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Deliverable Report

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Executive summary

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 and advanced nanomaterials, posing novel and different risk analysis issues, relevant from a regulatory point of view.
Unlike the processes that have been put in place since a long-time for the development and follow-up of research and technology roadmaps for nanotechnology (e.g. technology platforms, industrial roadmaps), 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 including development of regulation, standardisation and harmonisation practices, has a strong impact on market conditions, including regulatory and market acceptance of innovative nanotechnology products.
In this deliverable:
- **A systematic approach** is proposed in order to allow analysis of: developments in broader society potentially leading to new nanospecific regulatory issues and inherent regulatory research questions; and monitoring and evaluation of scientific evidence to address these emerging regulatory issues.
- **The most pressing transregulatory nanospecific risk assessment issues and research questions** have been identified based on two (trans)Regulatory Risk Analysis Summits (RRAS)
- **Initial ideas for a nanospecific transregulatory risk assessors platform** have been developed

Background

In Europe, research agendas for nanotechnology are generally prepared by European Technology Platforms (ETPs) or branche organisations. These ETPs were the first type of public-private partnerships in which industry-led stakeholders' defined and implemented a strategic research agenda (SRA), aiming at aligning research priorities in a technological area. SRAs, however, are often limited by insufficient awareness of regulatory risk assessment issues and the scientific questions behind those issues. The EU NanoSafetyCluster, an informal platform for nanosafety research connected to the NMBP (Nanotechnologies, (Advanced) Materials, Biotechnology and Production) Programme in the EU-H2020 research programme, has put effort to fill this gap. However, its status as an informal platform for nanosafety research, missed the essentials for a structural approach to develop a SRA on a regular basis. Discontinuation of the NMBP-Programme in HorizonEurope is perceived to hamper the efficient execution of a strategic regulatory risk assessment research agenda.

In December 2019, RIVM organized in the H2020 project Gov4nano, a successful TransRegulatory Risk Analysis Summit (RRAS2019) to identify nanospecific regulatory issues and research questions, encountered in various regulatory domains[1]. By the end of 2021 a clear need for a second RRAS (RRAS2022) became apparent, although the issues and questions identified in RRAS2019 seemed still valid. The RRAS2022 was not foreseen in the project proposal but is an example of the need for agility in risk governance, especially in times of transitions. The RRAS2022 anticipated the implications for

[1] Gov4Nano Deliverable 5.3: Report on Regulatory Road- and Research-Map. Susan Wijnhoven (01-RIVM), Lya Hernandez (01-RIVM), Adriënne Sips (01-RIVM), Andrea Porcari (11-AIRI). Approved by DG RTD: November 2020.

nanomaterials and products induced by a changing policy landscape, as set by the new EU Green Deal policy and its underlying goals, ambitions and strategies.

The current deliverable D5.9 (which builds on D5.3) addresses the reasoning for the two summits, the outcomes and the recommendations for follow-up. The outcomes and recommendations will be given from the three levels of perspective for risk governance, being the organisational structure, the process for follow-up and the regulatory issues and scientific questions identified. A workshop report was made shortly after the RRAS2022 and is included as a supplement to this deliverable.

A stepwise systematic nanospecific transregulatory approach

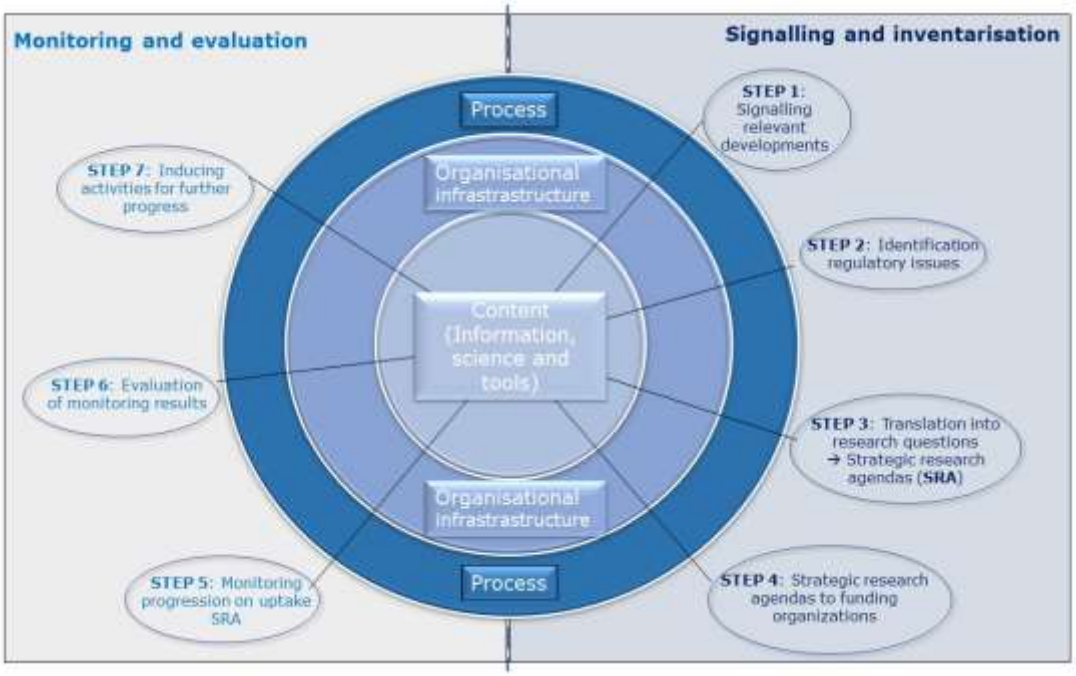
Stepwise: In order to solve regulatory risk assessment issues by strengthening the scientific bases, different types of actions have to be undertaken. It start with steps focusing on *Identifying relevant developments* and *Identifying regulatory risk assessment issues and knowledgde needs.* This can result in a nanospecific regulatory risk assessment research agenda or something alike, that once set, needs to be operationalized. The next steps of the approach therefore focus on *Monitoring progress in execution of the agenda*. The figure below depicts the different steps.

Systematic: The different steps need to be logical follow-ups of each other. For each step it needs to be clear what needs to be done, who can take ownership for each of the required steps and actions, and which content needs to be generated or which instruments are conditional for execution of the actions. These aspects are translated in the approach as 1) actions to be taken (process), 2) stakeholders and their roles (organisational infrastructure) and 3) topics to be addressed (content) in each step.

Nanospecific: Risk assessment and regulations for (advanced) nanomaterials and nanoproducts still is a field under development; insight when approaches and validity of test methods for chemicals do not cover that of nanomaterials and nanoproducts is needed.

Transregulatory: Available knowledge relevant for risk assessment of nanomaterials and nanoproducts (and several cases also for chemicals in general) is 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 scientific research in support of validation, standardisation and harmonisation is needed. Transregulatory approaches allow for increased efficiency in solving nanospecific risk assessment issues, and give insight to industry and innovators regarding experiences of other application domains facing similar issues.

Risk Assessment Approach: The approach is confined to risk assessment of (advanced) nanomaterials, products and production processes for consumer safety, workers safety and avoiding negative environmental impact.



Transregulatory nanospecific regulatory risk assessment issues and regulatory research questions

The most pressing regulatory risk assessment issues identified in RRAS2019, added with those of 2022 (issues of 2019 still were valid in 2022) are summarized below:

RRAS2019	RRAS2022
Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains	Lack of criteria for safe and sustainable by design
Lack of high-quality realistic exposure data throughout the life cycle;	Lack of knowledge on how to incorporate sustainability next to safety into a safe and sustainable by design approach
Lack of insight in reliability of in silico models and in vitro test methods for toxico-kinetics and hazard	Lack of knowledge on the use of New Approach Methodologies (NAMs) for dealing with existing and additional endpoints
Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, and toxicokinetic data	Lack of knowledge on the applicability of NM methods for advanced materials with respect to new endpoints and new functionalities

Also recommendations on data sharing and efficient data management were deemed in need of priority.
In addition, these regulatory issues were translated into regulatory research questions and are described in this deliverable.

Initial ideas for a nanospecific transregulatory risk assessors platform

In both RRAS, participants were interviewed about their information needs. A clear need for a platform to exchange experiences, issues and questions on how best dealing with nanospecific issues in risk assessment was expressed. Moreover, RRAS2022 showed that information about the impact of the Green Deal, about the impact of various new European strategies and initiatives regarding the CSS would be welcomed in order to consider nanospecific issues. Continuation of RRAS was mentioned as one of the ways forward.

Ownership of initiation of RRAS and execution of the stepwise approach remained unclear, as establishment of an NRGC or equivalent remains uncertain.

Conclusions

Process level

- A **structural process** to timely identify and address nanospecific (trans)regulatory risk assessment issues is missing. A stepwise systematic nanospecific transregulatory approach is proposed as an equivalent to processes followed by European Technology Platforms to develop Strategic Research Agendas (SRA). This stepwise approach would contribute to regulations in support of innovation rather than forming a barrier.
- The efficiency of a **transregulatory** character of the approach is shown by the emergence of several many commonly faced issues across a broad spectrum of regulatory domains.
  Both RRAS have made clear that the most pressing issues are similar in all regulatory domains dealing with nanomaterials and/or nanoproducts. This observation can likely be generalized at most key enabling technologies (KET)s, advanced materials in particular. Therefore our analysis shows there is a clear need for more transregulatory collaboration.

Organisational infrastructure level

- An **organisational infrastructure** is needed to secure a regular and transregulatory identification of nanospecific regulatory risk assessment issues, their translation into a strategic nanospecific regulatory research agenda and the required overview of the follow-up and execution of this agenda. This has become even more relevant by the increased need for safe and sustainable (advanced) nanomaterials being key for technological solutions to address the Green Deal ambitions.
- The participants in RRAS2019 and the subsequent survey expressed the need for more informal ways to share views and questions. Among the suggestions received from participants in both RRAS was the idea for a digital platform, besides expert groups to facilitate transdisciplinary exchange of expertise regarding risk assessment and risk management of nanomaterials and nanoproducts or yearly nanospecific RRAS meetings.

Content level (Information, science and tools)

- RRAS should be designed to enable more informal ways to share views and questions in an **transregulatory manner**. Examples of pressing issues identified in RRAS2019 are:
  - Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains;
  - Lack of high-quality realistic exposure data throughout the life cycle;
  - Lack of insight in reliability of in silico models and in vitro test methods for toxico-kinetics and hazard and
  - Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, and toxicokinetic data.

  Also recommendations on data sharing and efficient data management were deemed in need of priority. These issues were identified to be still valid in 2022.

Additional nano-specific risk assessment issues mentioned in RRAS2022 (which were linked to the goals and ambitions of the CSS) were mainly connected to the subject of

A safe an sustainable by design framework i.e.

