Deliverable D5.3 - Report on Regulatory Road- and Research-Map –

executive summary of the deliverable (interim version)

Introduction

For more than 10 years, nanomaterials have been a challenging issue for regulatory risk assessors. Regulators, while still facing uncertainties and challenges concerning a group of widely applied legacy materials[1], need to get prepared for an increasing number of multi-component and more complex nanomaterials, posing novel and different regulatory issues. Unlike the systems in place for development and follow-up of research roadmaps for nanotechnology, there is no structural or transregulatory approach to develop a comparable research roadmap in support of *risk* governance of nanotechnology. This is a remarkable omission as sound risk governance such as regulation and standardisation determine market introduction and acceptance of innovative nanotechnology products. In this deliverable "Report on Regulatory Road- and Research-Map" a six-step approach is proposed to address this omission. Part of the approach has been put into practice by identifying the most pressing transregulatory research issues.

Background

In Europe, research agendas for nanotechnology are generally prepared by European Technology Platforms (ETPs). These ETPs were the first type of public-private partnerships where industry-led stakeholders' define and implement a strategic research agenda (SRA) aiming at aligning research priorities in a technological area. SRAs often lack awareness of regulatory risk assessment issues. The EU NanoSafetyCluster was formed but, only being an informal platform for nanosafety research, missed the essentials for a structural approach to develop their own SRA on regular basis.

As nanotechnology has reached the point of widespread market penetration, the need for supportive regulations, test guidance and guidelines is evident. Risk assessors and risk managers, within both regulatory and inspection bodies, struggle to gain an overview of the scientific knowledge necessary for evidence based decisions on risk assessment. This is caused by a variety of factors, including:

- Lack of systematic inventarisation of scientific needs for regulatory science development
- Limited connection between the developments of regulatory science and activities of funding and innovation agencies

Knowledge relevant for risk assessment is scattered, and fragmented across a multitude of regulatory domains or is missing. These gaps sometimes require exploratory research of a more fundamental nature where in other cases research in support of validation and standardisation is needed. This whole range of research topics requires structured inventarisations, transdisciplinary collaborations and involvement of (regulatory) risk assessors and scientists.

Work performed

The figure below depicts the work performed to develop a six-step approach and bring the first steps to practice. It illustrates the need for a further iterative process embedded in activities regarding design of the NRGC activities, stakeholder engagement and development of monitoring schemes. This report should therefore be seen as an interim report, an update will be delivered ultimately by M42.

