing strategies. Then, some complex issues are discussed, for instance, transgenerational effects, reversibility of and adaptation to nanotoxicity, and environmental/biological coronas beyond the protein corona. Subsequently, high-throughput assays, biological responses beyond individual levels, control of nanotoxicity and specific mechanisms of nanotoxicity are explored. Finally, global perspectives in nanotoxicology and nanosafety are proposed.

2. Choosing remarkable toxicological results or objective nanosafety

Being different from the traditional design of experiments used for biomacromolecules, small organic molecules or metals, there are many uncertain factors that influence the results and conclusions of studies relevant to nanomaterials. Generally, the concentrations of nanomaterials in the environment are very low, and biological responses may be not significant at environmentally relevant concentrations. To achieve