- Lack of criteria for safe and sustainable by design and the
- Lack of knowledge on how to incorporate sustainability next to safety into a safe and sustainable by design approach

New endpoints for risk assessment i.e.

- Lack of knowledge on the use of New Approach Methodologies (NAMs) for dealing with existing and additional endpoints and
- Lack of knowledge on the applicability of NM methods for advanced materials with respect to new endpoints and new functionalities.

- The experiences in RRAS2019 and RRAS2022 in formulating regulatory research questions underscored the essence, as recommendated in the ProSafe White Paper[2], to give clear instruction on e.g. choice of materials, test methods to be applied, SOPs and data management in order to ensure regulatory relevance.
- Although most regulatory issues and research questions formulated during RRAS2019 and RRAS2022 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).
- RRAS2022 brought to light that the operationalization of the EU Chemicals Strategy for Sustainability is lacking attention for the nanospecific issues and scientific knowledge needed. Lessons learned from the past 15 years of nanosafety research stressed the urgency for a clear connection between research and innovation in the (European) nanosafety community and in innovation in the chemicals risk assessment community (like the Horizon Europe partnership programme PARC). New methods need to be investigated for their applicability and validity for small particles. Moreover, hypotheses about the 'small particle' effect need to be formulated and tested for specific endpoints mentioned in the CSS, like endocrine disrupting effects.

[2] 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

1 Description of task

Task 5.2 Widening the network: transdisciplinary alignment of regulatory questions and needs

Lead: AIST; partners: RIVM, IenW, IOM, AIRI, NIA, EMPA, BAuA

The task aims to identify, assess and support research on transdisciplinary information needs for safety testing, risk assessment and regulation of nanomaterials and nanoproducts, involving risk assessors, regulatory bodies, research and innovation players and other stakeholders, in developing a Regulatory Road- and Research-Map' and promoting and participating in Joint Calls using the SAF€RA network structure. Activities will provide added value to the NRGC, widening its network and informing its scope and activities.

The roadmap will take into account the "regulatory preparedness" of the different sectors of applications of nanotechnologies, both defining regulatory paths for (nano-enabled) from the laboratory to market, and assessing research needs to inform developments in regulation. It will ultimately be used to formulate scientific questions that will be addressed in a series of Joint Calls to be funded by the Member States using the existing SAF€RA network structure. This Task will work closely with Task 5.4, in order both inform the selection of case-study subjects, and building on the (interim) experience of case-studies to develop the roadmap and the joint calls.
Activities are organized in two sub-tasks, with contribution of all tasks partners:

Sub-task 5.2.1: Plotting a Regulatory Road- and Research-Map: transdisciplinary identification and alignment of (regulatory) questions and information needs
The sub-task aims to develop the Regulatory Road- and Research-Map (D5.3), through a series of interactions with stakeholders: a two-day regulatory risk assessor summit will be organised. This summit aims to attract risk assessors from a broad spectrum of disciplines, and to establish a constructive dialogue between them and the main nanotechnology stakeholder groups. An inventory of needs will be made via scrimmage sessions during the summit. In addition a dialogue platform will be established with a few participants to conduct follow-up tasks in smaller groups and discussion fora subsequent to the summit.
These activities will lead to an overview of the outstanding transdisciplinary research needs, on which a list of research questions and recommendations can be based. Results will feed into D5.3, informing both the activities of the Nano Risk Governance Council (NRGC), and more specifically of Task 5.2.2.

2 Approach and methodology

2.1 Background, aim of task and goal of the deliverable

In December 2019, RIVM organized in the H2020 project Gov4Nano, a successful TransRegulatory Risk Analysis Summit (RRAS2019) to identify nanospecific regulatory issues and research questions, encountered in various regulatory domains. By the end of 2021 a clear need for a second RRAS (RRAS2022) became apparent, despite the issues and questions identified in RRAS2019 seemed still valid.

This report addresses the reasoning for the two summits, the outcomes and the recommendations for follow-up. The outcomes and recommendations will be given from the three levels of perspective for risk governance, being the organisational structure, the process for follow-up and the regulatory issues and scientific questions identified.

The RRAS2022 was not foreseen in the project proposal but recognizes the essence for agility in risk governance of (advanced) nanomaterials, especially in times of transitions. It anticipated the implications for nanomaterials and products induced by a changing policy landscape, as set by the new EU Green Deal policy and its underlying goals, ambitions and strategies.

2.1.1 Background RRAS2019

The RRAS2019 was organized to address the omission for a structural process of identification and inventarisation of transregulatory nanospecific regulatory issues and accompanying research questions. As described into detail in D5.3 [pages 16-20] 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 for regulatory risk assessment issues. The EU NanoSafetyCluster was formed partially in response to that omission, but being an informal platform for nanosafety research, missed the essentials for a structural approach to develop their own SRA on a 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 available and needed scientific knowledge necessary for evidence based decisions in 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 development of regulatory science and activities of funding and innovation agencies

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, need to get prepared for an increasing number of multi-component and more complex nanomaterials, posing novel and different regulatory issues. In this situation 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 lack of overview is caused by a variety of factors:

1) At the level of process:
    a. No systematic inventarisation of scientific needs for regulatory science development is available,

b. Present regulatory research agendas focus only on particular domains of application (e.g. REACH) and often do not consult regulatory risk assessors who deal directly with dossiers

c. The development of regulatory science has no structural link to funding agencies

2) At the level of organisational infrastructure:

a. No structure is available that provides or facilitates this inventarisation

b. No structure is available that facilitates a regular exchange of information and insights

3) At the level of content (information, science and tools):

a. Information is scattered, and fragmented across a multitude of regulatory domains.

As a result, risk assessment questions and issues are insufficiently identified and often remain unresolved. This situation hampers the full exploitation of the economic potential of (safe) innovations based on nanomaterials. Especially in times where the European Commission stresses the need for a cost-effective way of addressing the Green Deal goal of nontoxic chemicals, these dilemmas need to be solved as quickly as possible [EU Recovery plan[3] and the Green Deal[4]].

2.1.2 Background RRAS 2022 – aligning to new policy goals

2.1.2.1 Nanosafety in an increasingly complex innovation landscape

Especially for new types of materials like nanomaterials the landscape is becoming increasingly complex, as both regulators/risk assessors as well as industry needs to deal with 3 directions of developments all driven by the widely supported goals and ambitions of the European Green Deal (GD) policy. Figure 1 illustrates these directions of development which take place concomitantly, are interdependent, but despite many interrelations are given shape in distinctive insufficiently connected communities. Complexity is added by the urgency and pace at which the developments in all directions have to take place. The goals at each axis in Figure 1 originate from European strategies[5] and action plans (like the Zero Pollution) underlying the European Green Deal. The road to achieve these goals is of a transitional nature and is based on a one of learning-by-doing approach. The complexity combined with the learning-by-doing approach urges for activities focusing on connecting, communicating and operationalizing:

- Connecting between the communities active within and between the respective lines of development.
- Communicating about lessons learned, state of the art, etc.
- Operationalizing roadmaps, identification of lessons learned, development of toolboxes and transferring (regulatory) science to standardization

So the road towards the goals at each axis is depending on or influenced by the pace and activities at the other axes. Connections between communities/actors at each axis and operationalization towards goals as depicted in Figure 1 are essential to achieve all goals in an efficient way.

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[3] https://ec.europa.eu/info/live-work-travel-eu/health/coronavirus-response/recovery-plan-europe_en (2020, last visited July 2020)

[4] https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en (2019, last visited July 2020)

[5] Strategy.pdf (europa.eu)

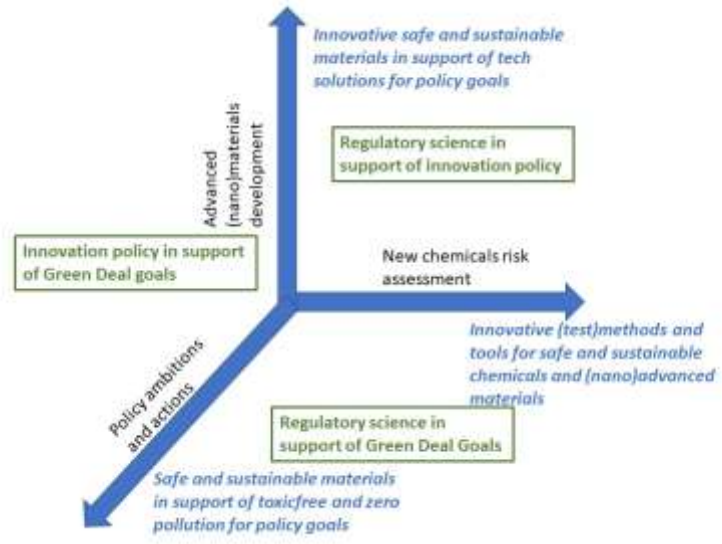

Figure 1: *Schematic illustration of the three orthogonal axes that need to be considered when developing safe and sustainable nanomaterials in an emerging developing policy and risk assessment environment.*

We regard the connections between the axes pivotal to come to innovation supportive regulations in an efficient and effective way. The importance of innovation supportive regulations is laid down in the European Innovation Principle[6] and the toolbox within this Principle toolbox[7] to secure timely and appropriate regulation, harmonization and standardization. In the present situation risk governance and risk management seem to be decoupled from the development of innovative materials like nanomaterials and other advanced materials. However, the application of new safe and sustainable nano/advanced materials to contribute to technological solutions for sustainability goals demands alignment with innovation policies.

2.1.2.2 Intensification of work at the science-policy interface needed

Risk governance as dealt with in the Gov4Nano project demands working at the science-policy interface. In 2020 the new European Green Deal (GD) policy was presented whereas in 2021 the underlying strategies and action plans to achieve the goals and ambitions were formulated. The GD is considered a growth strategy to transform the EU in a climate neutral and circular economy, while preserving Europe's competitiveness. It is the aim to tackle climate change and environmental degradation as they form an existential threat to man and its environment. The EU GD aims to improve the well-being and health of citizens and future generations[8].

Climate change, environmental pollution, biodiversity loss and an unsustainable use of natural resources pose multiple risks to human, animal and ecosystem health. To build a healthy planet for all, the EU GD calls for the EU to better monitor, report, prevent and remedy air, water, soil and consumer products pollution, among other things. In 2021 the EC published their Zero Pollution Action Plan[9]: "Air, water and soil pollution is reduced to levels no longer considered harmful to health and natural ecosystems and that respect the boundaries our planet can cope with, thus creating a toxic-free environment".