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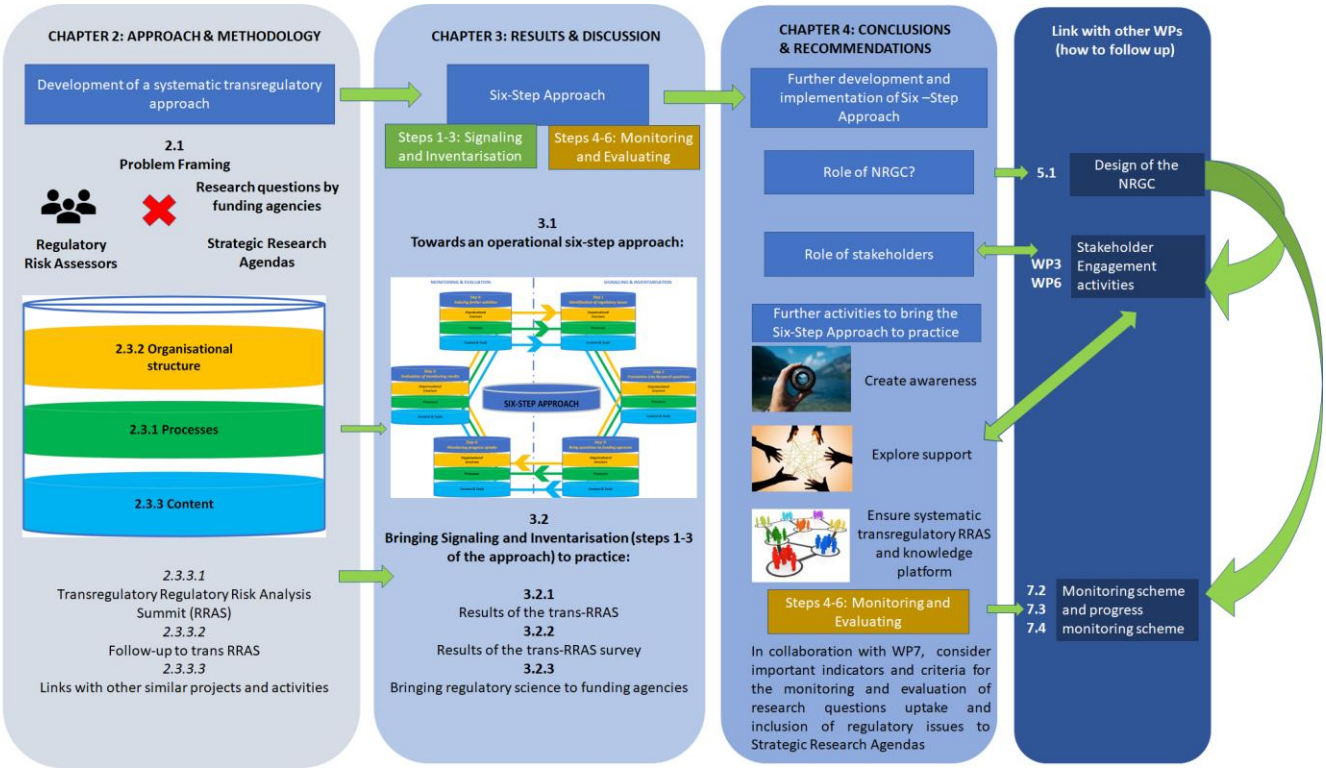
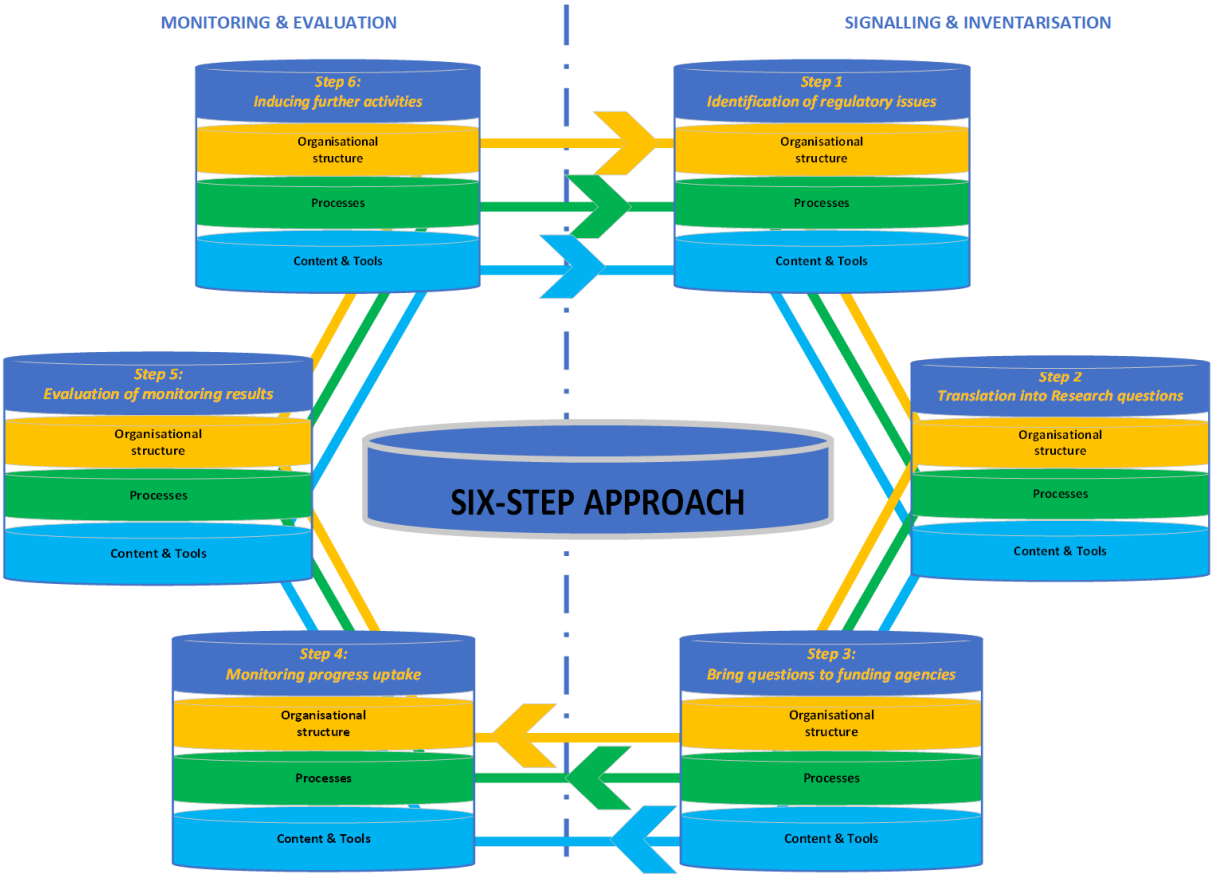


