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Review article

Risk assessment frameworks for nanomaterials: Scope, link to regulations, applicability, and outline for future directions in view of needed increase in efficiency

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ABSTRACT

The increasing application of nanomaterials and the notion that their distinct features compared to larger sized counterparts should be considered in safety assessment, has led to the development of risk assessment frameworks that are specific to nanomaterials. These frameworks aim to prioritise, rank or assess the safety of a nanomaterial efficiently by targeting critical information in order to conserve resources. The present overview shows that each nanomaterial framework has its own scope, advantages and disadvantages and all except one lack details such as decision criteria to come to conclusions and enable actual application. Those frameworks directed towards gaining information and making decisions on regulatory submissions at national and EU level are principally of interest. Additionally, those aimed at informing decision-making in the innovation chain are important.

This manuscript also discusses issues relevant for exposure and hazard assessment of nanomaterials such as life cycle, bioaccumulation and delivered dose that should be considered in risk assessment frameworks. Elements for improving the feasibility to perform risk assessment in practice include standardised testing, knowledge on in vitro-in vivo comparison and functional assays. With this information and the need to increase the efficiency in risk assessment, future perspectives are outlined. Grouping and read-across approaches can bring some efficiency compared to a case-by-case approach. However, science is at present not advanced enough to fully substantiate decision criteria and specific protocols needed to considerably increase the efficiency. A possible way forward would be to pursue the development of a pragmatic and internationally accepted nanomaterial decision framework with decision criteria that can only be partially scientifically based. This would require the cooperation of policy makers, scientists and industry.

1. Introduction

Nanomaterials are increasingly used as their different features, compared to their larger sized counterparts, can be applied in innovative products and materials. Such changes in functionality can be made by modifying chemical make-up, size, shape, surface characteristics *et cetera*. The physicochemical properties that provide specific functionality, can also affect the behaviour of nanomaterials in the environment and humans, which may result in different exposures (including different sites in the environment or within the human body) and subsequent hazards. It is therefore relevant to consider the potential risks of nanomaterials. This should be done in such a manner that sufficient information becomes available to assess the risk of each nanomaterial and allows innovative nanotechnologies to be developed.

The basic components of risk assessment of chemicals are hazard and exposure assessments, dose-response estimation, risk characterisation, and accounting for uncertainty in the overall assessment. While this traditional risk assessment paradigm also holds for nanomaterials (SCENIHR, 2005, 2007, 2009; Sayre and Steinhäuser, 2016; OECD, 2012a), many of the tools, test protocols and guidelines for determination and assessment of physicochemical properties, fate, exposures, and effects used for conventional chemicals, need modifications when applied to (the regulatory) evaluation of nanomaterials (Sayre and Steinhäuser, 2016).

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In the context of this article, the term risk assessment "framework" is used in the same context that it is used by the National Academy of Sciences (NAS, 2009): it is intended to incorporate the traditional risk assessment paradigm applied to chemicals (NAS, 1983) in broader sense to allow for a flexible risk assessment approach for decision-making. This encompasses both human health and environmental endpoints, and incorporates concepts such as the following: default assumptions, read-across, overarching general risk assessment paradigms, and specific tiered-testing schemes. Recently, more risk assessment frameworks and assessment methodologies, sometimes also referred to as tiered-testing approaches or schemes, strategies or methodologies, have emerged that are specific to nanomaterials. These frameworks aim to prioritise, rank or assess the safety of a substance/nanomaterial efficiently by targeting critical information, *i.e.* aiming to obtain the necessary information for risk assessment, while conserving resources.

The aim of the present manuscript is to assess nanomaterial testing and assessment frameworks that are most useful in a regulatory context. Those frameworks, which are mainly directed towards gaining information and making decisions on regulatory submissions at national and EU-wide levels are principally of interest. Additionally, frameworks to inform decision-making in the innovation chain are important. Several nanospecific issues in risk assessment and elements for improving the feasibility to assess the risks of nanomaterials are addressed. The frameworks are discussed in relation to the need to increase the efficiency in information gathering for risk assessment of nanomaterials. Finally, recommendations, future perspectives and conclusions are provided and discussed. These include process-related considerations on how such perspectives can be achieved.

2. Methods and criteria to select and evaluating risk assessment frameworks

As noted in Sayre et al. (2017), experts in nine different disciplines (including those with expertise in regulatory assessments, physicochemical properties, fate, effects, modelling, and risk assessment) reviewed the relevant publications and reports of 23 research and regulatory bodies from the EU, the US, the OECD, and Germany, as well as references from open literature. In total, approximately 1000 references from both the peer-reviewed and grey literature were evaluated (Steinhäuser and Sayre, 2017). All experts commented on the utility of the risk assessment frameworks, and their components, that were contained in these publications.