[6] https://ec.europa.eu/info/sites/default/files/research_and_innovation/knowledge_publications_tools_and_data/documents/ec_rtd_factsheet-innovation-principle_2019.pdf
[7] br_toolbox_-_nov_2021_-_chapter_3.pdf (europa.eu)
[8] A European Green Deal | European Commission (europa.eu)
[9] Zero pollution action plan (europa.eu)

Chemicals are considered to play an important role in both the cause of pollution and the solution to reach zero pollution. They are everywhere in our daily life, for the good but also as a main contributor to pollution. On the other hand, chemicals are also pivotal to lead us to low-carbon, zero pollution and energy- and resource-efficient technologies, materials and products. Increased investment and innovative capacity of the chemicals industry to provide safe and sustainable chemicals will be vital to offer new solutions and support both to the green and the digital transitions of our economy and society.

The Chemicals Strategy for Sustainability[10] (CSS) connects to the Zero Pollution Action Plan in their ambition for a toxic-free environment by protecting environment and human health, in particular that of vulnerable groups. It requires that the existing EU chemicals policy must evolve and respond more rapidly and effectively to the challenges posed by hazardous chemicals. It must be ensured that all chemicals are used more safely and sustainably, promoting that chemicals having a chronic effect for human health and the environment - substances of concern – are minimised and substituted as far as possible, and phasing out the most harmful ones for non-essential societal use, in particular in consumer products.

The CSS has formulated a number of actions including the establishment of a high-level roundtable with representatives from industry including SMEs, science and civil society. Discussions of the roundtable are envisaged to focus in particular on how to make the chemicals legislation work more efficiently and effectively and how to boost the development and uptake of innovative safe and sustainable chemicals across sectors.

Overall the GD acknowledges the need for new types of materials, like advanced nanomaterials, in support of technological solutions for addressing goals of a climate neutral and circular economy, while preserving Europe's competitiveness.

2.1.2.3 The role of nanomaterials and other advanced materials – rationale for RRAS2022

Sustainable advanced (nano)materials are considered a key driver for innovation, creating new opportunities on multiple dimensions and sectors. A vision on how to achieve this was laid down in the MATERIALS 2030 MANIFESTO -Systemic Approach of Advanced Materials for Prosperity – A 2030 Perspective[11]. The Advanced Materials Initiative[12] further operationalizes this Manifesto and the subsequent Advanced Materials Roadmap[13] addresses the vision to enable the EU's twin green and digital transitions which is anchored in good design principles combined with synergies between advanced materials, circularity, digital and industrial technologies. Nanomaterials are considered in these documents as advanced materials. As a key strategic milestone towards a structured European Materials Initiative, this draft Materials 2030 Roadmap[14] amongst others highlights the importance of an enabling policy framework through harmonised criteria for safe and sustainable by design chemicals and materials, evidence based life-cycle assessments, harmonised norms and standards, robust health and safety protocols as well as targeted education and training actions across the value chains. The draft 'Materials 2030 Roadmap was jointly produced by European Technology Platforms (ETP) (EUMAT, SUSCHEM, MANUFUTURE), the Materials Industrial Initiative (EMIRI), and the Materials 2030 Manifesto signatories[15].

In the due course of 2021 it became clear that activities foreseen under the Chemicals Strategy for Sustainability and related activities in the Zero Pollution Action Plan or the Materials 2030 Manifesto were focusing on safe and sustainable chemicals, products and

[10] Chemicals strategy (europa.eu)
[11] advanced-materials-2030-manifesto.pdf (europa.eu)
[12] https://www.ami2030.eu/
[13] Materials 2030 Roadmap (ami2030.eu)
[14] Materials 2030 Roadmap (ami2030.eu)
[15] Materials 2030 Roadmap (ami2030.eu); page 12

processes, but lacked dedicated actions to identify nano/advanced specific regulatory issues. One of the big lessons learned from the past 15 years on nanosafety research is the need to identify and address potential regulatory safety issues in close connection to the pace of the development of new types of advanced (nano)materials and their applications[16][17] besides stimulation of Safe and Sustainable by Design (SSbD) approaches. This situation urgently called to our opinion for the organisation of a second RRAS, the RRAS2022, to anticipate the timelines and actions underway for chemicals. The RRAS2022 had the title "Keeping pace with European ambitions for safe and sustainable nanomaterials and products".

2.1.2.4 New policy demands, new regulatory issues, new research questions

The new strategies are not only challenging regulatory risk assessors and researchers to deal with the more demanding technical requests, but are also challenging to meet the challenging timelines set by the European Commission. Nanomaterials provide a learning case, given, on the one hand the existing uncertainties, the lack of sufficient harmonized and standardized test methods and challenges for risk governance, while on the other hand valuable knowledge and experience has been gathered in series of European projects on how to reach for safe and sustainable practices for these materials timely.

Risk assessment practices will have to be adapted and developed to fulfil CSS requirements, for (advanced) nanomaterials (e.g. immune, neurological or respiratory systems or specific organ toxicity). Moreover, as illustrated in figure 1, there is an appeal to modernize chemicals risk assessment using modern techniques and latest scientific insights. The European Partnership Programme PARC[18], started in May 2022 under the Horizon Europe Programme, focuses on the development of this modernization. From a legal perspective nanomaterials and advanced nanomaterials are to be regarded as chemicals, however the nanodossier has learned that validity of test methods and risk assessment procedures for this type of chemicals needs specific expertise and attention. H2020 projects like NANoREG, CALIBRATE and GRACIOUS have demonstrated that upfront the development of valid dedicated test methods, a scientific basis for testing demands needs to be developed. The sound scientific basis for identification of health and environmental risks for chemicals is still under development for nanomaterials and might need further development for more advanced (nano)materials like graphene or 2D-materials.

Another challenge posed by the goals and ambitions of the CSS is how to assess the combined regulatory demands for safety and sustainability. The identification of nanospecific sustainability issues and the combined assessment of safety and sustainability was beyond the scope of RRAS2022.

The goal of "One substance, one assessment"[19] in the CSS again urged for more transregulatory approaches. The potential profit of transregulatory identification of risk assessment issues for nanomaterials was the cause for including RRAS2019 in the Gov4nano project proposal. The outcomes of RRAS2019 underscored the added value of transregulatory exchange of views and knowledge. It appeared that some regulatory issues where present in all regulatory domains and needed scientific input based on shared

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[16] Perspective on how regulators can keep pace with innovation: Outcomes of a European Regulatory Preparedness Workshop on nanomaterials and nano-enabled products - ScienceDirect https://doi.org/10.1016/j.impact.2019.100166

[17] Safe Innovation Approach: Towards an agile system for dealing with innovations DOI: 10.1016/j.mtcomm.2019.100548

[18] European Partnership for the Assessment of Risks from Chemicals (PARC) | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (dedicated website under development)

[19] Information session on 'one substance, one assessment' for stakeholders and citizens (europa.eu)

research questions. Teaming up between domains will help avoiding doubling of research, will help to seek funding more easily and will address the regulatory issues more quickly and potentially more uniformly. To that end, the RRAS2022 included a shared session on harmonisation and standardisation with the H2020 project REFINE[20].

2.1.3 Aim of task 5.2.1.

The aim of Task 5.2.1 is to develop a systematic approach to ensure that nanospecific regulatory issues are identified in a transregulatory way, translated into research questions and the follow-up is monitored and evaluated for addressing the issues. The approach was defined at the three levels of governance, i.e. the level of process, organisational infrastructure and content.

Goal of deliverable

The goal of this deliverable is to design such a systematic approach and test at least the steps of identification of transregulatory nanospecific regulatory issues and the translation into research questions by means of Transregulatory Risk Analysis Summits (RRAS). Such a systematic approach needs to target all three levels:

1) *At the level of Process:* building a novel approach that can reduce the gap between the knowledge needs of the *regulatory risk assessors community* and the research actions of the *nano-safety research community*. This novel approach should help to translate the regulatory risk assessment issues into research questions to feed into nano-safety research, in particular guiding priorities of research funding agencies in this field. This approach should also include a monitoring and evaluation process which not only monitors the progress of uptake of research questions by funding agencies but also evaluates and interprets the monitoring results to ensure follow-up activities when needed. NB: New policy goals and ambitions might lead to new (nanospecific) regulatory risk assessment issues.
2) *At the level of Organisational infrastructure:* ensuring that the process is inclusive and involves not only transdisciplinary and transregulatory stakeholders but also ensuring all stakeholder pillars are represented if needed (industry and business, policy makers, authorities and regulators, and research/academia).
3) *At the level of Content (Information, science and tools):* identifying regulatory risk assessment issues in a transdisciplinary and transdomain manner. For example:
    a. To identify the minimal panel of nanospecific parameters to determine equivalence/similarity in the different areas of regulatory risk assessment
    b. To identify nanospecific parameters and criteria for grouping and read across

2.2 Description of the work carried out

First a proposal for a systematic approach to these three levels was developed and described in D5.3. Based on lessons learned from RRAS 2022, the proposed approach was elaborated with an initiating step.

Two RRAS were organized in 2019 and 2022 respectively. RRAS2022 was extended with an extra session in collaboration with the Knowledge Exchange Conference of the H2020-project REFINE (a project on the development of a nanospecific scientific regulatory framework). RRAS2019 was a physical meeting, and a questionnaire on nanospecific regulatory issues and related scientific questions as follow-up. RRAS2022 was due to

[20] Refine Nanomed — About Refine Framework (refine-nanomed.eu)

COVID-19 restrictions limited to an online meeting. Outcomes of RRAS2022 were taken up in publications of the REFINE project in a special issue of the journal Drug Delivery and Translational Research[21].

2.3 Methodology

This report therefore integrates these three main activities:

1) *At the level of Process:* The development of a proposal for a novel structural nanospecific transdisciplinary and transdomain stepwise approach for the timely identification of transregulatory nanospecific regulatory risk assessment issues, their translation into research questions, and steps to monitor and evaluate follow-up.
2) *At the level of Organisational infrastructure:* D5.3 gave a first proposal for the organisational infrastructure that considers who could perform each of the activities outlined in Activity 1 (Process-level) including a link to closely related tasks in the Gov4Nano project. However, the relevance of this proposal was questioned given the ongoing discussions for the development of an NRGC and new initiatives like the Advanced Materials Initiative, induced by the strategies and plans in support of the Green Deal. Therefore no activities were undertaken to adapt the proposal in D5.3, neither to further describe this proposal in the present deliverable D5.9.
3) *At the level of Content (Information, science and tools):* Reporting the first experiences in the operationalisation of Activities 1 and 2 and the practical execution of the initial steps of the proposed systematic process.

A detailed description of the methodology used for these three activities for RRAS2019 can be found in D5.3 [pages 13-14].

