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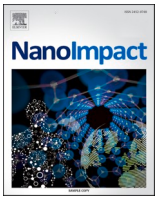

Review article

A roadmap to strengthen standardisation efforts in risk governance of nanotechnology

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ABSTRACT

A roadmap was developed to strengthen standardisation activities for risk governance of nanotechnology. Its baseline is the available standardised and harmonised methods for nanotechnology developed by the International Organization for Standardization (ISO), the European Committee for Standardization (CEN), and the Organisation for Economic Co-operation and Development (OECD). In order to identify improvements and needs for new themes in standardisation work, an analysis of the state-of-the-art concepts and interpretations of risk governance of nanotechnology was performed. Eleven overall areas of action were identified, each including a subset of specific topics. Themes addressed include physical chemical characterisation, assessment of hazard, exposure, risk and socio-economic factors, as well as education & training and social dialogue. This has been visualised in a standardisation roadmap spanning a timeframe of ten years and including key outcomes and highlights of the analysis. Furthermore, the roadmap indicates potential areas of action for harmonisation and standardisation (H&S) for nanomaterials and nanotechnology. It also includes an evaluation of the current level (limited, moderate, intense) of ongoing H&S activities and indicates the time horizon for the different areas of action. As the identified areas differ in their state of development, the number and type of actions varied widely amongst the different actions towards achieving standardisation. Thus, priority areas were also identified. The overall objective of these actions is to strengthen risk governance towards a safe use of nanomaterials and nano-related products. Though not explicitly addressed, risk-based legislation and policies are supported via the proposed H&S actions.

Abbreviations: CEN, European Committee for Standardization; CSS, Chemicals Strategy for Sustainability; EC, European Commission; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; EU, European Union; FAIR, Findable, Accessible, Interoperable and Reusable; Gov4Nano, Implementation of Risk Governance: meeting the needs of nanotechnology; GD, OECD Guidance Document; H&S, Harmonisation and Standardisation; IATAs, Integrated Approaches to Testing and Assessment; ISO, International Organization for Standardization; MAD, Mutual Acceptance of Data; OECD, Organisation for Economic Co-operation and Development; SSbD, Safe and Sustainable by Design; TC, Technical Committee; TG, OECD Test Guideline.

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1. Introduction

1.1. Policy initiatives

The concept of risk governance covers all usual dimensions of risks analysis (identification, assessment, management, evaluation and communication of risks) as well as the way decisions concerning the risks are taken by the different actors involved (researchers, industry, policy makers, regulators, etc.). Risk governance thus helps to better understand and interpret the knowledge needed to properly assess and manage risks arising from the wide-ranging and complex properties and applications of nanotechnology. It requires agreed methodologies for the assessment of various aspects and properties of nanomaterials and nanotechnology.

This paper focusses on standardisation for risk governance of nanotechnology and nanomaterials (nano risk governance) in the European Union (EU) to support related regulatory frameworks, e.g. [European Communities, 2006 and 2009; European Union, 2012 and 2015; European Commission., 2011a]. The aim of the EU Horizon 2020 project *Gov4Nano* (Implementation of Risk Governance: meeting the needs of nanotechnology) was to increase knowledge and to develop frameworks to guide further research related to the different aspects of nano risk governance. This included the development of a roadmap to inform future standardisation work and set priorities for specific topics related to nano risk governance [Gov4Nano D6.10, 2023]. Standardised methodologies, or in short (documentary) "standards", are essential for the harmonisation of procedures and for ensuring the reliability and reproducibility of results and include method performance characteristics and acceptance criteria.

Risk governance of nanotechnology supports the EU policies for sustainability, e.g. [European Commission, 2019a; 2020a; 2020b; 2021]. The Chemicals Strategy for Sustainability (CSS) [European Commission, 2020a] towards a toxic-free environment underlines that sustainability is the ultimate goal of appropriate risk (and innovation) governance of new technologies and products. This includes safety, reuse and recycling, while avoiding chemical properties and volumes that may be harmful to human health or the environment as well as avoiding 'regrettable substitutions'. This is in line with the United Nations Sustainable Development Goals [United Nations]. The EU initiatives are complemented by national initiatives in the member states, e.g. on Perfluoroalkyl and Polyfluoroalkyl Substances (ECHA, PFAS). Also traceability in the Business-to-Business and the Business-to-Consumer value chains will push the development towards risk governance, and may be mandated by legislation (European Union, 2017a). The policy initiatives are backed by methodological approaches and decision support tools, such as Life Cycle Assessment, Life Cycle Cost Analysis (LCCA) and Safe and Sustainable by Design (SSbD) [Caldeira et al., 2022a; European Commission, 2022b], as well as the OECD (Organisation for Economic Co-operation and Development) Safe and Sustainable Innovation Approach [OECD, 2021a; 2022a]. When developing new chemicals, application of SSbD approaches at the design stage (e.g. as part of pro-active risk management) can help to reduce uncertainties and address potential risks at an early stage and throughout their life cycle [European Commission, 2020a]. For chemicals already on the market, the application of SSbD might indicate whether their safety and sustainability could be improved. SSbD needs to be underpinned by agreed methods and standards.

In line with the CSS [European Commission, 2020a], the aim for chemicals, including nanomaterials, is that they are SSbD. As part of the CSS, the EC published a Strategic Research and Innovation Plan for Safe and Sustainable Chemicals and Materials [European Commission, 2022a]. It predicts future needs for toxicity and eco-toxicity testing, for release and exposure assessment, for risk management measures and other assessment tools. In addition, it predicts a need for FAIR (Findable, Accessible, Interoperable and Reusable) data and databases, cost-benefit analysis, education, monitoring, indicators etc. The CSS should promote the use of one coherent framework for SSbD chemicals across different stakeholders, e.g. industry and policy makers. The EC proposed and adopted a framework [Caldeira et al., 2022a; Caldeira et al., 2022b; European Commission, 2022b] that addresses the safety and sustainability of chemicals throughout their entire life cycle.

