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Review article

Progress towards standardized and validated characterizations for measuring physicochemical properties of manufactured nanomaterials relevant to nano health and safety risks

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A B S T R A C T

Managing the risks of manufactured nanomaterials requires the ability to accurately and reproducibly measure the physical and chemical properties of these materials that are relevant to their risk assessment. However, many properties of manufactured nanomaterials and their non-equilibrium system-dependent behaviors challenge many of the conventional characterization methods used to characterize them. New methods and modifications to conventional methods are being developed to address some of these shortcomings. Here, we critically review *progress towards standardization and validation* of methods used to characterize manufactured nanomaterials to assess their health and safety risks. The limitations and accessibility of each method are presented, and recommendations towards improving method standardization are made where appropriate. The properties considered include intrinsic (system independent) nanomaterial properties; particle size distribution, specific surface area, particle shape, hydrophobicity, chemical composition, redox potential and band gap, and extrinsic (system dependent) properties; density, dustiness, zeta potential, agglomeration rate and surface affinity, dissolution rate and solubility, and reactive oxygen species generation. The methods evaluated include organisation for economic cooperation and development (OECD) test guidelines, NanoValid standard operating procedures, NANoREG protocols and methods being proposed by peer-reviewed publications. Compared with the characterization of intrinsic properties, the characterization of extrinsic properties is generally less validated and less reproducible. This is mainly because the medium properties may have significant effects on the result. Thus, reporting of extrinsic properties will need to include associated meta-data to make them comparable across studies. While some methods are becoming standardized and even automated, the full range of factors influencing the reliability and reproducibility of those measurements had not yet been well characterized.

1. Introduction

The unique properties of manufactured nanomaterials (MNMs), also called engineered nanomaterials (ENMs), give rise to their extraordinary behaviours. Those same properties can also lead to unanticipated effects on the environment and human health. While still being debated, there is a growing consensus on which nanomaterial properties should be measured and reported to assess its exposure and hazard potential. For example, the European Chemical Agency (ECHA) recently provided a recommended list of nanomaterial properties that should be measured as part of a chemical safety assessment for nanomaterial registration (ECHA, 2016). Critical to any regulatory action for nanomaterials is the ability to identify a particular material as a nanomaterial according to the definition of a nanomaterial (Bleeker et al., 2013), and to develop robust methods to measure the other selected properties of those materials to assess the potential for risk. This requires accurate and reproducible methods to measure these nanomaterial properties for the wide range of nanomaterials that are currently being produced, or that will someday be produced. A brief summary of the programs developing these methods, and the methods cited, is provided in Table.1.

There are two primary drivers for developing standardized and reliable methods to determine nanomaterial properties. The first driver is the need to determine if a given material is indeed a nanomaterial according to the definition. Here, we refer to the recommended EU definition (EU Commission, 2011), because it provides the most specific measurable parameters of nanomaterials compared to other definitions such as NNI definition or EPA's definition (EPA, n.d.; National Nanotechnology Initiative, n.d.). Namely, in order to qualify as a nanomaterial at least 50% of the constituent particles by number must

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Table 1
Summary of projects/organizations and the related test guidelines/protocols/regulations that are relevant to this paper.