The road to structural road map development: A six-step approach

A six-step approach (see below) is proposed covering the three levels of 1) steps to be taken (process), 2) stakeholders and their roles (organisational infrastructure) and 3) topics to be addressed (content) in each step. The report gives some first suggestions for elaborating the three levels. The updated version of this report will deal with further completion of all steps and all levels.

Steps 1-3 of this approach deal with Signalling and Inventarisation of regulatory risk assessment research needs, while Steps 4-6 deal with Monitoring and Evaluation of how efficient the inventarisation is taken up by (academic) research through funding agencies, identifying state of the art by sound monitoring systems and evaluation of this state of the art, resulting in advice on follow-up steps.



Step 1 and 2: Identification of transregulatory research questions

As a first activity to bring the six-step approach into practice, a transRegulatory Risk Analysis Summit (RRAS) was organised. Regulatory risk assessors expressed their issues, commonalities in issues were inventarised and the most pressing issues were translated into a list of research questions which are captured in the table below. Subsequently, a wider group of risk assessment experts was consulted to seek support for the relevance of topics on this list. The next step will consist of involvement of national and European funding organizations in order to make the step towards solving the issues.

The most important regulatory risk assessment issues and related research questions resulting from the RRAS are listed in the table below.

Research question to pursue (challenge)	Regulatory risk assessment issues to overcome (scope)
Develop case studies on prediction/measurement of the toxicokinetic behaviour, including - **transformation of NMs inside the body (internal exposure)** - **testing methods** - **measured data , considering issues of data quality and reliability** **Use- to the extent possible- lessons learned from other nanomaterials**	Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains (definition) Lack of guidance in dealing with toxico-kinetics of nanomaterials (exposure) Lack of understanding of the exposure pathways inside (human) body and outside (human) body (exposure) Lack of insight in reliability of in silico, in-vitro and in-vivo models toxico-kinetics and hazard (hazard) Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, toxicokinetic data (risk assessment/ risk management) Data quality and reliability for the purpose of characterization and testing is questionable (definition)
Identify the minimal panel of parameters to determine equivalence/similarity in the different areas of regulatory risk assessment (identity is covered in this), with respect to: - **Phys-chem (intrinsic and extrinsic),** - **Biological interactions,** - **Toxicokinetics (ADME).** **Speed up the adoption of described parameters** **Identify parameters and criteria for grouping and read across (equivalence)**	Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains (definition). Lack of harmonised understanding of equivalence of nanomaterials in regulatory context (e.g. parameters and methods to test equivalence) (definition) Lack of grouping strategies (when are NM similar?) (definition)
Identify the usefulness of currently available non-nanomaterials exposure models for nanomaterials (external exposure). **If useful, validate the models for nanomaterials with measured data: share data, generate new data, incentives**	Lack of validated exposure models (exposure) Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, toxicokinetic data (risk assessment/ risk management)

Conclusions

AT THE PROCESS LEVEL

Conclusion 1: A structural process connecting regulatory knowledge needs (risk assessors) and research (scientists) is needed to bridge gap between regulatory needs and research

At the level of process, structural activities are missing to inventarise state of the art knowledge needs and scientific insights. European Technology Platforms (ETPs) are organized to gather views and strategic goals, however identification of regulatory issues is not a dedicated activity so far. In addition, (regulatory) risk assessors or risk managers are hardly involved. Scientific reviews have been written, the NSC has delivered a Regulatory roadmap and the H2020 project ProSafe delivered a White Paper[1], but all these

[1] ProSafe (2017) The Prosafe White paper: Towards a more effective and efficient governance and regulation of nanomaterials.
https://www.rivm.nl/sites/default/files/2018-11/ProSafe%20White%20Paper%20updated%20version%2020170922.pdf
last visited July 2020

activities had a one-off character. Moreover, they missed the link with demands driven by ongoing material innovations.