For substances and materials *nanoscale* generally refers to the size range of 1 nm to 100 nm. Nanotechnology is viewed as an "enabling" technology with applications in almost all manufacturing sectors, e.g. chemicals, materials, electronics, energy, medicine, and transportation. Exploiting the potential benefits of nanotechnology requires that potential risks are taken into consideration, and that safety is assured through appropriate risk governance actions. Nanotechnology is an evolving field, and in 2006 the International Risk Governance Council proposed that nanomaterials and nanotechnologies would develop in a number of increasingly sophisticated and overlapping generations, reflecting convergence of different science and engineering disciplines [Roco, 2018; ECHA, 2019]. This evolution creates a need for (new) assessment tools, including validated analytical methods, that can address the increasingly complex and changing physical and chemical properties and possible (eco)toxicological effects of nanomaterials.

In the EU, nanomaterials are covered by legislation addressing chemicals, e.g. REACH [European Communities, 2006]. A regulatory definition of 'nanomaterial' makes their identification and assessment more straightforward. The European Commission (EC) published a Recommendation on the definition of nanomaterial in 2011 [European Commission, 2011b], which has been taken up by e.g. REACH [European Communities, 2006], the Biocidal Products Regulation [European Union, 2012], the Medical Devices Regulation [European Union, 2017b], and In Vitro Diagnostic Medical Devices [European Union, 2017c], whereas the Cosmetic Products Regulation [European Communities, 2009], Novel Foods [European Union, 2015] and Food Information to Consumers [European Commission, 2011a] have their own definitions. The Recommendation was updated in 2022 [European Commission., 2022c] and is expected to be taken up by all EU legislation, thus further harmonising the regulatory definition of nanomaterial across EU legislation. REACH uses the term 'nanoform' (of a substance) [European Commission., 2018] and one substance may have several nanoforms that differ for example in particle size distribution or crystal structure.

OECD Test Guidelines (TGs) are crucial to regulatory testing of chemicals including nanomaterials, as they are covered by the OECD agreement of Mutual Acceptance of Data (MAD) [OECD, 1981]. This stipulates that if a test is conducted following an OECD TG, and according to Good Laboratory Practice, the test data are acceptable in countries adhering to MAD. MAD is a key component for international harmonisation of approaches to chemical safety, and it is of utmost importance that TGs for testing are available that cover all regulatory relevant properties of chemicals, including nanomaterials. Risk is identified by combining the known hazardous properties with exposure. The on member countries legally binding OECD Council Recommendation [OECD, 1981] states [that]…. *Members, to manage the risks of manufactured nanomaterials, apply the existing international and national chemical regulatory frameworks or other management systems, adapted to take into account the specific properties of manufactured nanomaterials*…, The ability to assess the hazards and exposure through agreed methods adapted to nanomaterials is thus fundamental for nano risk governance. Early on, the OECD Working Party on Manufactured Nanomaterials reviewed the OECD TGs for their applicability to nanomaterials [OECD, 2009], which led to gradual revision of these TGs to adapt some of them to testing nanomaterials, while also new TGs were developed specifically for testing nanomaterials. Some European countries later kickstarted the Malta Initiative [The Malta Initiative] that supports the further development of TGs for nanomaterials. S1 provides an overview of TGs, as well as OECD Guidance Documents, that have been, or are being, amended, or drafted, to cater for nanomaterials.

The identification and assessment of more elaborate nanomaterials,

such as multicomponent (advanced) materials and 'smart' nanomaterials [Gottardo et al., 2021], is complicated. Consequently, their status under legislation is complicated as well. A study by the European Chemicals Agency (ECHA) [ECHA, 2019] noted that, occasionally, it is unclear which of the REACH terms *substance*, *mixture* or *article*[1] is the best fit for such elaborate materials. Moreover, boundaries between different materials are not always clear, which may create legal ambiguity.

While recognising their importance, medicinal products, including nanomedicines, are regulated very differently from chemical substances, leading to different information needs and procedures. They are thus not included in the standardisation roadmap presented here. Similarly, advanced materials, which is a broader group of materials than nanomaterials, are only addressed in the roadmap in the context of nanomaterials and nanotechnology, in line with the OECD working description of Advanced Materials [OECD, 2022b]. Furthermore, the standardisation bodies often develop separate standards for individual materials, specific methods and/or instrumentation. The need for such specialised standards will not be addressed here.

Policies and legislation for nano risk governance are important, but are not explicitly included in the roadmap. The focus was on technical scientific standardisation and harmonisation. Nevertheless, contribute towards supporting and improving risk-based legislation and policies.

The Gov4Nano Risk Governance Framework [OECD, 2022b] outlines risk governance themes for nanotechnology which reflect traditional hazard- and exposure-based risk assessment of a substance. The themes furthermore emphasise risks along the complete life cycle of a (complex) material from its production to end-of-life (waste), as well as additional areas such as education and communication. The availability of methods to address each theme should be evaluated, as should the extent to which additional standardised tools and methodologies are needed. Additionally, the design of the roadmap reflects the policy elements, such as the CSS and SSbD, and gaps identified elsewhere, e.g. via the Malta Initiative [The Malta Initiative]. The additional needs are described below, after an outline of the already available standards.

