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Editorial

Reliability of methods and data for regulatory assessment of nanomaterial risks

Both the EU and other OECD member states have understood the increasing need for dedicated research focussed on assessing the potential environmental and health risks of commercial nanomaterials. 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 have 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 (see National Science and Technology Council, 2016 and www.nanosafetycluster.eu). While this has led to many advances in our understanding of the processes and interactions of nanomaterials, which are often published in peer reviewed journals, the regulatory relevance of these results has not been systematically examined. In order to remedy this shortcoming, the Horizon 2020 ProSafe project commissioned a review of the literature by nine international experts to determine which research results from the programmes in the preceding decade have regulatory relevance. This effort was guided by a detailed set of regulatory questions, (Sayre et al., 2017). The two key criteria used for the evaluation of the documented research were *reliability* and *relevance,* as defined by the OECD.

The key findings of the ProSafe review and associated research gaps have been presented 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 also included in the articles in this special issue, which address most of the central topics in human health and environmental safety that are relevant to regulatory review of commercial nanomaterials.

This special issue 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 such as size, shape, and surface chemistry. These properties create concern as functionality of nanomaterials plays as important a role as chemistry. Nanomaterials of the same chemical composition may occur in different nanoforms: these nanoforms can vary with respect to size, surface characteristics *etc.*, and may therefore exhibit different hazard and fate profiles. Whereas the methods and tools for conventional chemicals are in principle suitable for manufactured nanomaterials, the unique physicochemical properties of nanomaterials require that some existing methods have to be adapted, while in other cases new ones must be developed.

The scientific evidence compiled in this special issue clearly shows that reliable methods are already available for many parameters and endpoints. These methods are either validated to be used for regulatory decisions, or at least have some degree of demonstrated reliability and are therefore promising for near-term regulatory use. An overarching conclusion is that hazard, exposure, and risk assessment evaluations of nanomaterials can be extremely complex, time-consuming, costly, and limited in their utility. However, it is not realistic to investigate every nanoform by applying all test methods. Therefore, effective benchmarking methods for the assessment of hazard and exposure/fate, tiered testing and assessment schemes, grouping frameworks, read across and modelling approaches for environmental exposure all play important roles in the regulatory assessment of manufactured nanomaterials. Conclusions on these methods are presented in this special issue.

There are numerous methods that are acceptable or nearing acceptability, for physicochemical characterisation as well as hazard and exposure endpoints relevant to regulatory risk assessment. Many properties that characterise nanomaterials such as surface affinity, ROS generation and dissolution rate depend not only on the substance investigated but also on the surrounding environment (Gao and Lowry, 2018). Such extrinsic properties can be determined by functional assays that estimate the kinetic behaviours of nanomaterials in specific environments. Functional assays are not only relevant for the characterisation of nanomaterials, but may also predict their fate and effects and can thus play an important role as first tiers in testing schemes. Their development, validation and inclusion in regulatory risk assessment frameworks are therefore needed.

Several new OECD test guidelines specific to assessing the environmental fate of nanomaterials, including those for determination of dissolution rate and sludge retention, are almost ready for regulatory use (Baun et al., 2017). The recently adopted OECD test guideline on dispersion stability in environmental media (OECD, 2017a) will aid in the assessment of both environmental fate and in the conduct of aquatic ecotoxicity tests, since these tests are highly dependent on the (homo)agglomeration behaviour of nanomaterials in test solutions. The OECD plans to develop a Guidance Document for tiered testing of environmental fate that is highly needed. Numerous advances in assessing the ecotoxicity of nanomaterials have been made (Hjorth et al., 2017), including a key OECD guidance document on aquatic and sediment toxicity testing that is near to completion.

Mammalian hazard endpoints are often the most involved to address (in terms of time, costs, and animal usage). In particular, subchronic *in vivo* inhalation test protocols are often required, and quite complex. While these *in vivo* protocols to address both subacute and subchronic endpoints for nanomaterials have recently been released by OECD (2017b,c), there is still a pressing need to reduce the frequency with which these tests are

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required. Proposals are now available to reduce the need for *in vivo* subchronic inhalation testing, by supplementing these test results in testing schemes that also employ the findings from short-term *in vivo* tests, additional *in vitro* and historical long-term study results to lessen the need for new subchronic *in vivo* studies (Oberdörster and Kuhlbusch, 2018). The article of Drasler et al. (2017) in this special issue demonstrates how *in vitro* tests can be standardized to meet regulatory requirements, and thus allow linkage with *in vivo* results. It presents recommendations how to conduct *in vitro* tests, thus allowing their findings to be used in more efficient testing and grouping schemes.

In silico methods such as structure-activity relationships show promise for regulatory application (Burello, 2017). However, they still need sufficiently large robust and reliable datasets in order to allow their broader use. A close cooperation between experimentalists, modellers and regulators is strongly recommended to further their use.

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 (Kuhlbusch et al., 2018). For estimating consumer exposure the determination of release from nanoproducts is a crucial step, and advances in simulation methods for releases of nanomaterials from consumer products have recently been achieved. While reliable data on concentrations in environmental media is rare, environmental exposure models currently exist that are well developed and applicable for regulatory purposes (Nowack, 2017). Further development of these models would be aided by better data from studies that measure concentrations, heteroagglomeration, and transformation of nanomaterials in real or simulated environmental media.

Finally, Oomen et al. (2018) review existing risk assessment frameworks and assess their utility when applied to the regulatory assessment of nanomaterials. Current risk assessment frameworks are evolving, and attempt to balance flexibility with assessment of quantitative risks.

The recommendations in this special issue should be taken into consideration by the OECD member states as they continue to develop nanomaterial test guidelines and guidances. These recommendations should also be considered, in conjunction with other key regulatory science policy documents (Gottardo et al., 2017), as the EU continues to amend the nanomaterial-related annexes and guidance documents of REACH. Finally, the gaps that have been identified in this issue, should stimulate regulatory-relevant research by the respective authorities and research programmes in OECD member countries.

This special issue may help to strengthen the dialogue between scientists and regulators and help to establish scientifically sound and cost effective regulatory approaches for nanomaterials. Since nanomaterial structures are becoming increasingly complex the properties of future nanomaterials will be more and more dominated by their functionality. Keeping pace with this scientific and technical progress means that nanosafety research with focus on regulatory application must not reduce its efforts in future (Steinhäuser and Sayre, 2017).

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Klaus Günter Steinhäuser[a], Philip G. Sayre[b], Bernd Nowack[c,*]

[a] *Derfflingerstr. 14, 12249 Berlin, Germany*

[b] *nanoRisk Analytics, LLC, Auburn, CA, USA*

[c] *Empa, Swiss Federal Laboratories for Materials Science and Technology, Technology and Society Laboratory, Lerchenfeldstrasse 5, CH-9014 St. Gallen, Switzerland*

E-mail address: nowack@empa.ch

[*] Corresponding author.