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Reliability of Methods and Data for Regulatory Assessment of Nanomaterial Risks – Executive Summary

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Executive summary

Both the EU and other OECD member states have understood the increasing need for dedicated research into the environmental, health and safety aspects of nano-materials. As a result, significant amounts of funding have been allocated in Europe by national governments as well as the Commission on an EU level, while the US has promoted EHS integration in its NNI programme since its inception. The EU and the US supported close to 100 research programmes and major projects over the past decade. While this has led to many advances in our understanding of the processes and interactions of nano-materials, often published in peer reviewed journals, the regulatory relevance of the results has not been examined.

In order to remedy this shortcoming, the H2020 ProSafe project has commissioned a review of literature by nine international experts to determine which research results from the programmes in the preceding decade have regulatory relevance. This review was guided by a detailed set of regulatory questions which are critical to answer in order to have efficient and timely regulatory reviews of nanomaterials.

This review identifies which test protocols, data sets, models, guidances, and assessment methods are most relevant to regulatory needs. Adoption of these regulatory-ready procedures could lead to an improved regulatory review process for nanomaterials, despite the complexities related to their physicochemical properties. These properties create concern as functionality plays as important a role as chemistry. Whereas the methods and tools for conventional chemicals are in principle suitable for manufactured nanomaterials (MN), the unique properties of nanomaterials require that harmonized methods and tools have to be adapted, as well as new ones developed.

The scientific evidence compiled in this report clearly shows that reliable methods and approaches are already available for many parameters and endpoints, which are either validated to be used for regulatory decisions, or at least have been demonstrated repeatedly, and are promising for near-term regulatory use after further development and validation.

This ProSafe study, reviewed approximately 1,000 published articles and research reports which were specifically selected and sorted into a database on their main topic, and reviewed by nine internationally recognized nanomaterial experts to prepare this analysis of those key findings. The two key criteria used for the evaluation of the documented research were *reliability* and *relevance,* as defined by the OECD. The nine areas of concern studied in this report are: (1) physicochemical characterisation, (2) exposures through the life cycle, (3) fate, persistence and bioaccumulation, (4) exposure modelling, (5) ecological effects and biokinetics, [review not yet completed] (6) human health effects and biokinetics *in vivo*,
(7) human health effects and biokinetics *in vitro*, (8) (Q)SAR modelling of nanomaterials and (9) risk assessment. Each section has specific recommendations on the most appropriate protocols of regulatory relevance, while gap analyses revealed specific high priority areas for further regulatory relevant research. Since it is not possible to list all procedures and data sets in this summary a detailed list of all procedures and data sets that are ready for regulatory consideration and possibly use are identified in this document, and summarized in Chapter 6. In this chapter it is also attempted to prioritize future near- to medium-term regulatory research needs, based on whether the key questions posed in the attached annex.

The characteristics of nanomaterials, as well as an assessment of their hazard and fate, depends not only on their chemical composition but also their physico-chemical properties such as size, shape, and surface chemistry. Many parameters can vary from nanoform to nanoform or even within the same nanoforms, depending on the medium they exist in.

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It is therefore essential to characterize nanomaterials thoroughly before performing effect or fate tests, and subsequently to follow significant changes of their characteristics throughout the life cycle. A selected list of approximately 16 physico-chemical characteristics has been linked with the most acceptable current protocols for their assessment. Furthermore, specific physico-chemical properties (e.g. zeta potential) that represent the interplay between a NM's surrounding environment and the NM itself may be determining for risk assessment, enabling with a single measurement the estimation of multiple fate and effects endpoints. Such functional assays, which mimic modes of action of nanomaterials such as surface affinity, ROS production, or dissolution rate should to be validated and standardized for their inclusion as screening tests in risk assessment frameworks.

An overarching conclusion is that hazard, exposure, and risk assessment of nanomaterials can be extremely complex, time consuming, and as a result costly, and hampered with uncertainties. In any case it is not realistic to investigate every nanoform by applying all test methods. So effective benchmarking methods for the assessment of hazard and exposure/fate, tiered testing schemes, grouping frameworks, and modelling approaches all play important roles in the assessment of MNs.

Ecotoxicity tests with pelagic organisms are most advanced, but the preparation of test dispersions is still a matter of debate. An example of a major advance in this area, which addresses key questions for conducting aquatic toxicity tests, is the newly developed OECD draft aquatic toxicity guidance by OECD. . Most nanomaterials are predicted to be released in freshwater aquatic systems. However, many nanomaterials may partition to sediments, or become deposited in soils, making testing of sediment and soil organisms also important for many MNs and uses. While the standard set of organisms for testing conventional chemicals is applicable for the current time under these scenarios, procedures on spiking soil and sediment have to be further developed and standardized.