Hence, this paper identifies priority areas of nano risk governance for which additional standardisation and harmonisation could be relevant. It presents a roadmap that refers to the Baseline (as per May 2023) presented in the Supplementary Information S1.

1.2. Background information for preparing the roadmap

At the conceptual level, Kraegeloh et al. [2018] identified the need for a new pro-active approach for nanotechnology governance. The approach combines Safe-by-Design with Trusted Environments to achieve pre-regulatory safety assessment including a dialogue between stakeholders, e.g. regulators and industry. Its basis includes a centralised inventory of tools and methods for nanomaterial characterisation, safety and sustainability assessment. The vision is that by increasing the transparency of the overall process the public's trust will increase. The authors suggested introducing a marketing approach such as a "Safe-by-Design label", which would require standardisation of approaches to Safe-by-Design, allowing to refer to the same issues and follow the same approach. The further evolution of this subject includes development into a safe innovation approach. Soeteman-Hernandez et al. [2019b and 2021] analysed how to address the innovation processes through a safe innovation approach that additionally includes regulatory preparedness.

Two European projects, NanoStreeM [NANOmaterials] and caLIBRAte [caLIBRAte], held a joint workshop on governance of emerging nanotechnology risks in the semiconductor industry [Watjanatepin et al., 2020]. It concluded that promoting an open culture of communication of identified hazards, exposures and risks is very important to maximise the potential of nanomaterials. Some of the key challenges and data gaps identified were the lack of reliable data on nanoform toxicity, release and exposure. This leads to uncertainty in legislation that has a direct cost and impact on human health and the environment. It was noted that the acceptable level of uncertainty should be identified.

At the operational level, an overview of documentary standards relevant nanomaterials and published or under development until May 2023 was generated as the baseline for the roadmap. Supplementary Information S1 lists these standards. They are published by the European Committee for Standardization (CEN) and the International Organization for Standardization (ISO). Though understanding matter and processes at the nanoscale, i.e. approximately 1 nm to 100 nm, in one or more dimensions, CEN/TC (Technical Committee) 352 [CEN] and ISO/TC 229 [ISO] (both "Nanotechnologies") develop standards for nanotechnology on terminology and nomenclature, metrology and instrumentation (including specifications for reference materials) test methodologies, modelling and simulations, and science-based health, safety, and environmental practices. Relevant standards from other TCs are also listed, e.g. from CEN/TC 195 (Air filters for general air cleaning), CEN/TC 137 (Assessment of workplace exposure), and ISO/TC 24 Sub-Committee 4 (on Particle Characterisation). Regulatory test guidelines (TGs) and guidance documents (GDs) by the Organisation for Economic Co-operation and Development (OECD) are also included in this overview [OECD, 2023]. The EU Member States work together via Malta Initiative to find possibilities for developing and amending TGs for nanomaterials.

In addition to the Baseline (S1) that informs on available standards, several outcomes of Gov4Nano point towards additional themes for standardisation and harmonisation that are relevant for developing a standardisation roadmap. Amongst these are a series of analyses and stakeholder consultations performed to capture the most significant risk governance elements. Thus, as one of its activities, Gov4Nano performed an analysis of important topics [Gov4Nano D6.2, 2020], and descriptions of harmonisation of tools, frameworks, methods, guidance documents for risk management and exposure assessment [Gov4Nano D 4.1, 2020; D 5.3, 2020]. The project provided an overview [Gov4Nano, D 4.1, 2020] of existing and near-future next generation tools and models to support the "house for risk governance" and industrial safer-by-design, as well as the availability of harmonised test methods (OECD TGs) [Gov4Nano D2.3, 2022]. It provided an overview [Gov4Nano D4.2, 2020] of stakeholder views on, and needs for, support tools for safer-by-design and nano risk governance.

Furthermore, Gov4Nano provided an overview of topics considered important for legislation and policies that are based on risk evaluation as well as of existing challenges and stakeholder views [Gov4Nano, D6.2, 2020]. Moreover, Gov4Nano developed the TRAAC (Transparency, Reliability, Accessibility, Applicability and Completeness) framework that addresses regulatory acceptance and wider usability of tools and methods for safe innovation and sustainability of nanomaterials [Shandilya et al., 2023]. The aim was to quantify the readiness of different tools and methods towards their wider regulatory acceptance and downstream use by different stakeholders. Furthermore, two trans-Regulatory Risk Assessment Summits [Gov4Nano D 5.3, 2020] were held. The first one provided insights into regulatory risk assessment and identified gaps. This led to a list of research questions at the process, content and organisational structure levels from which the appropriate conclusions were drawn, supporting recommendations from the ProSafe White Paper [ProSafe White Paper, 2017]. The second trans-Regulatory Risk Assessment Summit [Gov4Nano D5.9, 2022] discussed

[1] REACH (see reference 1), Article 3. Definitions*1.* ***substance****: means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition; 2.* ***mixture****: means a mixture or solution composed of two or more substances;3.* ***article****: means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition;*

nanospecific implications of the CSS [European Commission, 2020a], resulting in an inventory of regulatory issues and research questions covering some of the CSS aims.

Additionally, other sources and projects also presented areas for standardisation and harmonisation. The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has given opinions on nanotechnology [SCENIHR, 2006, 2007a, 2007b, 2009] and some of the issues still remain, such as the most relevant dose metrics for nanomaterials, a need for validated in vitro assays for evaluation of nanoparticles, and further development of the methodology for both exposure estimation and hazard identification.