Overall the following activities undertaken have led to:

- A structural stepwise nanospecific approach to identify regulatory risk assessment issues, to formulate research questions to address the issues and to monitor and evaluate follow-up.
- A list of transregulatory nanospecific risk assessment issues and research questions to address them.
- Identification of the need for transregulatory nanospecific risk assessors community.

2.3.1.1 Regulatory Risk Analysis Summit (RRAS2019)

In order to take a first step in identifying transregulatory nanospecific risk assessment issues, a transdisciplinary and transdomain Regulatory Risk Analysis Summit (RRAS2019) was organized by the RIVM in Bilthoven, the Netherlands (4-5 December, 2019). The primary goal of the Summit was to provide a forum to discuss knowledge needs for risk assessment, and to translate these needs into research questions for the scientific community.

[21] Halamoda et. al. Future perspectives for advancing regulatory science of nanotechnology-enabled health products. June 2022. Drug Delivery and Translational Research. DOI: 10.1007/s13346-022-01165-y

RRAS2019 addressed the following topics:

1) *Rationale for RRAS2019:* Knowledge on human and environmental health risks of nanomaterials is fragmented across a multitude of regulatory domains. This hampers an efficient way of dealing with comparable nanospecific regulatory risk assessment issues in different regulatory domains. In addition, regulatory risk assessors who deal directly with dossiers are often not enough connected to arenas developing nanosafety research agendas.
2) *Methodology used during RRAS2019:*
   - Identify the regulatory risk assessment issues per domain and select top two,
   - Present the domain specific top two in a transdisciplinary group,
   - Select relevant issues that can be translated into research questions,
   - Formulate the identified research questions in a format compelling for funding organisations,
   - Identify how a Nano Risk Governance Council could provide support for addressing upcoming or additional transregulatory nanospecific risk assessment issues.

As a follow-up to the RRAS, a survey was developed in order to check the results from the RRAS for completeness and seeking for support and follow up. The survey included various questions regarding the identified research themes, transdisciplinary risk assessment issues as well as research questions formulated during RRAS2019.

2.3.1.2 Second Regulatory Risk Analysis Summit (RRAS2022)

The second TransRegulatory nanospecific Risk Analysis Summit (RRAS 2022) was initiated to provide a forum to (further) discuss required updates of nanospecific transregulatory risk assessment issues and their implications for nanospecific regulatory research agendas. To that end, also policy makers, and other stakeholders involved in managing novel and emerging risks were invited apart from regulatory risk assessors. Participants from a broad spectrum of disciplines were encouraged to participate, although vast experience in risk management, policy making, or regulatory risk assessment was preferred.

In total, 45-60 people participated daily during 3 days of the meeting (see Annex I for the program). The meeting was executed online via the platform spatial chat[22]. Apart from plenary sessions, dedicated interactive break-out sessions were organised, addressing the topics:

- Domain-specific research needs for RA, recap of old an identification of new research needs
- Implications of new endpoints in the CSS on risk assessment needs

In the session on domain-specific research needs for risk assessment, the regulatory risk assessment issues of RRAS2019 (see Table 1 below) were taken as starting point, and additional issues were formulated by the participants. These were subsequently linked to the following goals and ambitions specified in the CSS:

1: Promoting safe and sustainable by design chemicals
2: Achieving safe products and non-toxic material cycles
3: Protection of consumer, vulnerable groups and workers from the most harmful chemicals
4: Protecting people and the environment for the combination effects of chemicals
5: One substance one assessment; make risk assessment processes simpler and more transparent

[22] in3 Solutions – Virtual scientific symposiums that are Interactive, Insightful and Intuitive

Shortly after the RRAS2022 a workshop report was drafted, describing the input given by the participants and the main conclusions drawn from this input. The report was checked with all participants for completeness and correctness (see Supplement I).

In follow-up to RRAS2022 the regulatory issues were translated into the most pressing (transregulatory) nanospecific research questions (see Table 2 below). It needs to be stressed that Table 2 reflects the regulatory issues as formulated by the participants, thereby reflecting their perception of state of the art.

In general, many of the regulatory issues from RRAS2019 were considered still valid, although it was not evaluated specifically to which extent the issues were considered valid.

3 Results and Discussion

3.1 Design of the process: A systematic transregulatory approach

The motivation for RRAS2019 was given in by a lack of proper understanding how the development of strategic regulatory research agendas for risk assessment issues compares to research agendas for technological innovations. A background analysis was performed to better understand the present landscape on how Strategic Research Agendas are currently developed in Europe. The role of European Technology Platforms in the development of European Strategic Research Agendas was therefore evaluated. In particular the attention for inclusion of regulatory science development by these ETPs was considered.

3.1.1 Background analysis: The present landscape and the role and contribution of European Tech Platforms in the development of Strategic Research Agendas

European Technology Platforms (ETPs) play a central and pivotal role in the development of European Strategic Research Agendas. These platforms consisting of industries and academia lead the process to define and implement a strategic research agenda (SRA) aiming at aligning research priorities in a technological area. ETPs merely are coordination and advisory structures, helping to define the topics of research programmes at European, national and regional level[23].

ETPs develop research and innovation agendas and roadmaps for action at EU and national level to be supported by both private and public funding. They mobilise stakeholders to deliver on agreed priorities and share information across the EU. By working effectively together, they also help deliver solutions to major challenges of key concern to citizens such as the ageing society, the environment and food and energy security. ETPs are independent and self-financing entities. They conduct their activities in a transparent manner and are open to new members[24].

Their objective is also to strengthen European industrial competitiveness and economic growth. The ETPs are considered as key players in the European innovation ecosystem and provide strategic insights into market opportunities and needs, and mobilise and network innovation actors across the EU in order to enable European companies gain competitive advantage in global markets[5].

An analysis for nanospecific ETPs and their scoping learned that there are at least 9 ETPs and the EU NanoSafetyCluster. Only the ETP Nanomedicin takes the development of a scientific regulatory framework into account in their Strategic Research Agenda, as made operational through the H2020 project REFINE. For further detailed information see D5.3 [pages 16 to 20 and Annex II].

3.2 Proposed stepwise systematic nanospecific transregulatory approach

3.2.1 Addressing the conditions

Stepwise: In order to solve regulatory risk assessment issues by strengthening the scientific bases, different types of actions have to be undertaken. It start with steps focusing on Identifying relevant developments and Identifying regulatory risk assessment issues and knowledge needs. This can result in a nanospecific regulatory risk assessment research agenda or something alike, that needs to be operationalized. The next steps of

[23] https://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_ATA(2017)603935, (2017, last visited July 2020)

[24] https://op.europa.eu/en/publication-detail/-/publication/dd0ecd11-5123-45a7-9bbb-ce244203a9d7/language-en/format-PDF/source-search (2015, last visited July 2020)

the approach therefore focus on Monitoring progress in execution of the agenda. Figure 2 depicts the different steps.

Systematic: The different steps need to be logical follow-ups of each other. For each step it needs to be clear what needs to be done, who can take ownership for each of the required steps and actions, and which content needs to be generated or which instruments are conditional for execution of the actions. These aspects are translated in the approach as 1) actions to be taken (process), 2) stakeholders and their roles (organisational infrastructure) and 3) topics to be addressed (content) in each step.

Nanospecific: As risk assessment and regulations for (advanced) nanomaterials and nanoproducts still is an emerging field, the approach cannot be generalized to the whole chemicals domain.

Transregulatory: Available knowledge relevant for risk assessment of nanomaterials and nanoproducts is 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 scientific research in support of validation and standardisation is needed. Transregulatory approaches not only contribute to more efficiency in solving nanospecific risk assessment issues, but also give insight to industry which application domains face similar issues.

Risk Assessment Approach: The approach is confined to risk assessment of (advanced) nanomaterials, products and production processes for consumer safety, workers safety and avoiding negative environmental impact.

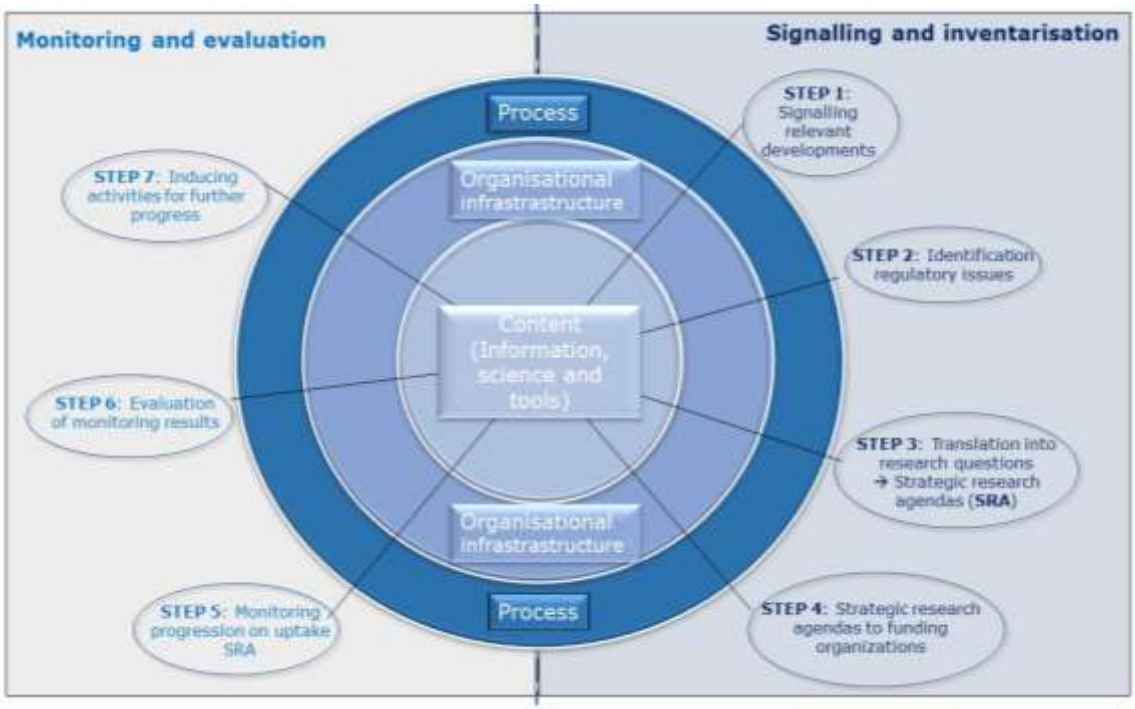

Figure 2: *Stepwise systematic transregulatory risk assessment approach describing a structural process from identification of regulatory issues to evaluation of addressing these issues.*

3.2.2 The systematic transregulatory approach

Outcomes of RRAS2019 led to the conclusion that a structural process connecting regulatory knowledge needs (risk assessors) and research (scientists) is needed to bridge the gap between regulatory knowledge needs and safety research. Moreover, it appeared that structural activities are missing to inventarise nanospecific regulatory risk assessment issues in a transregulatory way. Some known concepts such as 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[25], but all these activities had a one-off character. Moreover, they missed the link with demands driven by ongoing material innovations.

