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Review article

Methods and data for regulatory risk assessment of nanomaterials: Questions for an expert consultation

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ABSTRACT

While the general risk assessment paradigm, and associated endpoints for regulatory review and approval of conventional chemicals in essence apply to nanomaterials, two problems have arisen that must be addressed. Due to the physicochemical properties of nanomaterials, additional parameters, in addition to their chemical composition, are needed to identify a manufactured nanomaterial for regulatory purposes. Second, new methods for material characterization, hazard, exposure, fate, and risk assessment are needed to supplement those that exist for the regulatory risk assessment of conventional chemicals. While this area has received extensive funding in the EU, the US and other countries, the resulting range of research results are broad, and it remains unclear how well these current research efforts have answered detailed regulatory needs for nanomaterials. These needs for are driven by applicable statutes such as REACH, and are aimed at questions that must be answered in an efficient and cost-effective manner through the use of reliable protocols and methods. The direct applicability of that research to these regulatory needs has not been comprehensively assessed. In part this is due to the fact that a detailed set of regulatory questions for nanomaterials has not been presented in the open literature. In addition, regulatory questions for emerging areas of science take time to formulate in detail.

One purpose for this paper is to provide the context for nanomaterial regulatory risk assessment questions. Second, we present, in detail and for the first time, what these prominent regulatory questions are for all relevant risk assessment endpoints. These detailed regulatory questions were derived in part from the EU FP 7 research programme NANoREG, and then augmented by additional questions that have been raised by regulatory authorities. These questions address the following areas: (1) physicochemical characterization, (2) exposure through the lifecycle, (3) fate – persistence – bioaccumulation, (4) modeling of environmental fate and exposure, (5) ecological effects and biokinetics, (6) human health effects and biokinetics *in vivo*, (7) human health effects and biokinetics *in vitro*, (8) *in silico* strategies – (Q)SAR modeling, and (9) risk assessment. Answers to these questions were provided by an expert solicitation in the EU H2020 coordination activity ProSafe, were presented and discussed at a scientific conference at OECD in November 2016, and are now published separately in this special issue of *NanoImpact*.

The methods deemed acceptable for regulatory use, and targeted regulatory gaps, will be incorporated into a 2017 draft white paper. This white paper will mesh EU regulatory policy with new available and proposed methods, and other future-oriented needs, aimed at streamlining the assessment of nanomaterial risks. The white paper will then receive comments from Member States, industry, and others *via* an interactive process, resulting in a final white paper in the September 2017 timeframe.

1. Introduction

From the regulators' perspective, while the traditional risk assessment paradigm holds for nanomaterials (OECD, 2012a), many of the test guidelines and guidance documents for assessment of physicochemical properties, fate, exposure and effects used for conventional chemicals need to be modified when applied to nanomaterials (Rasmussen et al., 2016). It is recognized that regulators' views on nanomaterial risks are conservative, as compared to the engineers and scientists that produce the nanomaterials (Beaudrie et al., 2014), but such conservative approaches are designed to be adequately protective of human health and the environment.

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Nanomaterials have been the subject of intensive research efforts across the world with the aim of developing new products for consumers and industry. The rate of commercialization has been increasing from $339 billion in 2010 to more than $1 trillion in 2013 worldwide (Lux Research, 2014). However, there have been ongoing concerns expressed by all stakeholders that acceptable regulatory data and methods for assessing the environmental, health and safety (EHS) of nanomaterials are not fully available (NAS, 2012; OECD, 2016a).

The lack of regulatory data and methods has led, at least in part, to regulatory uncertainty. As an example, consider the variations in definitions and concern cut-offs for nanomaterials expressed by different regulatory bodies such as The Food and Drug Administration (FDA, 2017), the Environmental Protection Agency (EPA, 2017a), and the European Commission (EC, 2011). These definitions are reflected to some degree in the ISO TS 27687 definition, which defines nanoobjects as material with one, two or three dimensions in the size range from approximately 1 nm to 100 nm. Variations in both size (from below 1 nm up to 1 μm), and other physicochemical parameters (with some agencies proposing to examine seven or more physicochemical properties to determine if the material is subject to reporting as a nanomaterial), affect the initial decision point that determines whether a material is to be considered as a nanomaterial or not as part of the regulatory review or approval process. Some of these differences in definitions are driven by different nanomaterial uses and related specific regulations; however, it is also recognized that there are gaps that exist in methods and endpoints that are associated with these definitions.

Beyond this, once a nanomaterial has entered the regulatory process, there is further uncertainty with regard to additional nanomaterial characterization, health and environmental data that are needed once a nanomaterial is in the marketplace, and with regard to the related methods needed to obtain these data (ACC, 2015). When conducting experiments or tests with nanomaterials, the results may correlate not only with new physicochemical parameters but also with how the surface chemistry of the particle is altered. Characteristics, fate and effects may change from nanoform to nanoform and throughout the life cycle. Hazard and fate are influenced not only by the chemical composition but also by functionalities. Recently, ECHA published a draft guidance defining a nanoform as a substance that meets the requirements of the definition of a nanomaterial (of EU Commission), and provided information to describe the specific shape and surface chemistry of a nanoform (ECHA, 2017). Particle size (distribution), shape and surface chemistry are listed as minimum information requirements in registration dossiers for REACH. However, the guidance is limited in terms of the decision criteria for when two nanoforms can be considered as same or different.