Based on the outcomes of the OECD Testing and Assessment programme [Rasmussen et al., 2016, 2018, 2019] needs for specific OECD TGs or OECD GDs for testing nanomaterials were identified, and many of these needs have been or are being addressed. Remaining areas include additional guidance for sample preparation and dispersion (including stability) in appropriate media. NanoDefine [NanoDefine] developed a series of Standard Operating Procedures for dispersing each nanomaterial tested in the project. Previous projects [e.g. Nanogenotox, 2011; NIST; Prospect, 2010] have also worked towards developing dispersion protocols. Compiling such different protocols in one document has clear benefits towards harmonising procedures and test methods.

A study analysed EU legislation addressing chemicals [Bleeker et al., 2023] to identify scientific issues that might still need to be resolved for nanotechnology to address gaps in the availability of methods for regulatory information requirements. The study highlighted overarching issues relevant for multiple information requirements and across several regulatory areas, noting that i) issues remain for nanomaterial dispersion stability and dosing in toxicity testing, ii) additional tests or guidance for organic nanomaterials or nanomaterials with organic components on nanomaterial degradation and transformation is needed and iii) additional tests and guidance is needed to measure (a)cellular reactivity of nanomaterials. Throughout this analysis, the need to develop in vitro methods and confirm their validity, is a recurring theme. The supplementary information in [Bleeker et al., 2023] provided an endpoint-by-endpoint overview of regulatory information requirements across EU chemicals legislation and the possible need for developing nanospecific methods.

The above information and actions led to the identification of a number of areas for standardisation, including a list of relevant topics for future standardisation work, see Fig. 1.

2. The roadmap structure

From the Baseline (S1) as well as outcomes of Gov4Nano activities and other research projects outlined above, it was evident that the information could be grouped into subject areas, see Fig. 1. Current standardisation efforts for nano risk governance mainly concern risk assessment and risk management. The need for additional nano-relevant regulatory test methods was identified through analysis of regulatory data requirements for nanomaterials [Bleeker et al., 2023]. Other aspects of nano risk governance, e.g. concern & risk profile, risk evaluation & decision making, monitoring & implementation, and connecting & engaging stakeholders are covered to a much lesser extent by current standardisation and harmonisation work, and so is education on the different aspects of nano risk governance. Also methods for regulatory preparedness [Soeteman-Hernandez et al., 2019a; Jantunen et al., 2018], which requires knowledge of upcoming technologies combined with future-proof methods for assessing these technologies, could be standardised. The achievement of Regulatory Preparedness is based on information in form of for example exchanges with all stakeholders, knowledge platforms, horizon scans and foresight studies, and for all of these procedures, i.e. standards, can be developed. Often the information and tools are scattered, i.e. not collected in one or only a few information points and hence more difficult to identify.

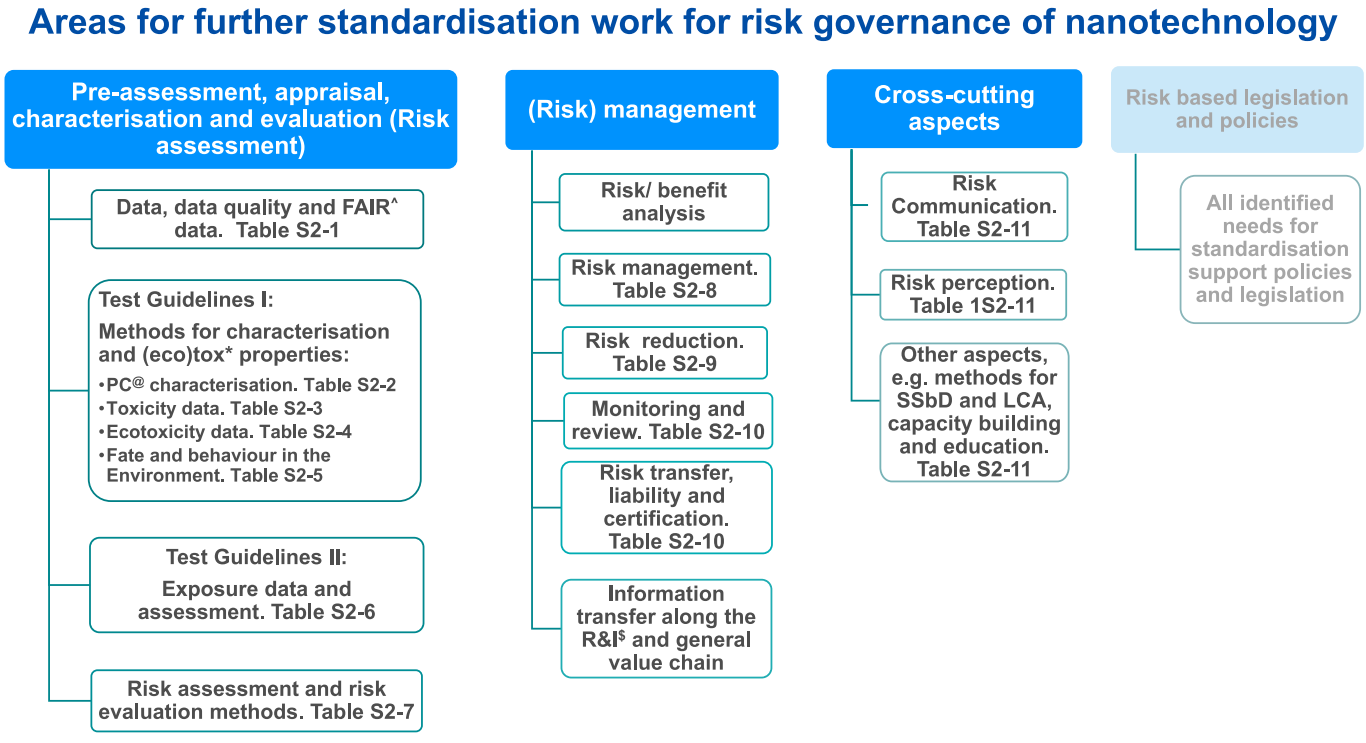

Fig. 1. Overview of areas for further standardisation for risk governance of nanotechnology. Details of identified possibilities for standardisation and harmonisation for each area are provided in the Supplementary Information S2. Standardisation for *Risk based Legislation and Policies* is not explicitly addressed in the paper, hence the fainter colouring. (^FAIR: Findable, Accessible, Interoperable and Reusable. @PC: physical chemical; *(eco)tox: toxicological and ecotoxicological; $R&I: research and Innovation)