Conclusion 2: A transregulatory approach leads to a more efficient process given the many common issues faced across regulatory domains

The RRAS and the subsequent survey have made clear that the most pressing issues are similar in all regulatory domains dealing with nanomaterials and/or nanoproducts. Especially in key enabling technologies (KET) like nanotechnology or advanced materials there is a clear need for more transregulatory collaboration.

Examples of pressing issues identified in the current work are 1) Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains; 2) Lack of high-quality realistic exposure data throughout the life cycle; 3) Lack of insight in reliability of in silico models and in vitro test methods for toxico-kinetics and hazard and 4) Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, and toxicokinetic data.

Most of these issues have clearly been reflected in the recommendations of the ProSafe White paper (2017), for instance Recommendation 3:

Recommendation 3: *The European Commission should initiate (at least one) demand-driven project to generate experimental nanoEHS data. Such a project should include adequately characterized materials that have different properties and include appropriate assays for examining interactions or endpoints. Materials that should be included in such a project are (1) "real-world" materials, (2) well-characterized reference materials of varied size, shape, aspect ratio, surface charge, and surface functionality and (3) standard materials for calibrating various assays and measurement tools.*

AT THE CONTENT LEVEL (INFORMATION AND TOOLS)

Conclusion 3: A structured approach is needed to identify regulatory risk assessment issues and research questions and go from this first theoretical proposal to a more practical and operational approach

The identification of most pressing transregulatory regulatory risk assessment issues and research questions gave shape to the first two steps of the six-step approach. However, this should be regarded as first attempt to cover the three levels (organisational structure, processes and concepts & tools) of these steps. By positioning the RRAS in a more structured approach it is envisaged that RRAS brings forward roadmaps and inventarisations as previously performed by the NSC (Strategic Research Agenda, 2013) and the H2020 project ProSafe (White Paper, 2017).

Conclusion 4: The RRAS supported recommendations from the ProSafe White Paper (2017) and showed that there was a need to have more informal ways to share views and questions in an transregulatory manner

From the RRAS, it can be concluded that the most pressing knowledge needs within all regulatory frameworks was already (more or less) reflected in the recommendations of the ProSafe White Paper (2017). Besides the recommendations mentioned under conclusion 2, also recommendations on sharing of data (number 4) and efficient data management (number 5) are still valid. Recommendation 6 was confirmed as highly relevant and was partly addressed by organizing the RRAS.

Recommendation 6: Where possible, calls for nanosafety projects should be far more specific in giving clear instructions to ensure that data and results generated are of a type and form which allows their use in topics of regulatory relevance, such as choice of materials, test methods to be applied, SOPs and data management. The NanoSafety Cluster could play a role in defining such conditions.

Although most regulatory issues and research questions formulated during the RRAS were transdisciplinary, some frameworks have specific issues that are not shared by other disciplines. For instance on issues on safe exposure levels for workers (worker), determining toxicity in absence of animal testing (cosmetics), electromagnetic fields as endpoint (environment), or validation of specific ISO requirements (medical devices).

The participants in the RRAS and the subsequent survey expressed the need for more informal ways to share views and questions. It was suggested to add a digital platform or expert groups to the organizational structure level of step 1 and 2 of the six-step approach.

AT THE ORGANIZATIONAL STRUCTURE LEVEL

Conclusion 5: An organizational infrastructure is needed to connect the many stakeholders

At the level of organisational infrastructure, i.e. involved stakeholders and their roles, it is obvious that regulatory risk assessors and scientists should be involved. It is however less obvious but pivotal that the process of organizing the regular activities needs to be taken up by a stakeholder who has the ability to monitor whether stakeholders in the six-step approach are connected, and which progress and impact achieved in addressing the regulatory issues. The designers of the NRGC are recommended to consider whether such tasks would fit the NRGCs mandate.

Conclusion 6: A place is needed for information sharing (interaction platform)

One efficient and successful possibility for signalling and evaluation of the regulatory issues in the six-step approach is therefore to organise a meeting like the RRAS in which experts from different disciplines are invited. However, from the results of the survey, in which part of the respondents also participated in the RRAS, it can be concluded that for the follow up there is a clear need by risk assessors for other forms/ ways of meeting each other. This could be a digital platform, or expert groups that facilitate transdisciplinary exchange of expertise regarding risk assessment and risk management of nanomaterials and nanoproducts.

For more details about the Gov4Nano project please visit the Gov4Nano website. Public deliverables will be made available in due time via this website.