Such regulatory uncertainty affects the ability of industry to develop and use new nanomaterials. Hence such EHS research needs – as recognized by the U.S. National Nanotechnology Initiative (NNI) and others – is still critical to both current regulatory approval and the development of safer nanomaterials at the early stages of product development: One of NNI's goals in its current strategic research plan is to "Adopt or develop and validate measurement tools and decision-making models to enable hazard and exposure quantification for human and environmental risk assessment and management" (OSTP, 2016). The U.S. Government Accountability Office (an independent Agency of the Congress) study showed a clear need for continued EHS research on nanomaterials for regulatory use in their study on Nanomanufacturing (GAO, 2014): "Participants said significant research was needed to discern or anticipate EHS implications of manufacturing with nanomaterials and using Nanotechnologies". Also, "some feared regulation to address EHS concerns could damage U.S. competitiveness", while others noted similar concerns if the precautionary principle is employed by regulators. The need specifically for this tools-oriented research has also been recognized in 2016 as an ongoing need by the Chemical Industry associations in both the EU (CEFIC, 2017) and the U.S. (ACC, 2016).

Test guidelines and guidances – that take into account the differing characteristics of nanomaterials as compared to conventional chemicals – are key enablers that allow reliable and relevant data to be gathered by regulatory agencies. While these may require extensive modifications or may need to be developed *de novo* to address relevant regulatory endpoints, organizations such as the OECD have made significant progress in this area. OECD nanomaterial guidance documents that have been completed include those on sample preparation and dosimetry and worker exposure estimation (OECD, 2012b and OECD, 2015). As of 2016, there were approximately eight test guidelines and guidance documents in preparation or drafted: endpoints addressed include inhalation toxicity, agglomeration and dissolution, aquatic toxicity, bioaccumulation, and retention in activated sludge (Rasmussen et al., 2016). Since then, there are at least two more test guideline efforts that are newly underway to address soil column leaching and genotoxicity. Finally, additional work on physicochemical parameter estimation is foreseen in the near future.

There is also a lack of adequate, reproducible data to validate modeling approaches and risk assessment strategies for manufactured nanomaterials (MNs) and develop a science-based understanding of how to quantify and predict the potential risks of many nanomaterials. Experimental data for nanomaterials found in literature are often contradictory or inconclusive. Indeed, when dealing with MNs there are particular problems related to sample preparation, stability of test solutions, quantification, characterization, and dosimetry. Many publications and reports lack credibility since the nanomaterials being investigated are insufficiently characterised, and/or fluctuations in concentrations or changes in physicochemical properties occurring during the experiments are not taken into account, leading to unreliable data (Krug, 2014, Wagner et al., 2014). Nevertheless many old publications are still helpful, and their data can be used in a recalculation of their results by applying new knowledge on dosimetry. Moreover, scientists had to learn how to deal with the particular characteristics of nanomaterials. When conducting experiments or tests with nanomaterials, the results depend not only on chemical composition but also on physicochemical parameters.

Despite these concerns, approximately 160 nanomaterials have been approved under TSCA (EPA, 2017b). Twenty-one nanomaterials or nanomaterial containing chemicals have been registered under REACH (ECHA, 2017, personal communication). Seven of these are subject to the substance evaluation by the member states, other dossiers are evaluated by the EU Member States, while other dossiers are evaluated by ECHA. Furthermore some nanomaterials (*e.g.* nano-silver and nano-silica) are evaluated under the biocidal products regulations, and EFSA lists 39 uses of nanomaterials in plant protection products as active ingredients, or co-formulants (EFSA, 2014).

The investments in EHS research have been high, with almost $100 million more projected for the US in 2017 (NNI, 2017a). Cumulative EHS investments by the US government from 2006 through 2015 have now reached more than $1 billion (NNI, 2017b). In its FP6 and FP7 research programmes the EU Commission funded €208 million. The total project costs across all EU-funded nanomaterial EHS research were €312 million (EU Commission, 2017, personal communication). Given these investments in EHS research, it was the goal of the H2020 Programme ProSafe in part to harvest the nanosafety work already done that would be most useful to regulatory review and assessment and to identify significant regulatory gaps for future regulatory research. Such a broad effort to gather information, and then pass relevant results through expert and regulatory review, has not been attempted up to this time. In order to conduct such a review, the first need that had to be addressed was to identify the most pertinent current regulatory questions. The purpose of this article is to identify those questions.

The questions posed by regulatory authorities are difficult to access since they are emerging, and are usually identified as part of the review of commercial nanomaterial submissions (therefore not directly