This led to the development of a set of risk governance areas themes and topics for future standardisation and harmonisation work. Table 1 lists these areas, which are described in detail in Tables S2–1 to S2–11 in the Supplementary Information S2. The tables in S2 provide overviews of the identified standardisation needs for each area (Fig. 2). The needs are mentioned only once in these tables, though methods may be important for more than one area.

3. The standardisation areas of the roadmap

3.1. Area 1: data, data quality and FAIR Data

Data quality [Comandella et al., 2020] and the availability of FAIR data [Wilkinson et al., 2016] are a priority. The reuse of data under the FAIR data approach is an important means to avoid duplication of testing, while still improving the reliability of risk assessment and management practices. A system for persistent identifiers of (different forms of) nanomaterials should be developed as one substance may exist in several nanoforms. For any data generated for risk governance purposes, data and data quality need to be agreed for testing, and harmonised, detailed reporting templates, suitable to the kind of data generated, are relevant for recording the data. FAIR data require the association of metadata that render the data re-useable in other contexts. Criteria, databases and infrastructures towards FAIR environment, health and safety data to support risk assessment are being developed [Jeliazkova et al., 2021; Haase and Klaessig, 2017]. Data curation is an essential aspect to ensure quality of data [Marchese Robinson et al., 2016]. For example, risk assessment models can work properly only when input data are of relevant quality. Table S2–1 provides an overview items that could be standardised and harmonised to achieve FAIR data.

3.2. Area 2: characterising physical chemical properties of nanomaterials

Appropriate methods and guidance are needed for detecting and identifying nanomaterials, see e.g. [Bleeker et al., 2023; Rasmussen et al., 2018] in all types of media, including tissues. For nanomaterial characterisation, a first step is to understand the method(s) needed to appropriately measure each relevant physical chemical end-point. In a second step the characterisation procedure, including sample preparation protocols and the best way to perform measurements, would need to be standardised to ensure that the method delivers FAIR characterisation data.

Table 1
Overview of tables in Supplementary Information S2. S2 provides details of the roadmap.

Risk governance macro areas (Fig. 1)	Supplementary Information – S2: Tables Presenting an Overview of Identified risk governance areas that could be Standardised and/or Harmonised
Pre-assessment	Area table S2–1: data, data quality and FAIR data. Area table S2–2: characterising physical chemical properties of nanomaterials. Area Table S2-3: identifying the toxicological properties of nanomaterials.
Risk assessment	Area table S2–4: identifying the eco-toxicological properties of nanomaterials. Area table S2–5: identifying the environmental fate and behaviour of nanomaterials. Area Table S2-6: exposure to products of nanotechnology.
Risk evaluation and management, decision making	Area table S2–7: risk assessment and risk evaluation. Area table S2–8: risk management. Area table S2–9: risk reduction. Area Table S2-10: risk monitoring and review, transfer and liability.
Concerns and risk profiles, monitoring and implementation, communication	Area Table S2-11: other (cross-cutting) areas of possible standardisation and harmonisation.

For several characterisation methods for various physical chemical properties, Radnik et al. [2022] provided an overview of the type of sample preparation that is needed/relevant for the different analytical methods, also depending on the specific form of material (e.g. powder, suspension, aerosol, prepared on a substrate or embedded in a matrix). Validated procedures could be needed for these sample preparation methods.

Furthermore, agreement on parameters as well as methods to be used for determining the equivalence of nanomaterials are needed, e.g. to allow grouping of similar nanomaterials. Additionally, methods for determining the stability of nanomaterials in relevant media are needed, including methods for determining the identity of relevant degradation products, and the dissociation constant. Methods for determining oxidising properties and zeta potential are also needed.

The OECD adopted Test Guideline 125 [OECD, 2022c] that explains how to measure particle size and size distribution of nanomaterials which is the fundamental step to understand if the material at hand is indeed a nanomaterial. TG 125 does not explain which particles to count and how to count them. As this can be a complicated matter [Bresch et al., 2022], guidance is needed.

In addition to intrinsic properties, such as chemical composition, the physical-chemical characterisation of nanomaterials should also include extrinsic properties, e.g. agglomeration / aggregation. These are properties that depend on the environment to which the nanomaterial is exposed (e.g. the dispersion medium). Table S2–2 provides further details on identified standardisation and harmonisation needs for characterising physical chemical properties of nanomaterials.

In a wider context than the regulatory one, a need for additional standardisation of measurement methods has been identified, e.g. for specific properties of individual nanomaterials such as silicon dioxide.

3.3. Area 3 and area 4: identifying the (eco)toxicological properties of nanomaterials

For the determination of inherent (eco)toxicological properties of nanomaterials, and especially for hazard identification, several needs for standardisation and harmonisation have been identified so that regulatory data requirements can be addressed, see e.g. Bleeker et al. [2023].