In the area of human health, health *in vivo* test protocols have advanced significantly, with OECD-driven draft test guidelines for subchronic and subacute testing now able to provide the most accurate information on the human health risks of nanomaterials. For *in vitro* health testing, seventeen specific recommendations are presented, related to how to conduct mammalian *in vitro* tests in order to make them more acceptable to both the scientific and regulatory communities. Specific *in vitro* protocols are reviewed which are applied to assessment of cytotoxicity, genotoxicity, and biokinetics. In addition, a number of short-term health *in vivo* and abiotic methods are also recommended for near-term use.

Unifying dose metrics for health effects are also discussed, and a proposal made for combining the diverse findings of *in vivo and in vitro* tests to allow for more efficient estimation of the relative hazard potency of nanomaterials via the inhalation route.

Advances have also been made in tiered measurement and assessment methods for exposure in the workplace, models to estimate worker exposures, and in understanding how personal protective equipment and engineering controls reduce workplace exposures (all specifically tailored to application to nanomaterials, versus conventional chemicals). . Numerous methods for estimating exposure to nanomaterials in the workplace are evaluated, and one exposure model for estimating worker exposures is viewed as appropriate for regulatory use. For estimating consumer exposure the determination of release from nanomaterial-bearing products is a crucial step. A set of such release-simulating methods has been developed and could be applied, following validation. A consumer exposure models specific to inhalation of nanomaterials has also been recently developed and appears to hold promise for regulatory application.

Several methods to determine the environmental fate of nanomaterials are currently standardized by the OECD (e. g. dissolution rate, [homo-]agglomeration behaviour, retention in sewage sludge and bioaccumulation in fish by dietary uptake), and therefore understandings of fate of MN will improve via use of these methods and the resulting data should be useful for environmental exposure modelling. Gaps do however exist in test methods for environmental fate, such as methods to estimate heteroagglomeration or the tendency to transformations in the environment. .

Environmental exposure modelling helps to predict how nanomaterials will be distributed in the technosphere and subsequently in the environment. Advanced models specific to nanomaterials are available and can be used for regulatory purposes. However, these models still suffer from lack of robust experimental data to allow validation of predictions and/or elimination of some of the unrealistic assumptions currently inherent in these models. Two models for material flow analysis and two environmental fate models were found promising for environmental fate predictions.

(Q)SAR modelling for human health effects also shows promise, but it is still in an early phase, since sufficiently large robust and reliable datasets for the development and validation of broadly deployable models are not available Models based on the conduction energy band level Ec and on the dissolution of nanomaterials seem most promising and should be further developed and eventually applied. There is promise to also apply (Q)SAR modelling to additional endpoints such as ecotoxicity and fate, but these areas are less developed at this time.

In order to facilitate risk assessment, many general, but few specific frameworks for risk assessment, tiered testing, and grouping have been developed. These general frameworks take into account the need to group the great variety of nanomaterials, and to identify the most hazardous for a more thorough assessment. However, these general frameworks still must be applied on a case-by-case basis in the context of each new nanomaterial. Thus, such frameworks may be more easily applied at the pre-commercial and pre-regulatory stage of development where selection of one nanomaterial from a group of candidates is being considered.

More specific frameworks that have explicit triggers to move from tier to tier, and/or explicit methods to assess effects or fate components within each tier, may be more practical in the context of formal regulatory use since they provide a clear means to assess nanomaterials. However, they are fewer in number (as compared to general frameworks). Such specific frameworks may be exposure route specific, or specific to a given receptor, which increases the complexity in applying them. Finally, the tenets of these frameworks such as the specific triggers and methods need further independent evaluation and case study analysis before being fully implemented. Over a half dozen general and specific frameworks were identified that hold promise for immediate use and/or further near-term development.

The key findings of this document, and associated research gaps have been considered in a joint OECD-ProSafe conference attended by 170 academic experts, regulators, policy makers, industry representatives, and designated delegates from the OECD member countries in November 2016. Critical comments and suggestions from conference delegates and participants are included in this final version of this report. This document forms the basis for a publication in a scientific journal. The recommendations of this report summarized in Chapter 6 are all of regulatory relevance, and should be taken into consideration by the OECD member states and especially the EU in its process to revise the annexes of REACH. Gaps, which have been identified during the review, should stimulate regulatory relevant research by the respective authorities in OECD member countries.