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Review

Chemistry

Use of compositional and combinatorial nanomaterial libraries for biological studies

Zhaoxia Ji

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Abstract The rapid development and production of nanomaterials has created some concerns about their potential hazard on the environment, human health and safety. However, since the list of materials that may generate such concerns is very long, it is impossible to test them all. It is therefore usually recommended to use some small compositional nanomaterial libraries to perform initial toxicity screening, based on which combinatorial libraries are then introduced for more in-depth studies. All nanomaterials in the compositional and combinatorial libraries must be rigorously characterized before any biological studies. In this review, several major categories of physicochemical properties that must be characterized are discussed, along with different analytical techniques that are commonly used. Some case studies from the University of California Center for Environmental Implications of Nanotechnology are also chosen to demonstrate the effective use of compositional and combinatorial nanomaterials libraries to identify the role of some key physicochemical properties and to establish true quantitative structure–activity relationships. Examples on how to use the knowledge generated from those studies to design safer nanomaterials for improved biological applications are also presented.

Keywords Nanomaterial · Physicochemical property · Characterization · Nanotechnology · Toxicity · Compositional library · Combinatorial library

Z. Ji (✉)
Center for Environmental Implications of Nanotechnology, California NanoSystems Institute, University of California, Los Angeles, CA 90095, USA
e-mail: zji@cnsi.ucla.edu

1 Introduction

Nanoscience and nanotechnology are among the fastest growing research and technology areas [1]. As a result, engineered nanomaterials (ENMs) are rapidly becoming a part of our daily life in the form of cosmetics [2, 3], food packaging [4, 5], therapeutics [6–9], biosensors etc. [7, 10]. According to the Nanotechnology Consumer Products Inventory (CPI), new nanotechnology-based consumer products are coming on the market at the rate of 3–4 per week [11]. By March 2015, CPI had identified 1,814 products, which represents a 30-fold increase over the 54 products originally listed in 2005 [11]. With the widespread applications of these new materials, there is also a growing concern about what impact they may have on consumers, workers, and the environment [12–14]. Therefore, it is imperative to assess the potential hazard of nanomaterials. Nevertheless, apparently it is impossible to test all nanomaterials that can generate environmental, health and safety concerns. Therefore, more realistically, one may prioritize a limited number of nanomaterials, for example, using a small compositional ENM library (a set of ENMs with different chemical compositions but similar size, shape, and other physicochemical properties) to perform initial toxicity screening and hazard ranking [13, 15]. Based on the initial screening results, we can then introduce some combinatorial libraries (libraries containing materials with the same chemical composition but with one physicochemical property systematically altered) to explore in more detail the role of each physicochemical property. To fully understand the ENM toxicity mechanisms, the ENM physicochemical properties both in the as-produced form and under the biological testing conditions must be well characterized. These include intrinsic properties such as chemical composition, primary size and size distribution, shape, (im)purity, crystal structure, and surface area; extrinsic properties including agglomerate size and distribution, agglomeration kinetics, surface charge, dissolution rate, reactive oxygen species (ROS) generation; and some emerging properties that may be revealed during biological experimentation and quantitative structure–activity relationship (QSAR) analysis [15]. Since complete characterization of all properties listed above can be extremely time consuming, expensive, and complete, it is usually recommended to start with a base set of characterization which is appropriate and sufficient to the claims and conclusions of the study [16–18]. In this review, major categories of physicochemical properties required to be characterized are discussed, followed by representative microscopic, spectroscopic, and many other analytical techniques used for their measurement. To elucidate the role of some of the key physicochemical properties on biological outcomes, we also present a number of case studies from the University of California Center for Environmental Implications of Nanotechnology (UC CEIN). These include the use of various compositional and combinatorial ENM libraries such as 24 metal oxide compositional library to study the role of conduction band energy [19–21], a rear earth oxide (REO) library to understand the role of dissolution and biotransformation [22], a silica library to study the relationship of crystallinity and surface chemistry to the silica toxicity [23], a cerium oxide combinatorial library to explore the effect of aspect ratio [24, 25], and a multi-walled carbon nanotube combinatorial library to investigate the impact of surface charge [26]. Examples on how to use these findings to design safer nanomaterials for future biological or medical applications are also presented [27, 28].

2 Establishment of compositional and combinatorial ENM libraries

2.1 Nanomaterial selection considerations

When selecting materials for toxicological studies and safety testing, one should take into consideration the commercial production volume of ENMs as well as their exposure potential. For example, nanomaterials that are produced in high volumes on the market, widespread in applications, or of high innovation potential should attract the most attention. These include some traditional high production volume nanomaterials like amorphous silica, which is used as fillers in rubber and tires, anti-caking agents in food powders, or flatting agents in paper and paints [29]; and carbon black that can be used in various applications from black coloring pigment to electric conductive agent [30]. Although materials like carbon nanotubes (CNTs) [6, 7, 31], nano ZnO [2, 32], nano TiO_2 [3, 33, 34], nano Ag [35, 36] were developed more recently, this group of materials also covers a wide range of applications varying from catalysts, electronics, cosmetics, energy storage, coatings, therapeutics, sensors, and others [2, 6, 7, 31–34]. Additionally, new two dimensional (2D) nanomaterials such as graphene and graphene oxide are evolving on a regular basis and their uses are increasing much more rapidly than those for the traditional nanomaterials [37–40]. For example, the global market of graphene, a newly developed 2D carbonaceous material, is expected to grow at an annualized rate of 42.8 % from 2015 and 2020 and reach USD 278.47 million by 2020 (http://www.researchandmarkets.com/research/nhj8fn/graphene_market).

Apparently, the list of ENMs that may potentially generate environmental, health and safety concerns can be very long, therefore it is impossible to test all of them. Instead, more realistically, one may prioritize a limited number of nanomaterials to perform initial toxicity screening and hazard ranking, and to obtain mechanistic information that can be used for further studies of other materials [13]. Based on this consideration, in 2009 the Organization for Economic Co-operation and Development (OECD), an international economic organization that works to stimulate economic progress and world trade in more than 30 countries, came up with a list of prioritized ENMs which covers several major categories of nanomaterials, including inorganic metal (silver, gold), metal oxide (aluminium oxide, cerium oxide, iron oxide, titanium dioxide, silicon dioxide, zinc oxide), carbon-based (fullerene, single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs)) nanomaterials, nanoclays, as well as organic nanomaterials like dendrimers [41]. This list has since then been used as a guideline by many research groups including UC CEIN for initial nanomaterial selection. In UC CEIN, we began with three metal oxides (MO_x) on the OECD list, i.e., TiO_2, CeO_2, and ZnO. The physicochemical properties of all three materials were rigorously characterized and their toxicity was evaluated using single-parameter toxicity screening assays to look at cell viability, oxygen radical generation, and pro-inflammatory responses in cells [42]. The key mechanism of ENM toxicity evolved from this study, which will be discussed in more detail later, allowed us to gradually increase the number of materials that can be studied. Since its inception in 2008, UC CEIN has studied more than 300 different nanomaterials, varying from metals, metal oxides, to carbon nanotubes, silica, graphene and other 2D ENMs, each with tunable physicochemical properties.

2.2 Compositional and combinatorial ENM libraries

Our usual practice with establishing ENM libraries is to start with a compositional library. This will allow us to