For the generation of toxicological data, the identified needs for validated and reproducible methods can be further divided into in vitro methods, other non-animal methods, and in vivo methods. Additionally, the dosimetry needs to be further clarified, as the classical dose metric (e.g. mg test substance per kg test animal) might not be the best to reflect a nanomaterial dose [SCENIHR, 2007b]. Guidance is needed for nanomaterial dispersion stability. Dosing in toxicity testing should be developed, including strategies to select testing doses for in vitro testing. In general, for in vitro tests the applicability of existing methods to nanomaterials needs to be confirmed, and the same is the case for (quantitative) structure activity relationships (SARs and QSARs). It should be noted that some of the methodological needs for nanomaterials are also relevant for general chemicals. For instance there is no in vitro method for carcinogenicity testing, and in vitro – in vivo data extrapolation is not yet completely understood.

Additionally, the development of intelligent testing strategies is needed [Stone et al., 2014], e.g. via integrated approaches to testing and assessment (IATAs). The OECD has recommended approaches to the design of IATAs [OECD, 2018]. Such IATAs provide structured strategies for collecting the required evidence through identification and description of the most appropriate data sources, models and test methods currently available for each endpoint. The development of general IATAs is one element in promoting alternative testing.

Table S2-3 gives an overview of issues that would be relevant to

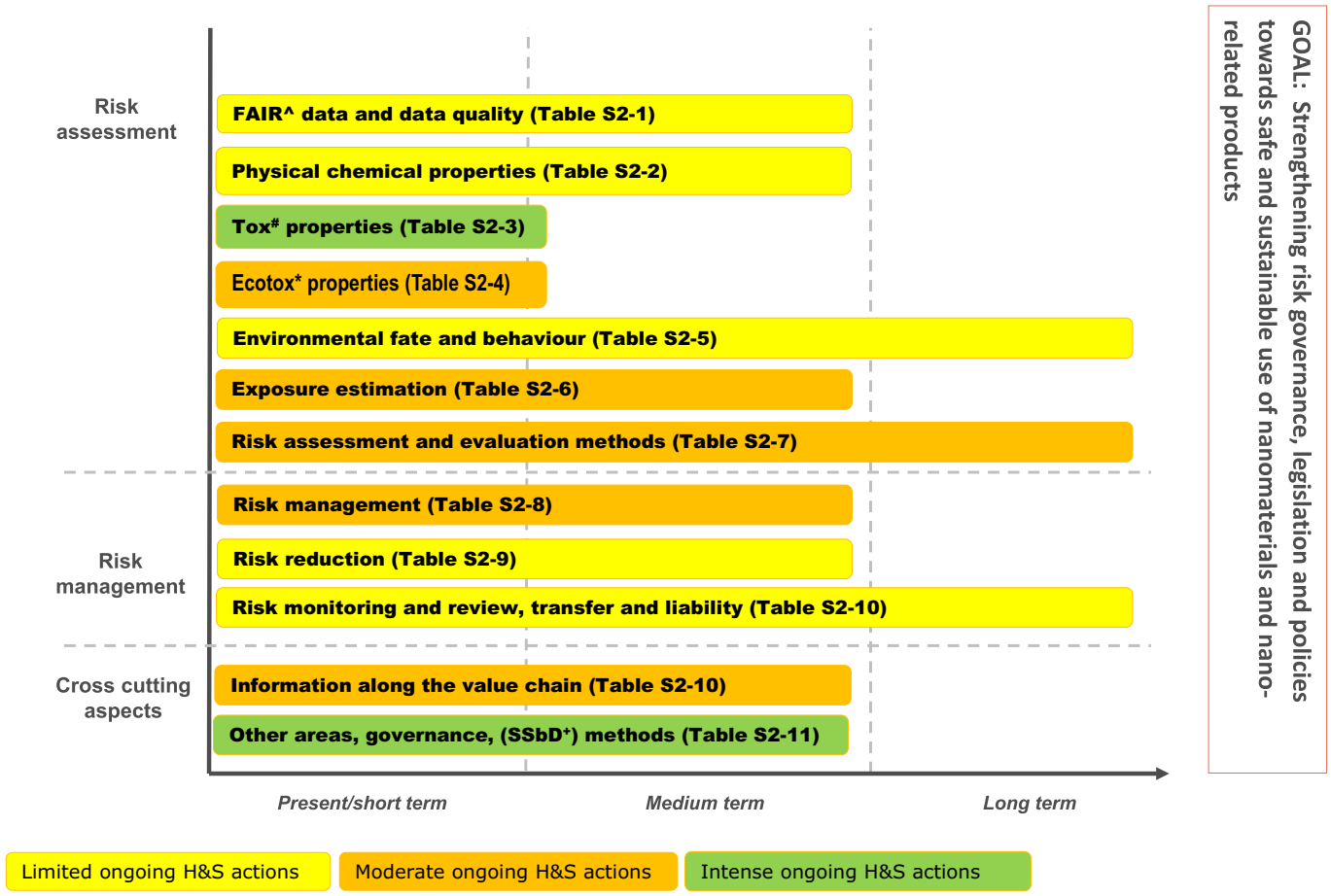

Fig. 2. Harmonisation and Standardisation roadmap for nanotechnology risk governance. (^FAIR: findable, accessible, interoperable, re-usable; #Tox: toxicological; *Ecotox: ecotoxicological; +SSbD: safe and sustainable by design; H&S: Harmonisation and Standardisation) Print information: Fig. 2 should be printed in colour.

address for toxicology. Addressing these issues includes development of both regulatory test guidelines and documentary standards.