In the due course of Gov4nano it became clear that a variety of developments outside the regulatory arena required a new analysis to identify the potential for new regulatory issues. A quick scan of strategies like the CSS induced the initiation of RRAS2022. An initiating step was therefore added to the 6-step approach developed earlier and described in D5.3 [pages 21-24]. The initiating step should address the agility required to deal with regulatory risk assessment issues. To our opinion agility is especially in times of transitions and innovation highly required. First then the pacing problem between innovation and regulation can be tackled.

3.2.3 Description of various steps

Two perspectives of steps have been distinguished that cover 1) identification of issues and 2) status of addressing of issues. To that end 4 steps related to "signalling & inventarisation" and 3 steps related to "monitoring & evaluation" were formulated. In response to RRAS2022, Step 1 was added to an initial proposal of a stepwise approach described in D5.3. The following steps were formulated:

***Table 1**: Different steps in the development of the stepwise nanospecific transregulatory risk assessment approach*

Signalling & Inventarisation	Step 1	Signalling of relevant developments
	Step 2	Identification of regulatory issues
	Step 3	Translation into research questions
	Step 4	Strategic Regulatory Research Agenda (SRA) to funding agencies
Monitoring & Evaluation	Step 5	Monitoring progression on uptake SRA
	Step 6	Evaluation of monitoring results
	Step 7	Inducing activities for further progress

Explanation of the steps

Table 2 represents a general overview of the different steps, the main process, suggestions for organisational infrastructure and information, science and tools. It needs to be stressed

[25] 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

that the description of the steps should be regarded as suggestions, rather than an exhaustive list or a commonly agreed overview.

Step 1: Signalling of relevant developments; this step requires specified description as it refers to identification of issues outside the direct scope of (advanced) nanomaterials.

Organisational infrastructure: Panel to identify and flag signals

The European Commission states in its GD that new technologies, sustainable solutions and disruptive innovation are critical to achieve the objectives of the GD. It aims for synchronicity of all policy levels: regulation and standardisation, investment and innovation, national reforms, dialogue with social partners and international cooperation.

This description of the present situation and ambitions demonstrate the complex world driving the demands for appropriate risk governance of a Key Enabling Technology (KET) as nanotechnology, and more specific (advanced) nanomaterials and their applications in products. The present risk governance system for chemicals including nanomaterials is put to test by many technological innovations, by transitions needed to address the GD goals and on top of that by changing political priorities (e.g. due to crises).

As a consequence, a proactive and anticipative attitude is needed to come to an agile governance system for nanotechnology. An organisation to structurally monitor, identify and flag developments for their potential to cause new (advanced) nanospecific regulatory issues is lacking.

We therefore suggest to install a panel, whether inside or outside the new organisation as suggested in G4N-D5.5, to execute such activities.

Process: Identification and interpretation of relevant development

Signals pointing at developments with potential impact for risk assessment can be of diverse nature. Some signals come from the development of innovative materials, some from new goals and ambitions in policies, others from technological developments with potential for application in risk assessment. Moreover, developments with potential to indirectly affecting risk assessment, like geopolitics, public interests, etc. should be spotted and interpreted.

In comparison to RRAS2019 we learned that signals need to be collected and weighed for their potential impact on identification of new regulatory issues and new research questions. This means that signalling should become a separate activity in this approach.

Content (Information, science and tools): Putting signals into regulatory context for regulatory risk assessors

During the initiation of RRAS2022 it became known that regulatory risk assessors had to be informed about the identified signals that implied for call for action from the (regulatory) risk assessment community. So, risk assessors attending the RRAS2022 first needed to be informed about demands and potential impact of the European Green Deal goals and underlying strategies. This activity could be generalized into 'putting signals into regulatory context'.

Table 2: *Different steps in the development of the stepwise nanospecific transregulatory risk assessment approach, further divided in process (how), organisational infrastructure (who) and tools (what)*

	Step	Process	Infrastructure	Tools
1	Signalling of relevant developments	Informing risk assessors about relevant signals	Ownership?	See step 2
2	Identification (trans)regulatory issues	Translating signals into impact for risk assessment	Ownership for organizing RRAS and platform?	Development of a transregulatory knowledge platform; organizing RRAS
3	Translation into research questions	Translating regulatory issues into research questions and a Regulatory SRA	Ownership?	RRAS, online survey and consultation procedures
4	Regulatory SRA to funding agencies	Inform funding agencies Check potentials for funding	Ownership?	
5	Monitoring progress uptake Regulatory SRA	Run monitoring activities	Ownership?	Monitoring scheme (e.g. G4N-D7.2)[26]
6	Evaluation of monitoring results	Identify state of the art in addressing regulatory issues	Ownership?	Evaluation and management scheme Evaluation reports
7	Inducing further activities	Identify need for further or adapted research	Ownership?	Evaluation and management scheme; rationale for new RRAS, etc.

3.3 Outcome of RRAS2019 and RRAS2022

3.3.1 Overall outcomes of RRAS2019 and RRAS2022

The RRAS2019 and the subsequent survey have made clear that the most pressing nanospecific regulatory risk assessment issues are similar in all regulatory domains dealing with nanomaterials and/or nanoproducts. In a key enabling technologies (KET) like nanotechnology or advanced materials there is a clear need for more transregulatory collaboration.

[26] Gov4nano D7.2 Criteria for monitoring of progress in implementation of risk governance (November 2021)

The most important regulatory risk assessment issues and related research questions resulting from the RRAS2019 (and later confirmed by a larger group of experts in the survey) are listed in Table 3 below:

***Table 3**. Outcome of RRAS2019, an overview of research questions (challenge) which are based on regulatory risk assessment issues (scope)*

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)

A detailed and more comprehensive background to this table can be found in D5.3 [pages 28-33].

RRAS2022 was initiated in order to identify whether the new ambitions of the Green Deal and the goals of the CSS will pose new nanospecific regulatory risk assessment issues that require new scientific insights or whether some earlier identified issues have become more prominent to address. Table 4 summarizes the issues identified in the context of specific goals described in the CSS. A more detailed overview of input by the participants of RRAS2022 can be found in Supplement I (workshop report). The issues are expressed as stated by the participants and thus reflect their perception of state of the art regarding CSS goals. Meanwhile dynamics around operationalization of the CSS are high and difficult for the participants to keep up with that.

Table 4: *An overview of additional research questions (challenge) based on additional regulatory risk assessment issues (scope) as identified in relation to goals and ambitions of the CSS.*

Research question to pursue (challenge)	Regulatory risk assessment issues to overcome (scope) as formulated by the participants
CSS goal 1: Promoting safe and sustainable by design chemicals Pre-market approach, avoiding chemical properties harmful to human health or environment Develop EU safe and sustainable by design criteria for chemicals	
Identify nanospecific information (including for advanced materials) to address the safe and sustainable by design framework and criteria as under development by the European Commission.	Lack of agreement on ideas, concepts and terms; what is sustainability? What is safe and what is safer? Lack of criteria for safe and sustainable by design: wait for the commission to define criteria Companies are still far away
Identify to which extent the information needed in the phase of premarketing (SSbD) is different as compared to a market approach (regulatory requirements) **Solve the issues concerning information sharing early in the innovation process, like IP issues.**	Lack of knowledge on the difference between marketing and pre-marketing Pre-market is surrounded by issues such as IP - Pre-marketing: Need to develop test beds to address this in the pre-market stage - Paradigm shift to allow innovators to discuss with regulators under specific rules and conditions; start working out solutions together to improve safety and sustainability; you have to get people together to do this.
Develop consensus on how to address the nanospecific issues around safe(ty) and sustainability (for instance the lack of CLP information for many nanomaterials keeping in mind that CLP is the basis for the JRC framework for SSbD criteria) in an integral way. To facilitate this, dialogue between innovators and regulators is essential (regulatory preparedness). **• if possible, identify issues related to the applicability of current safety methods (including grouping and read across approaches) for NM to advanced materials** **• define the need for novel techniques to improve quality and use of data (e.g. analytical methods, AI)** **Nanospecific sustainability issues should be identified and aligned to ongoing sustainability initiatives such as the Sustainable Product Initiative, EcoDesign and the Environmental Footprint.**	Lack of knowledge on how to incorporate sustainability next to safety into a safe and sustainable by design approach Lack of connection between all the ongoing projects and initiatives -look at regulatory issues in other legislative frameworks--> find synergies

Regulatory preparedness: identify trends in innovations in NM and advanced materials at the national and EU level.	

CSS goal 2: Achieving safe products and non-toxic material cycles

Minimize the presence of substances of concern in products

Develop methods for chemical risk assessment taking into account whole life cycle of substances

Post marketing surveillance: Identifying trends on material use and presence of NM and advanced materials in products on the market in order to have • **More concise exposure assessments, and** • **Better monitoring system(s) for recalling hazardous products from the market, and** • **Pro-active risk assessment (regulatory preparedness)**	Lack of an overview where NMs are used in products at a national level Need for refinement/development of methods/tools for the measurement/determination of NM also in products Lack of attention for a life cycle thinking approach: - how to make end-of life product a no waste any longer
Develop regulatory and scientifically sound analytical methods for analyzing the presence of NM and advanced materials in different matrices and products.	Lack of knowledge on what is needed in terms of biomonitoring and opportunities of advanced techniques to improve quality of data
Develop a risk assessment in line with the goals and ambitions set in the CSS (e.g. additional endpoints) for NM and advanced materials at the product level, including life cycle approach (combination of human health and environment)	
Identify issues related to re-use and recycling of nanomaterials (and advanced materials), in particular those that do not degrade.	

CSS goal 3: Protection of consumer, vulnerable groups and workers from the most harmful chemicals

New endpoints of hazard assessment. Ensure that consumer products do not contain chemicals that cause cancers, gene mutations, affect the reproductive system, or are persistent and bioaccumulative.

