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Review article

Frameworks and tools for risk assessment of manufactured nanomaterials

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ABSTRACT

Commercialization of nanotechnologies entails a regulatory requirement for understanding their environmental, health and safety (EHS) risks. Today we face challenges to assess these risks, which emerge from uncertainties around the interactions of manufactured nanomaterials (MNs) with humans and the environment. In order to reduce these uncertainties, it is necessary to generate sound scientific data on hazard and exposure by means of relevant frameworks and tools. The development of such approaches to facilitate the risk assessment (RA) of MNs has become a dynamic area of research. The aim of this paper was to review and critically analyse these approaches against a set of relevant criteria. The analysis concluded that none of the reviewed frameworks were able to fulfill all evaluation criteria. Many of the existing modelling tools are designed to provide screening-level assessments rather than to support regulatory RA and risk management. Nevertheless, there is a tendency towards developing more quantitative, higher-tier models, capable of incorporating uncertainty into their analyses. There is also a trend towards developing validated experimental protocols for material identification and hazard testing, reproducible across laboratories. These tools could enable a shift from a costly case-by-case RA of MNs towards a targeted, flexible and efficient process, based on grouping and read-across strategies and compliant with the 3R (Replacement, Reduction, Refinement) principles. In order to facilitate this process, it is important to transform the current efforts on developing databases and computational models into creating an integrated data and tools infrastructure to support the risk assessment and management of MNs.

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1. Introduction

Nanotechnology is one of the key emerging technologies identified in the European Union (EU) 2020 Strategy (European Commission, 2010). It has enormous potential to contribute to innovation and economic growth, which has fostered large investments in developing new industrial applications. However, current uncertainties around the Environmental, Health and Safety (EHS) risks of manufactured nanomaterials (MNs) have raised societal concerns about the adequacy of their regulation (Hristozov et al., 2012). In order to protect nanotechnology innovation sound scientific analysis of the MNs implications is required, taking into consideration all stages of their lifecycles.

The paradigm for Risk Assessment (RA) of chemicals is considered applicable to MNs if properly adapted to address the complexity associated with their identity, biological and environmental interactions (OECD and European Commission, 2012, EFSA, 2010, Stone et al., 2013). RA systematically applies scientific principles to estimate the probability that adverse human health or environmental effects could emerge from exposure to chemicals. The RA framework is composed of problem formulation, exposure assessment, hazard assessment, and risk characterization (Van Leeuwen and Vermeire, 2007). Specifically, the problem formulation is a systematic planning activity that sets the goals and the scope of the RA. The exposure assessment formulates exposure scenarios describing how a chemical is used by workers or consumers or how it is released into the environment. This is followed by estimations of exposure for one or more routes (i.e. inhalation, ingestion or dermal) or environmental compartments (e.g. water, sediment, soil) under the conditions of use described in the exposure scenarios. This may involve monitoring of indoor or outdoor concentrations by means of suitable analytical instruments and/or the estimation of the amount of the substance reaching humans or target environmental species by means of models. The hazard assessment involves the analysis of available data on (eco)toxicological effects in order to establish dose-response relationships. The risk characterization combines hazard and exposure to estimate risk.

There is a considerable volume of research and regulatory activity in the nanoEHS area, pointing to the fact that the (eco)toxicology and exposure data obtained for larger particles or for chemicals are generally useful and relevant to the evaluation of MNs hazards and risks (Donaldson and Poland, 2013). Nevertheless, the feasibility study of performing RA for MNs has identified serious gaps in our basic understanding of key nano-bio interactions, mechanisms of biological uptake, fate, distribution and bioaccumulation that have led to ambiguous, largely qualitative risk estimations based on expert judgments, which may fail to support proper risk management decision making (Hristozov et al., 2012). In order to fill the gaps, the academic community has been working together with industries and regulators for more than 10 years to develop frameworks and tools for RA of MNs. RA strategies have been reviewed in the past (Hristozov et al., 2012, Grieger et al., 2012, Som et al., 2013, Olson and Gurian, 2012) but the field of nanoEHS has rapidly developed and significant advancements have been made, which requires an update of these reviews.

In an attempt to avoid confusion in using the terms “framework”, and “tool”, we provide provisional definitions of them in the context of RA. A “framework” is a conceptual paradigm of how RA should be understood and performed. An example is the Chemical Safety Assessment (CSA) required by the REACH (Registration, Evaluation, Authorisation and Restriction) regulation. “Tools” are implements used to carry out particular functions or accomplish specific tasks (e.g. estimate exposure, build a dose-response curve). They can be for example specific models, experimental protocols or databases.

The main aim of this review paper is to analyse and evaluate the available frameworks and tools for RA of MNs against relevant criteria and discuss their strengths and weaknesses. This analysis had a strong focus on ongoing advancements in EU and U.S. research projects.

2. Methodology

2.1. Critical review of peer-reviewed literature

Published literature from 2000 to 2015 was searched for studies on RA of MNs by querying the Web of Science database with 10 keywords (nano, risk assessment, framework, methodology, method, tool, protocol, database, library, inventory). The search [strings = (nano* and (risk assessment) and (framework or methodology or method or tool or protocol) and (database or library or inventory)] retrieved 1749 records, out of which 46 papers described 6 frameworks and 14 tools relevant for the RA of MNs. In addition, the regulatory frameworks within the EU were considered. In order to critically review the identified approaches against a set of criteria, the relevant papers were divided into two categories: i) review or opinion papers; and ii) research papers that described specific frameworks or tools. Our critical appraisal focused on the second type of papers as they represent primary sources of information, while the opinion and review papers were only used to identify evaluation criteria and research trends.

2.2. Critical review of grey literature and information collected through a survey

The analysis of peer-reviewed literature was complemented by a review of results from relevant research projects. In order to identify those, we performed a search on CORDIS with the same keywords. This revealed a number of EU-funded projects, which are reported in the European Nanosafety Cluster Compendium. The scientific findings from these projects were assessed through a review of their interim reports and deliverables that were publically available or accessible to the authors. The identified frameworks and tools were evaluated against the criteria reported in Table 1.

In addition, a “google docs” online questionnaire was developed to survey organisations that are involved in developing nanoEHS tools. Potential participants and their contact information were identified from the European NanoSafety Cluster Compendium and personal communications with relevant individuals. The questionnaire (cf. Supplemental Information) covered several aspects characterising a tool: Scope, application domain, regulatory relevance, input data requirements, analytical methodology, expected outputs/results, case studies used for demonstration, stakeholders' involvement, and future research directions. It was distributed to representatives of the identified EU projects through the channels of the NanoSafety Cluster as well as to key centres in the

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