Elements and issues that could be standardised and harmonised for eco-toxicology are listed in Table S2–4. Steinhäuser and Sayre [2017] give a summary of the best available characterisation methods. These are further detailed in Gao and Lowry [2018] who also provide key insights into characterising nanomaterials in environmental or biological media. In 2020, the OECD published GD no. 317 on Aquatic Toxicity Testing of Nanomaterials [OECD, 2022d], which currently is being further refined. The main message in GD 317 is that stability and control of exposure concentrations need to be carefully addressed in the testing of nanomaterials. GD 317 notes that interactions with environmental components and feed, as well as determining concentrations in biological and environmental media may pose challenges to the current methodologies. For the testing of invertebrate eco-toxicity, the testing of plants and algae potentially require further methods development, as does testing of microbial toxicity. In addition, the methods for long-term toxicity in birds and mammals might requires further development of methods.

3.4. Area 5: identifying the environmental fate and behaviour of nanomaterials

In many cases the standardisation needs relate to stability and control of exposure concentrations, although interactions with environmental components and feed as well as determining concentrations in biological and environmental media may pose further challenges to the current methodologies.

Specifically for determining environmental fate, Baun et al. [2017] provided an overview of regulatory relevant methods. The methods for testing (a)biotic degradation require further development, as do the methods for determining environmental fate and behaviour. Table S2–5 provides information on identified needs for standardisation and harmonisation that relate to identifying the environmental fate and behaviour of nanomaterials.

3.5. Area 6: exposure to products of nanotechnology

In order to evaluate the possible human health and environmental risks of a nanomaterial, exposure information is needed on environmental and human. This includes exposures in occupational settings, and for consumers/the general public (e.g. from consumer products and through the environment). Reliable methods for exposure estimation are essential. For human health risk assessment, the translation from external exposure levels to internal doses within the human body is essential. Some work on assessing exposure to nanomaterials has been done, e.g. [OECD, 2021b, 2021c, 2021d, 2021e; Ramos and Almeida, 2022], and Table S2-6 gives an overview of aspects of exposure for which standardisation would be beneficial for nano risk governance.

3.6. Area 7: risk assessment and risk evaluation

Risk assessment combines the hazard and exposure data, and an agreed (i.e. harmonised and standardised) methodology reduces the uncertainty and ensures more comparable outcomes. Comprehensive guidance on chemical risk assessment has been published e.g. by ECHA [ECHA] and by EFSA (European Food Safety Authority) [EFSA]. The OECD Council Recommendation [OECD, 1981] concluded that such

guidance is also applicable to nanomaterials but might have to be fine-tuned to them.

Table S2-6 outlines standardisation and harmonisation themes potentially to be addressed for risk assessment of nanomaterials and nanotechnology. No standardisation and harmonisation is proposed for nanospecific assessment (extrapolation) factors, as EFSA's Scientific Committee concluded that the scientific literature does not indicate a need for different assessment/uncertainty factors for nanomaterials [EFSA, 2021].

3.7. Area 8 and 9: risk management and risk reduction

In order to manage identified risks, the fundament for understanding and assessing risks is indispensable. Thus the completeness of methods for physical chemical characterisation, hazard assessment, exposure assessment, grouping etc. is of paramount importance. Hazards are inherent properties, and thus they cannot be modified, but must be eliminated (e.g. by substituting the nanomaterial used) or contained by minimising the exposure (e.g. by coating the material, or encasing the process).

The risk management is based on a structured approach that is supported by standardised methods. For occupational and consumer safety, possible hazards are identified, the likely exposure is evaluated and afterwards risks are identified. Then a plan is developed to either eliminate the risks or control them. A level of acceptable risk needs to be established and any remaining risk needs to be communicated to the relevant audience. For chemicals, the OECD (2022e) provided an overview of risk management methods currently in use by governments. The European Agency for the Safety and Health at Work has published guidance [European Commission, 2019b] for managing potential risks from nanomaterials at work. Table S2–8 outlines possibilities for standardisation and harmonisation for risk management, including risk reduction. Table S2–9 presents topics for risk prevention and cost-benefit analysis relevant to standardisation and harmonisation.

3.8. Area 10: Risk monitoring and review, transfer and liability

The monitoring and review of identified risks need standardised and harmonised methods as well, for example for traceability, certification, needs for insurance, or approaches to nano-enabled product recalls (e.g. due to outcomes of novel research on hazard). In addition, guidance on monitoring for environmental and health risk management may be needed.

Table S2-10 gives an overview of the identified needs for standardisation and harmonisation in the context of risk monitoring and review, transfer and liability.

3.9. Area 11: other (cross-cutting) areas of possible standardisation and harmonisation

Risk governance applies the principles of good governance to the identification, assessment, management and communication of risks, partly covered in the sections above. Cross-cutting aspects are outlined below.

Risk communication between the different actors along the value chain is a complex process which should include expert analysis to cover all potential problems. Traditional empirical approaches may communicate the wrong conclusions to the public [Critchley, 2018], since nanomaterials challenge basic toxicology rules. For example the key parameters to best describe toxicity for nanomaterial are still to be agreed upon, i.e. particle surface or number of particles versus the use of mass in traditional toxicology. Robust approaches to communicate risk aspects to the public may need to be developed to avoid misunderstandings and loss of business opportunities since public risk perception is key to business success. Communication of risks should be integrated early in risk management processes and communicated to stakeholders, including the general public, in good time. Risk communication may benefit from an authoritative source of information with centralised data accessible to stakeholders, including consumers. Parts of the risk communication has already been addressed by the inclusion of nanospecific information requirements in Safety Data Sheets [European Union., 2020]. Other communication tools may include specific liaison programs (regulators-industry) and Points of Contact for discussion. Researchers should engage all stakeholders early in the process, so that research activities can be tailored to making informed decisions.