Including endocrine disrupters, goal is to ensure that ED are banned in consumer products

Integrated RA approach for multiple endpoints: CMR, ED, chemicals affecting the immune, neurological or respiratory systems and chemicals to specific organs

Identify subpopulations extra vulnerable to nanospecific effects (e.g. babies, pregnant women, elderly or immunocompromised)	Lack of knowledge on the use of New Approach Methodologies (NAMs) for dealing with existing and additional endpoints
Create an inventory about the applicability of existing alternative in vitro/ in silico methods (new approach methodologies (NAMs)) for nanomaterials and advanced materials for • **long term effects including Carcinogenicity, Mutagenicity and Reprotoxicity, and** • **new endpoints like ED, cardiovascular effects, and effects of the immune, neurological and respiratory systems.**	Lack of knowledge on new endpoints like cardiovascular effects Lack of knowledge on the relevance of ED for nanomaterials/ advanced materials Lack of knowledge on how to assess ED effects for NM and advanced materials
Where possible, in vitro/ in silico methods should be optimized for nanomaterials and advanced materials	Lack of knowledge on in vitro methods for ED effects
Create an overview on the applicability of currently available (non-) nanomaterial exposure models for nanomaterials and advanced materials. Where possible, exposure modeling should be improved	Exposure modeling within context of RA needs to be improved Lack of knowledge of RA at product level:

Develop integrated risk assessment for NM and advanced materials for different exposure routes and multiple endpoints, including a vulnerable group assessment	- lack of methods to check whether it is a nano-enabled product (new guidances (EFSA)/ guidelines) - lack of grouping strategies - lack of integration of uptake into RA: impact of degree of agglomeration on uptake Lack of knowledge on the life cycle impacts Lack of an integrated RA approach for multiple endpoints (CMR, ED, other new endpoints), including a vulnurable group assessment Lack of standardized methods, how to keep track of progress in the state of the art process of standardization Lack of knowledge on uncertainties of applicability of NM methods for advanced materials with respect to - new endpoints - new functionalities
CSS goal 4: Protecting people and the environment for the combination effects of chemicals Assess how to best introduce a mixture assessment factor in REACH Introduce provisions to take account of the combination effects in other relevant legislation	
Identify which nano-specific aspects on mixtures are relevant, i.e. multi-component NM, a mixture of NM with different sizes **Identify which in vitro methods for mixtures need to be developed for NM and advanced materials** **Identify if and how the Mixture Assessment Factor is relevant in the risk assessment of NM and advanced materials**	Lack of knowledge on mixtures: - risk assessment challenges, one material with different forms and sizes. Multi components composed of different NM, advanced materials - need for methods development of mixtures
CSS goal 5: One substance one assessment Make risk assessment process simpler and more transparent	
Building a transregulatory community for: • **Knowledge sharing (content):** ▪ **EU repository that is based on FAIR principles with groups of hazardous nanomaterials and advanced materials, nanospecific exposure scenarios, nanospecific health-based limit values** • **Connecting and facilitating transregulatory collaboration (process and organizational infrastructure)** ▪ **of toxicity experts of different domains** ▪ **between tox and exposure experts** ▪ **between scientists and regulators**	Lack of transregulatory collaboration, alignment of different regulatory frameworks Lack of integration of different fields, not working on silos. Learn from other domains: - promote cooperation between tox and exposure experts (Possibly exposure cannot necessarily be used across regulations as the exposure form, routes, and hence characteristics will likely vary considerably between environments.) Need for the further exploration of one substance one assessment with respect to: - group of substances - share exposure scenarios - establishment of an EU repository of health-based limits values" Need for better data availability: no exposure data Need for better cooperation between different expertise (tox, exposure, epi)

*Regulatory research questions concerning process and organisational infrastructure are marked in **green** (other questions are more technical of origin)*

3.4 Facilitating exchange of information

In both RRAS participants were interviewed about their information needs. A clear need for a platform to exchange experiences, issues and questions on how best dealing with nanospecific issues in risk assessment was expressed. Moreover, RRAS2022 showed that information about the impact of the Green Deal, about the impact of various new European strategies and initiatives regarding the CSS would be welcomed in order to consider nanospecific issues. Continuation of RRAS was mentioned as one of the ways forward. Ownership of initiation of RRAS and execution of the stepwise approach remained unclear as establishment of an NRGC or equivalent remains uncertain.

4 Conclusions and recommendations

4.1 Conclusions

This report describes a stepwise systematic nanospecific transregulatory risk assessment approach for the governance of regulatory knowledge development to address risk assessment issues in a structural, efficient and transregulatory way. The approach was developed in response to the observation that a structural connection between regulatory risk research roadmap developers, funding agencies and a legal entity monitoring execution and outcomes of such a roadmap is lacking.

Process level

- A **structural process** for timely identification and addressing of nanospecific (trans)regulatory risk assessment issues is missing. A stepwise systematic nanospecific transregulatory approach is proposed as an equivalent to processes followed by ETPs to develop Strategic Research Agendas (SRA). Scientific reviews have been written, the NSC has delivered a Regulatory roadmap and the H2020 project ProSafe delivered a White Paper, but al these activities had a one-off character. Moreover, they missed the link with demands driven by ongoing material innovations. This stepwise approach would contribute to regulations in support of innovation rather than forming a barrier.
- The efficiency of a **transregulatory** character of the approach is underscored by the many commonly faced issues across a broad spectrum of regulatory domains. Both RRAS 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.
- The goals and ambitions of the Green Deal and European strategies like the CSS demand **a proactive attitude** towards timely identification of new (trans)regulatory nanospecific risk assessment issues in order to unlock the full societal and economical potential of nanomaterials and their applications. The new pressing nanospecific risk assessment issues resulting from the ambitious goals of the CSS (as become clear in the second RRAS) are mainly dealing with the subject of the safe and sustainable by design approach as well as new hazard endpoints (like ED effects) and vulnerable groups.

Organisational infrastructure level

- An organisational infrastructure is needed to secure a regular and transregulatory identification of nanospecific regulatory risk assessment issues, their translation into a strategic nanospecific regulatory research agenda and the required overview of the follow-up of this agenda. This has become even more relevant by the increased need for safe and sustainable (advanced) nanomaterials being key for technological solutions to address the Green Deal ambitions.
- The participants in the two RRAS and the subsequent survey expressed the need for more informal ways to share views and questions. Among the suggestions received from participants in both RRAS was the idea for a digital platform, besides expert groups to facilitate transdisciplinary exchange of expertise regarding risk assessment and risk management of nanomaterials and nanoproducts or yearly nanospecific RRAS meetings.

Content level (information, science and tools)

- RRAS should be designed to enable more informal ways to share views and questions in an transregulatory manner. Examples of pressing issues identified in RRAS2019 are
    - Lack of knowledge on which physico-chemical characteristics are essential for risk assessment purposes within and across domains;
    - Lack of high-quality realistic exposure data throughout the life cycle;
    - Lack of insight in reliability of in silico models and in vitro test methods for toxico-kinetics and hazard and
    - Limited availability of exposure/ release case studies, including measurements and guidance on exposure data, and toxicokinetic data.

  Also recommendations on data sharing and efficient data management were deemed in need of priority. These issues were identified to be still valid in 2022. Additional nano-specific risk assessment issues mentioned in RRAS2022 (which were linked to the goals and ambitions of the CSS) were mainly connected to the subject of

  A *safe an sustainable by design* framework i.e.
    - Lack of criteria for safe and sustainable by design and the
    - Lack of knowledge on how to incorporate sustainability next to safety into a safe and sustainable by design approach

  New endpoints for risk assessment i.e.
    - Lack of knowledge on the use of New Approach Methodologies (NAMs) for dealing with existing and additional endpoints and
    - Lack of knowledge on the applicability of NM methods for advanced materials with respect to new endpoints and new functionalities.
- The discussion held during the RRAS2019 furthermore led to the development of the *NanoSafety Cluster WG-B / WG-G Concept Paper: Regulatory Preparedness in Nanotechnology through Implementation Documents*; during the development of the paper, officials of the European Commission and ECHA were consulted, and an initial version of the paper was presented to the OECD WPMN in June 2021.
- Goals and ambitions in the Chemicals Strategy for Sustainability induces additional regulatory risk assessment issues, which have to be investigated for their nanospecific character. Since all these issues are similar for the majority of the regulatory domains, the CSS goal "one substance, one (hazard) assessment" was foreseen as a way to simplify risk assessment and increase transparency at the same time. The wording 'nanospecific' needs to be read as how the (small) particle character adds to chemical effects.
- The experiences in RRAS2019 and RRAS2022 in formulating regulatory research questions underscored the essence, as recommended in the ProSafe White Paper, to give clear instruction on e.g. choice of materials, test methods to be applied, SOPs and data management in order to ensure regulatory relevance.
- Although most regulatory issues and research questions formulated during RRAS2019 and RRAS2022 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).
- RRAS2022 brought to light that the operationalization of the EU Chemicals Strategy for Sustainability is lacking attention for the nanospecific issues and scientific

knowledge needed. Lessons learned from the past 15 years of nanosafety research stressed the urgency for a clear connection between research in the (European) nanosafety community and in innovation in chemicals risk assessment (like the Horizon Europe partnership programme PARC). New methods need to be investigated for their applicability and validity for small particles. Moreover, hypotheses about the ' small particle' effect need to be formulated and tested for specific endpoints mentioned in the CSS, like endocrine disrupting effects.

4.2 Recommendations

- The development and follow-up activities of a nanospecific Strategic Regulatory Research Agenda to address nanospecific regulatory issues is deemed relevant. There is however an urgent need to decide on ownership.
- Overview of European or global funding organisations with scoping on regulatory issues and advanced (nano)materials should be created to warrant uptake of the nanospecific Strategic Regulatory Research Agenda. The toolbox as part of the European Innovation Principle might support this.
- The European Nano Safety Cluster (NSC) acts as a well-established European nanosafety ecosystem with global impact. Their activities and specialized knowledge and experience in addressing nanospecific research questions, needs improved operational connections to Strategic Research and Innovation Plan (SRIP) of the EC to operationalize the Chemicals Strategy for Sustainability (CSS).
- Regulation policy and innovation policy require alignment as is stated in a.o. the toolbox of the European Innovation Principle. This underscores the need to search for operational connections between the nanospecific Strategic Regulatory Research Agenda and Roadmaps and Strategic Research Agenda as developed by ETPs focusing on nanotechnology or advanced materials.
- An online transregulatory risk assessors platform with scoping on (advanced) nanomaterials was requested by the participants in both RRAS. Ownership needs to become clear before such a platform can be created.

5 Deviations from the work plan

The current deliverable D5.9 builds upon D5.3. The work performed and described as well as the second Transregulatory Risk Analysis Summit (RRAS2022), which was the basis of the current deliverable, was not included as such in the DoA (section 1) and is a deviation from the work plan.
The first RRAS (RRAS2019) was already foreseen in the project proposal triggered by an omission at the process level, as a structural process for (transregulatory) identification of nanospecific regulatory issues and follow-up to solve these through research was lacking. Especially a process to include regulatory risk assessors structurally in development of regulatory and research roadmaps appeared to be lacking.