The overarching criteria used to select and evaluate the risk assessment frameworks, covering human health and/or environment, are those applied by the OECD to judge the utility of any regulatory method, protocol, or data set: is the risk assessment framework both relevant (to predicting endpoints of interest for regulatory purposes) and reliable (OECD, 2005)? In addition, the risk assessment frameworks and testing schemes were evaluated relative to how responsive they were to a set of regulatory questions specific to nanomaterials, as generated by regulatory programs and experts who are involved in nanomaterial regulatory risk assessments (Sayre et al., 2017). These questions were developed to determine which risk assessment frameworks were most useful for use early in the innovation process, *versus* those which could be applied at an EU or national level for regulatory decisions. Of those that could become applicable in regulatory context, focus is put on the risk assessment frameworks that are more detailed and cover a broad range of nanomaterials and exposure routes. All risk assessment frameworks would benefit from being tested for reliability in case studies. These issues were considered in Table 1, addressing the aim, regulatory readiness, advantages, and disadvantages for the various risk assessment frameworks. The obtained insights, and how the use of the frameworks can facilitate the need for increased efficiency in information gathering for risk assessment of nanomaterials constitute a different evaluation process, relative to those done in the recent past (Grieger et al., 2012; Hristozov et al., 2016). In addition, the present manuscript includes recent developments relative to the assessment of the regulatory perspective on early frameworks in Hristozov et al. (2012).

3. Overview of risk assessment frameworks

The selected risk assessment frameworks that are specific for nanomaterials are listed in Table 1. Although the frameworks are based on the same risk assessment paradigm, consisting of hazard identification, exposure assessment and risk characterisation, the frameworks are diverse in their aim, applicability domain, basic assumptions and alignment to one or more regulations. Since each framework is specific to a purpose, it is not possible to take various components from them to construct an adequate risk assessment framework to suit all routes of exposure for mammalian and ecological receptors. Almost all the frameworks lack the specific decision points and associated methods needed for decision making that are required for actual application. For the one framework that is specific enough, the decision points and associated methods cannot be fully evaluated based on current scientific knowledge. For these reasons, it is not possible to clearly indicate the best or most useful framework(s).

3.1. Scope, advantages and disadvantages

All but one of the frameworks lack the specific decision points and associated methods needed for decision making that are required for actual application. The DF4nanoGrouping framework is the only fully elaborated risk assessment framework that transparently and in detail includes clear decision criteria, triggers/cut-off values and tools to assess inhalation risks (Arts et al., 2015, 2016). The framework also has specific associated case studies (Arts et al., 2016; Landsiedel et al., 2017). Just like other frameworks, however, an independent evaluation of these criteria, triggers and methods has not yet been conducted. The properties required by regulations such as REACH do not match with the intrinsic material and system dependent properties needed by the DF4nanoGrouping framework. Therefore, while the approach is developed, detailed and includes decision criteria, allowing it for to be evaluated, the regulatory acceptability of this framework remains unclear.

The more elaborated of the risk assessment frameworks without decision criteria, are the NANoREG nanospecific approach for risk assessment described by Dekkers et al. (2016), and the NanoRiskCat by Hansen et al. (2014). These frameworks are transparent and detailed, and underpin their choices using scientific information (as far as possible) and build upon existing approaches for 'conventional' substances (*i.e.* non-nanomaterials). These frameworks consider materials and products, respectively. For screening of inhalation exposure in an occupational setting the general risk banding framework for inhalation of low aspect ratio nanoparticles by Oosterwijk et al. (2016) can be useful, whereas for environmental risks the general test strategy for assessing the risks of nanomaterials in the environment by Hund-Rinke et al. (2015) is more advanced. Further details on the different frameworks can be found in Table 1. It should be noted that these frameworks remain qualitative.

The ECHA/JRC/RIVM approach on read-across between nanoforms (ECHA/JRC/RIVM, 2016) constitutes scientifically-founded guidance aimed at gathering information for a nanomaterial on one or more hazard endpoints by using information from other materials, if possible. The ECHA/JRC/RIVM read-across approach describes steps to consider if existing information can be used in such a manner that sufficient information is available to assess the risk/safety of an unassessed nanoform, and how a read-across hypothesis can be substantiated (with existing or additional information) (ECHA/JRC/RIVM, 2016). Read-across between structurally similar substances is a generally applicable approach in regulatory risk assessment of 'conventional' substances, as