Additional areas that could be standardised and harmonised for nanomaterials and nanotechnology include life cycle aspects, methods for "safe and sustainable by design (SSbD)", methods for ensuring product safety of nano-enabled products, material specification and performance, waste management, governance, risk acceptance/perception, communication and education.

Table S2-11 presents an overview of the identified additional cross-cutting areas for harmonisation and standardisation.

4. Harmonisation and standardisation roadmap: Evaluation, conclusions and future steps

We have looked at nanotechnology through the lens of risk governance, with the aim to provide a more holistic approach to risk analysis. This approach seeks to integrate the traditional risk assessment paradigm, which assesses risk by combining hazard and exposure information, with other aspects that affect the way different stakeholders identify, assess and take decisions on risks. We used this lens to identify needs for additional harmonisation and standardisation activities for nanotechnology, compared to the currently available standards in this field (see Supplementary Information S1).

Based on the analysis outlined above, a roadmap was designed to visualise potential areas of action in the coming decade for harmonisation and standardisation (H&S) for nanomaterials and nano-related products (Fig. 2). It should be noted that some of the identified needs for standardisation and harmonisation for nano risk governance are yet unaddressed for chemicals (e.g. parts of the in vitro methods). Thus when embarking on methods development for nanotechnology, the greater chemicals picture should also be taken into account.

The roadmap (Fig. 2) summarises the areas of action for H&S as listed in Tables S2–1 to S2–11 in the Supplementary Information S2, where details are found. The roadmap includes an evaluation of the current level of ongoing H&S activities from relevant bodies (limited, moderate, intense) and an indication of the time horizon to consider to address these areas of action. These time horizons vary from short (1 to 5 years), to medium (5 to 10 years), or long-term (more than 10 years). Given the differences in state of development between these identified areas, the number and type of actions varied widely amongst actions to achieving standardisation. Thus, priority areas were also identified. The ambition of these actions is to strengthen risk governance towards a safe and sustainable use of nanomaterials and products containing nanomaterials. Nano risk governance also comprises legislative aspects, and though not addressed explicitly, the proposed actions facilitate implementation of existing legislation and policies. As such, the standardisation areas addressed by the roadmap could impact many different regulatory frameworks in Europe, including both horizontal legislation (e.g. chemicals [European Communities, 2006], safety and health at work [European Council, 1989.], consumer protection [e.g. European Commission, 2011a]), and vertical legislation (e.g. biocidal products [European Union, 2012], cosmetic products [European Communities, 2009.], food and feed [e.g. European Union, 2015], medical devices [European Union, 2017b; European Union, 2017c]).

The outcomes are summarised below:

Pre-assessment, appraisal, characterisation, and evaluation (risk assessment)

- Data quality (Table S2–1): description, curation and FAIR data: *limited H&S actions, short to medium term priority*
- Physical-chemical properties (Table S2–2): Identification and physical chemical properties: *intense H&S actions, short term priority*
- Toxicological properties (Table S2-3): screening, alternative testing, toxicokinetics, testing guidance: *intense H&S actions, medium to long term priority*
- Ecotoxicological properties (Table S2–4): environmentally sound use, long term toxicity, (a)biotic degradation in different media, combinatory and grouping approaches: *moderate H&S actions, medium to long term priority*
- Environmental fate and behaviour (Table S2–5): sound use, characterisation and measurement methods, traceability for use in LCA and waste management: *limited H&S actions, medium to long term priority*
- Product exposure estimations (Table S2-6): sampling, release testing, read-across of exposure measurement, modelling, exposure scenarios for humans (workers and consumers) and the environment: *moderate H&S actions, short to medium term priority*
- Risk assessment and evaluation methods (Table S2–7), methods development e.g. grouping and dose response models: *moderate H&S actions, medium to long term priority*

Risk management

- Risk management controls (Table S2–8): sampling, engineering and administrative controls, modelling, risk acceptance: *moderate H&S actions, short to medium term priority*
- Risk reduction (Table S2–9): prevention, reduction, costs/risk/benefit analysis: *limited H&S actions, medium term priority*
- Risk monitoring and review, transfer and liability (TS2–10) *limited H&S actions, long term priority*

Cross-cutting:

- Information along the value chain, starting by the raw materials, and including (nano)material processing until end-of-life (Table S2-11): material and product specification: *moderate H&S actions, short to medium term priority*
- Governance, safe and sustainable by design (SSbD) methods and LCA (Table S2-11): *intense H&S actions, short to medium term priority*

The standardisation overview presented here is meant as a guide for practitioners and decision-makers in selecting the most pressing and relevant needs for their specific context and sector of work. This should gradually address the standardisation and harmonisation needs.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

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CRediT authorship contribution statement

Kirsten Rasmussen: Writing – original draft, Validation, Investigation, Formal analysis, Conceptualization. **Eric A.J. Bleeker:** Writing – review & editing, Validation, Investigation, Conceptualization. **James Baker:** Writing – review & editing, Project administration. **Jacques Bouillard:** Writing – review & editing, Validation. **Wouter Fransman:** Writing – review & editing, Validation, Investigation, Conceptualization. **Thomas A.J. Kuhlbusch:** Writing – review & editing, Validation, Investigation. **Susanne Resch:** Writing – review & editing, Validation. **Jacques-Aurélien Sergent:** Writing – review & editing, Validation. **Lya G. Soeteman-Hernandez:** Writing – review & editing, Validation, Investigation. **Blanca Suarez-Merino:** Writing – review & editing, Validation. **Andrea Porcari:** Writing – review & editing, Visualization, Validation, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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