The current work has been organized due to clear need for a second RRAS (RRAS2022) which became apparent at the end of 2021. The RRAS2022 was not foreseen in the project proposal but is an example of the need for agility in risk governance, especially in times of transitions. The RRAS2022 anticipated the implications for nanomaterials and products induced by a changing policy landscape, as set by the new EU Green Deal policy and its underlying goals, ambitions and strategies.

In the current report, also an adapted version of the 6-step approach (now called stepwise systematic nanospecific transregulatory risk assessment approach) was developed for timely and efficient development of regulatory science and evidence based knowledge for the risk assessment of nanomaterials and nanoproducts.

6 Performance of the partners

Main part of this deliverable was carried out by RIVM (Adrienne Sips, Susan Wijnhoven and Lya Hernandez). Andrea Porcari (AIRI), Steffi Friedrichs (AIST) and Rob Aitken (IOM) commented to the draft version. Various WP5 partners (and other Gov4Nano and non-Gov4Nano partners) took part in both RRAS.

We would like to acknowledge Cornelle Noorlander for her support in organizing and executing RRAS2019 and Agnes Oomen (RIVM) for help in RRAS2022 in translating identified regulatory issues into research questions. We would like to thank Yvonne Linnebank (RIVM) and Joke Vroom (RIVM) for their advice and support in the organization of both RRAS.

7 Annexes and supplements

Annex I: Transregulatory risk analysis summit 2022 (RRAS2022)

Flyer for the summit

Supplement I:

Workshop report RRAS2022

Annex I: Flyer RRAS 2022

Transregulatory Risk Analysis Summit (RRAS 2022)

Keeping pace with European ambitions for safe and sustainable nanomaterials and products

24-26 January 2022, online

Why the summit?

The safety and sustainability of chemicals and materials and related applications is an imperative of the Green Deal. This is reflected in underlying strategies such as the Chemicals Strategy for Sustainability (CSS), the Pharmaceutical Strategy, and the Farm to Fork Strategy.

The new EU policies are challenging risk assessors in research and product development toward more demanding requests.

Nanomaterials provide an exemplar case, given, on the one hand the existing uncertainties and challenges for risk governance, on the other hand the knowledge and experience gathered on safe and sustainable practices on these materials.

Risk assessment practices will have to be adapted and developed to fulfill CSS requirements, in particular for nanomaterials (e.g., immune, neurological or respiratory systems or specific organ toxicity).

This second **Transregulatory Risk Analysis Summit (RRAS 2022)** will provide a forum to discuss required updates of risk assessment knowledge needs and its implications for research agendas.

Who will participate?

- Risk assessors, policy makers, regulatory bodies, companies, and research institutes and all other actors dealing with (advanced) materials, nanomaterials and nanoproducts.
- Participants from all regulatory domains are encouraged to participate, as the event will address trans-regulatory aspects.

How will the event be organised?

- Presenting results from the first RRAS,
- Providing a state-of-the-art overview on the development of guidelines for risk assessment nanomaterials, including novel toxicity and risk assessment methods.
- Discussing relevant developments in risk assessment strategies, in connection with recent EU and national safety and sustainability policies.

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What do we want to achieve?

- Research and regulatory needs induced by the goals and ambitions to obtain safe and sustainable chemicals;
- By translating these knowledge needs into (new) research questions and updating the list of regulatory knowledge needs and research questions as developed during RRAS-2019.

The **Transregulatory Risk Analysis Summit 2022** will provide a forum to discuss risk assessment needs and expectations of stakeholders across disciplines and domains, and together find solutions to address the complexity of risk analysis for nanomaterials. Participants will:

- **Share lessons:** facilitating mutual learning amongst experts and stakeholders in an interdisciplinary and inter-domain fashion.
- **Identify priorities:** ensuring that most urgent scientific information needs and regulatory issues are integrated in policy research agenda, in support to regulatory oversight and compliance.
- **Promote harmonisation:** finding common solutions to relevant topics such as data gaps, test guidelines and harmonisation of methods.
- **Identify operational research agendas:** translate nano-specific issues in inputs for research agendas, funding mechanisms and other incentives to support and further develop risk analysis approaches, knowledge and data.

When and where?

Online on 24-26 January 2022

We invite you as an expert in risk assessment to participate in the **Transregulatory Risk Analysis Summit 2022.**

Rijksinsitituut voor Volksgezondheid en Milieu (RIVM), coordinator and partner in Gov-4Nano, will host this workshop for participants from different regulatory domains, disciplines and organisations.

The Transregulatory Risk Analysis Summit 2022 is organised back-to-back with the **Knowledge Exchange Conference 3 (KEC3)** of the REFINE project which proposes a Regulatory Science Framework for the risk-benefit assessment of nanomaterials for medical applications.

Based on the analyses of the existing regulatory challenges and methodological gaps the REFINE partners selected and developed in vitro assays towards standardisation and studied biodistribution of model nanoparticles including IT based PBPK modelling. During KEC3 a state of the art comprehensive and realistic status of the current scientific regulatory framework and the existing and to be developed tools to meet the regulatory challenges within this framework will be presented.

The Gov4NAno (GA 814401), NanoRigo (GA 814530) and RiskGone (GA 814425) have received funding from the European Union's Horizon 2020 research and innovation programme.

Participants response to 2nd RRAS

Trans-Regulatory Risk Analysis Summit 2022

Keeping pace with European ambitions for safe and sustainable nanomaterials and products

Date: 24-26 January 2022
Place: Online via Spatial Chat
Participants: not included because of GDPR

READER
This document summarizes the agenda, reflections and discussions of the 2nd Trans-Regulatory Risk Analysis Summit for nanomaterials and products. Participants in this summit are requested to comment on inaccuracies or to add new reflections, thereby giving their consent that the content of the document represents the summit well. Comments will be taken into account in the official workshop report to be prepared by RIVM in due time.

This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement 814401

1. Introduction

1.1 Background

The safety and sustainability of chemicals and materials and related applications is imperative for the Green Deal[1]. This is reflected in underlying strategies such as the Chemicals Strategy for Sustainability (CSS)[2], the Pharmaceutical Strategy[3], and the Farm to Fork Strategy[4]. The new EU policies are challenging risk assessors in research and product development toward more demanding requests.

Nanomaterials provide an exemplar case. On the one hand, there remain existing uncertainties and challenges for risk governance, on the other hand there is knowledge and experience gathered on safe and sustainable practices on these materials. Risk assessment practices will have to be adapted and developed to fulfil CSS requirements, in particular for nanomaterials (e.g. on immune, neurological or respiratory systems or specific organ toxicity).

This second Trans-Regulatory Risk Analysis Summit (RRAS 2022) was foreseen to provide a forum to discuss required updates of risk assessment knowledge needs and their implications for research agendas.

1.2 Main goals of the Summit

The RRAS was organized to provide a forum to discuss risk assessment needs and expectations of stakeholders across disciplines and domains, and together find solutions to address the complexity of risk analysis for nanomaterials. The **main goals** of the meeting were:

1. To create awareness of implications of the new European strategies under the Green Deal such as the CSS
2. To identify additional nanospecific research needs to support the CSS:
   a. One substance, one assessment approach
   b. Additional endpoints for safety of consumer products (immunotoxicity, endocrine disruption, neurotoxicity, respiratory system)
3. To discuss how to establish a trans-regulatory community to have discussions in support of the CSS
   a. Need for a nanospecific infrastructure to facilitate trans-regulatory discussions

The trans-regulatory aspect was tuned to:

- **Share lessons**: facilitate mutual learning amongst experts and stakeholders in an interdisciplinary and inter-domain fashion.
- **Identify priorities**: ensuring the most urgent scientific information needs and regulatory issues are integrated in a policy research agenda, in support of regulatory oversight and compliance.
- **Promote harmonization**: finding common solutions to relevant topics, such as data gaps, test guidelines and harmonization of methods.
- **Identify operational research agendas**: translate nanospecific issues in inputs for research agendas, funding mechanisms and other incentives to support and further develop risk analysis approaches, knowledge and data.

[1] A European Green Deal | European Commission (europa.eu)
[2] Chemicals strategy (europa.eu)
[3] A pharmaceutical strategy for Europe (europa.eu)
[4] Farm to Fork Strategy (europa.eu)

To that end policy makers, regulatory bodies, companies and other stakeholders involved in managing novel and emerging risks were invited. Participants were encouraged from a broad spectrum of disciplines and should have sufficient risk management, regulatory and policy experience to be able to contribute to discussions.

1.3 Spatial chat platform

The meeting was organized in Spatial chat, an innovative platform with a main stage room and different breakout rooms. This platform has enabled formal and informal interactions between the participants during discussions and during social breaks. The main stage room provided possibilities for participants to take the floor from the stage to ask questions or to give input to discussions. This platform has been appreciated by the participants and had added value compared to other more static platforms like Zoom or MS Teams.
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2. Programme of the workshop

Day 1: Monday 24 January 2022

Impact of Green Deal - Keeping up with policy ambitions – One substance one assessment

I: Plenary session: Why a second summit?

Goal: To inform participants on the results of the first RRAS (2019) and new developments under the Green Deal (Chemical Strategy for Sustainability)

10.10-10.30u: Lessons learned from the first RRAS (Susan Wijnhoven, RIVM)
Recap of the results of the first Trans-Regulatory Risk Analysis Summit
10.30-11.00u: Impact of the Green Deal: New policy ambitions, new demands for nanotechnology (Adrienne Sips, RIVM)

II: Interactive plenary session

11.15-12.30u: Possible contributions of Summit to Chemical Strategy for Sustainability (CSS) implementation actions (Lya Hernandez, RIVM/ Susan Wijnhoven, RIVM)
Menti-questions and discussion (linking the results of Summit to the EC tracking table for the state of the implementation of the actions announced under the CSS)
***12.30-13.30u**: Lunch, including additional lunch sessions*
- Worker follow-up workshop (Andrea Porcari, AIRI)
- Case studies and posters of participants

III: Plenary session: One substance, one assessment from different perspectives

Goal: Overview of gaps from the previous Summit that relate to one substance, one assessment Identification of new research needs and research questions.

13.30-14.30u: Plenary session: Keynote lecture on CSS: One substance one assessment
Keynote speaker: Andrej Kobe, (DG Environment, EC)
Reflection from participants and discussion with the audience

IV: Breakout session: Domain specific research needs for RA, recap of old and identification of new research needs

15.00-15.10u: Plenary introduction to breakout carrousel
15.10-16.00u: Breakout carrousel round I (**per domain**):
Recap of research needs identified in first Trans-Regulatory Risk Analysis Summit per domain:
Give people possibility to add additional research needs on white board, and comments during the next days

- Chemicals
- Worker
- Environment
- Cosmetics, Food
- Medicine

Day 2: Tuesday 25 January 2022

Impact of Green Deal - Keeping up with policy ambitions – Implications of new endpoints on risk assessment needs

V: Plenary session: Continuation of day I, research needs for RA

Goal: Identification of possible solutions to support CSS, how can a trans-regulatory perspective lead to solutions to domain specific regulatory issues?