Organization/project name	Objectives of the organizations/projects that are related to Nano EHS	Name of specific test guideline/protocol/regulation assessed in this paper	Objective of the test guideline/protocol/regulation
NanoDefine	Explores and develops conceptual and technical tools for the classification of materials according to the EU definition of a Nano-Material.	NanoDefine Technical Report D3.1. Techniques evaluation report for selection of MNM characterization methods	Review current methods to measure the number based size distribution of MNMs according to the EU definition.
NANoREG	Develop a common European approach to the regulatory testing of Manufactured Nanomaterials.	Deliverable D 2.04 Protocol for quantitative analysis of inorganic and organic MNM surface coatings	Validate procedures to identify the organic and inorganic modifications to MNMs.
		Deliverable D 2.10 Protocol for size-distribution analysis of primary NM particles in air powders and liquids	Establish standard operating procedures for measuring the size distribution and shape of engineered nanomaterials.
		Deliverable D 2.11 Protocol(s) for VSSA analysis of primary MNM in objects air, powders, and liquids for compliance with the EU definition	Review and validate measurement methods for volume specific surface area (VSSA) of nanomaterials.
NanoValid	Develop a set of reliable reference methods and materials for the fabrication, physicochemical characterization, hazard identification and exposure assessment of engineered nanomaterials	Measurement of the size distribution of dispersed MNs by transmission scanning electron microscopy in (T-SEM)	Describe the measurement of the particle size and size distribution of roughly spherical nano-particles by T-SEM.
		Chemical purity by ICP-MS	Identifying the presence and concentration of impurities in MNMs by ICP-MS.
NanOximet	Develop prediction metrics for predicting toxicity of MNMs, surface area and oxidant generation.	Different SOPs for acellular assays to measure ROS generation	Compare and evaluate the effectiveness of each assay that measure ROS generation to predict toxicity of MNMs.
Prosafe	Coordinate and support the aims of EU Member and associated states in their EU and international efforts (OECD, COR, EU-USA) regarding risk assessment, management and governance by.	Deliverable D 5.0 Reliability of Methods and Data for Regulatory Assessment of Nanomaterial Risks	Review the protocols and guidance documents from NANoREG and OECD Working Party on Manufactured Streamlining data acquisition, collection and management on regulatory orientated toxicology testing of nanomaterials, exposure monitoring, LCA, and disposal and treatment of waste nanomaterials.
The Organization for Economic Co-operation and Development (OECD)	OECD identified the need to analyse the potential safety concerns caused by manufactured nanomaterials.	Agglomeration Behaviour of Nanomaterials in Different Aquatic Media	Provide reliable and reproducible results on the agglomeration behaviour of different types of nanomaterials in aquatic media.
		Series on the Safety of Manufactured Nanomaterials No. 63 entitled “Physical-chemical parameters: measurements and methods relevant for the regulation of nanomaterials”	Review the current OECD test guidelines for applicability to nanomaterials. Identify the need to develop new test guidelines.
US EPA Toxic Substances Control Act (TSCA)	Protect human health and environment	Control of Nanoscale Materials under the Toxic Substances Control Act	Gather information on the properties of NMNs, production volume, methods of manufacture, processing, use, exposure and release information, and available health and safety data.

be < 100 nm in one dimension, or the volume specific surface area (VSSA) must be greater than 60 m^2/cm^3. This requires reliable and accurate measurement of particle size distribution and/or measurements of the external specific surface area of the material. The second driver is the need to facilitate read-across and to *anticipate* possible fate and adverse effects for MNMs (Oomen et al., 2015). Read-across requires the ability to correlate the relevant physicochemical properties of a nanomaterial with specific fate and toxicity behaviour such that the behaviours of new nanomaterials can be predicted from measurements of their properties.

The specific ENM properties that were recently recommended by the Prosafe Task Force as necessary to characterize exposure and hazard risks (Steinhäuser and Sayre, 2017) are shown in Fig. 1. These properties can be placed into two categories: intrinsic particle properties (medium independent) and extrinsic particle properties (medium dependent) (Hendren et al., 2015). This list of properties goes well beyond those needed strictly for the EU regulatory definition of what constitutes a nanomaterial, and includes both physical and chemical properties. For example, the intrinsic property of number average primary particle size distribution is needed to define a nanomaterial. The extrinsic properties, like zeta potential and dissolution rate, can affect aggregation potential and toxicity (Berg et al., 2009), and fate and persistence in the environment(Franklin et al., 2007; Liu and Hurt, 2010). The “reactive” properties (e.g. solubility/dissolution rate and ROS generation) are thought to be important determinants of toxicity (Manke et al., 2013; Utembe et al., 2015).

The linkages between many of the intrinsic ENM properties (e.g. band gap) and either exposure or hazard characterization are not yet fully elucidated. However, many of the intrinsic ENM properties affect the extrinsic ENM properties that are better linked to exposure and hazard characterization. For example, particle shape (Misra et al., 2014), size and specific surface area (Peretyazhko et al., 2014), surface chemistry(Li et al., 2013) and existence of impurities (Xia et al., 2011) can all affect the dissolution rate of ENMs. ENMs with a higher dissolution rate can release toxic metals at a faster rate, leading to greater toxicity(Hang et al., 2016; Wu et al., 2017); crystalline phase (Su et al., 2011) and band gap (Zhang et al., 2012) can affect the photocatalytic properties of ENMs, which will affect the ROS generation. Surface chemistry and hydrophobicity of ENMs can affect their aggregation behaviour (Dominguez-Medina et al., 2013). Some examples of how ENM properties are directly related to exposure and/or hazard characterization are summarized in Table 2. Additional rational for selecting these properties is provided in each section below describing them and the standard tests available to measure them.

It is important to note that the distinction between intrinsic and extrinsic properties is primarily to highlight the fact that many “properties” cannot even be measured independently of the system in which they are contained, e.g. zeta potential only exists when particles are in contact with a solution with ions. However, there is not always a clear distinction between these two types of properties. For example, the