10.00-10.10u 6. Recap of day I, agenda and intro day II
10.10-11.10u: Identification of additional domain specific research needs and trans-regulatory discussion on solutions (Lya Hernandez, RIVM/ Susan Wijnhoven, RIVM)

VI: Plenary session: Regulatory needs within different legislative frameworks

Goal: To inform participants on the regulatory needs within different legislative frameworks and give an overview on new endpoints within the CSS. What are the implications on risk assessment needs?

11.30-11.50u: Overview regulatory frameworks (Eric Bleeker, RIVM)
11.50-12.15u: Reflection on overview from participants (interactive discussion)

***12.15-13.30u**: Lunch, including additional lunch sessions*
- Worker follow-up workshop (Andrea Porcari, AIRI)
- Case studies and posters of participants

VII: Breakout session: Implications of New Endpoints in the CSS on risk assessment needs
Goal: To give an overview on new endpoints within the CSS. What are the implications on risk assessment needs (for nano)?

13.30-13.40u: Plenary introduction to breakout session New Endpoints within CSS
- Introduction to new endpoints in CSS
- Agenda of breakout carrousel and timeslot

13.40-14.30u: Breakout carrousel round III: New Endpoints within CSS
Small introduction by expert and discussion on new endpoints within the breakout group
- Immunotoxicity (Rob Vandebriel, RIVM)
- Neurological endpoints (Harm Heusinkveld, RIVM)
- Endocrine disruption (Shalenie den Braver, RIVM)
- Respiratory system (Hedwig Braakhuis, RIVM)

15.00-16.00u: Plenary feedback session
New information needs for risk assessment to meet the CSS
- Plenary 10-min pitch of results of each group and plenary discussion

Day 3: Wednesday 26 January 2022
Joint Session REFINE with Gov4 Nano:

09:00-09:10 Welcome (Monique Groenewold / Klaus-M. Weltring)
09:10-09.40: Set the stage Green Deal, Chemical strategy for sustainability:

- New Chemical strategy for sustainability (CSS) and Green Deal (Adrienne Sips)
- One substance one assessment initiative (Susanne Bremer-Hoffmann)
- Update on NMPB 13 projects (Monique Groenewold)

09:40-10:40: State of the art:

- Medicine/Medical devices: White paper, feedback from KEC2 + Gap Analysis (Blanka Halamoda-Kenzaoui)
- ISO Standards: Harmonization of standardization practices - current status and future needs (Denis Koltsov)
- OECD Guidelines: Standardization (Malta, OECD TGs) (Eric Bleeker)

11.00-12:00: Case studies where the impact of trans-sectoral collaboration would be beneficial
11:00-11:15 Brief introduction of case studies plenary
11:15-12:00 Discussions in parallel breakout groups

Theme A: Harmonization of regulatory methodologies and standardization practices
(Iron Oxide) (Danail Hristozov, Virginia Cazzagon, Gerrit Borchard, Lisa Pizzol)

Theme B: Interdisciplinary knowledge sharing and implications for regulatory frameworks
(TiO_2) (Eric Bleeker, Ana Maria Rincon, Susan Wijnhoven, Robert Geertsma)

Theme C: Keeping pace with innovation to identify emerging risks
(Graphene) (Lya Hernandez, Peter Wick)

12:00-12:45 Plenary session with summary and conclusions (Klaus-M. Weltring, Monique Groenewold)

- Short report of results from the three breakout sessions
  - Discussion with the audience on: How to organize trans-regulatory discussion on a continuous basis and what do we need to make it happen; What are the perspectives from other projects and regulators and industry and how do we integrate them.
- Conclusion and perspective of the joint session

12:45-13:00 Closing

3. Results

In this section, results are described that were generated during plenary as well as breakout sessions and that are relevant for the outcome of the workshop. A bird's eye view of these results is provided in the text box below.

Bird's eye view of results of the 2nd Trans-Regulatory Risk Analysis Summit (RRAS2022)

The aim of the 2nd Trans-Regulatory Risk Analysis Summit (RRAS2022) was to raise awareness for (new) challenges for risk analysis of nanomaterials posed by the goals and ambitions of the Green Deal (GD) and underlying relevant strategies. With emphasis on the potential impact of the Chemical Strategy for Sustainability (CSS). Moreover, specific topics from the CSS, e.g. one substance, one assessment, and new toxicological endpoints to be addressed (like endocrine disruption) were discussed from a trans-regulatory perspective.

- **Share lessons**: Nanospecific issues and lessons learned need to be identified in the context of the 87 actions under the CSS. Trans-regulatory exchange of knowledge and information (e.g. through meetings like an RRAS) are essential to meet the required timelines to address the new issues. Share lessons learned in the nanosafety community and share this with other relevant communities (like the new HE-PARC programme on chemicals risk assessment). Relate to the transitional character in addressing the goals and ambitions of the CSS, by continuous learning and continuous improvement.

- **Identify priorities**: Develop *activities* to identify, prioritize and address nanospecific needs and issues related to the 87 actions of the CSS. Update regulatory and research roadmaps for nanomaterials frequently.

- **Promote harmonization**: Complexity will increase as transitions will take place in three dimensions, i.e. 1) achieving ambitious policy goals addressing an integrated approach for safety, sustainability and circularity, 2) modernization of chemicals risk assessment by means of dealing with mixtures, new techniques and digitalisation (e.g. the role of AI) and 3) the stimulus by modern innovation policies to develop new and more advanced (nano)materials. These transitions will follow a path of continuous improvement. Risk (and sustainability) governance will therefore be challenged to deal with the dynamic character of a transition, in which sharing state-of-the art information on all three dimensions is critical.

3.1 Triggers for the 2nd RRAS?

- The results of the 1st RRAS (2019) were presented in a priority list of regulatory issues and research questions.
- The Green Deal is the new policy strategy of the EU aiming to 1) become climate neutral by 2050, 2) protect human life, animals and plants by cutting pollution, 3) help companies become world leaders in clean productions and technologies and 4) help ensure a just and inclusive transition. The development of new types of (nano)materials, so-called advanced materials, is very much stimulated as they are regarded pivotal for technological solutions to address the Green Deal goals.
- Better protection of human life, animals and the environment by cutting pollution is translated into goals as toxic-free environments and zero-pollution. To achieve that, the Chemical Strategy for Sustainability describes new approaches like one substance, one assessment; more attention to specific toxicological endpoints to control consumer safety; or Safe-and-Sustainable-by-Design.

- The nanosafety community is urged to identify the nanospecific knowledge needed to address these new aspects.

3.2 Aligning to the Chemical Strategy for Sustainability (CSS)

- In the second session of the day, the goal was to create awareness among the audience with regards of the implications of the CSS and reflect and identify potential risk assessment challenges. For this highly interactive session, the Mentimeter tool has been used to gather input from the audience through targeted questions that were answered live.
- Figure 1 depicts the broad spectrum of regulatory domains represented by the participants.

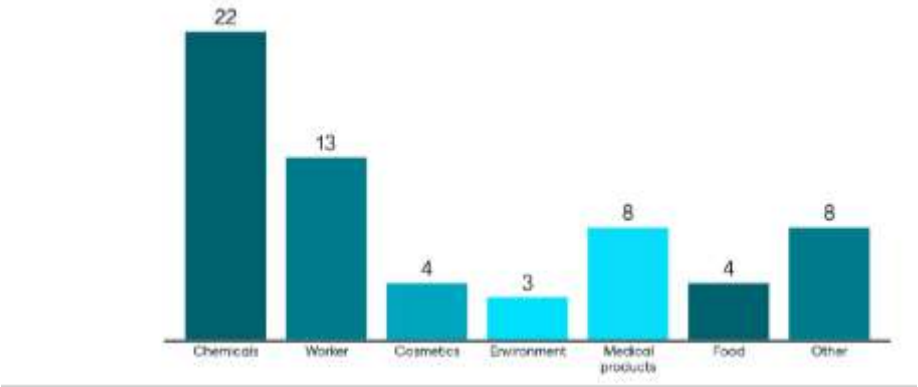


Figure 1: Overview of domains in which participants of the Summit are working (34 participants answered, multiple answers were possible).

3.2.1 Reflections on observations of 1st RRAS (2019)

Participants were asked whether they recognized the following observations of the first RRAS in 2019 (Figure 2):

At the level of process:
- Systematic stock-taking of scientific knowledge needs for regulatory purposes is absent
- Present regulatory research agendas are too much focused on one or a few regulatory domains; lack of trans-regulatory approach
- Risk assessors are not structurally consulted for knowledge needs
- The development of regulatory science lacks a structural link to funding agencies

At the level of content (information, science and tools):
- Information is scattered and fragmented across a multitude of regulatory domains.

At the level of organisational infrastructure:
- No structure is available that provides or facilitates this stock-taking
- No structure is available that facilitates a regular exchange of information and insights

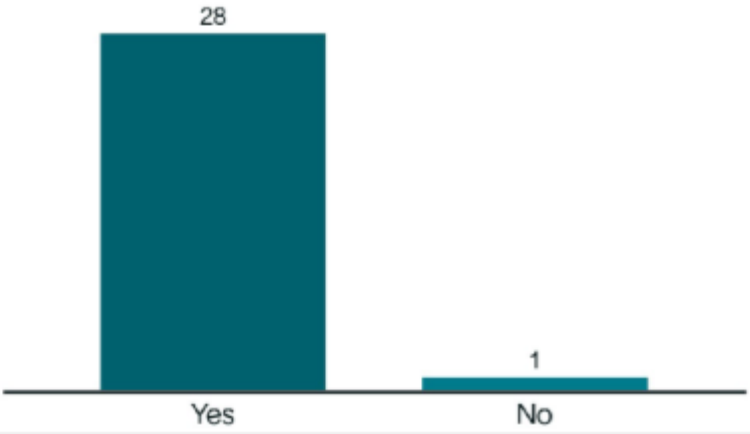


Figure 2: Do you recognize abovementioned observations of the first RRAS (29 participants answered)?

3.2.2 Input on the additions to meet new policy ambitions of the European Commission such as CSS

In the following two questions, participants have been asked to give input on the additions needed to meet the new policy ambitions of the European Commission, such as the Chemical Strategy for Sustainability (Annex II, Figure A - 1). A subsequent question was posed on the awareness of any activities to fill in the gaps mentioned (Annex II, Figure A - 2).

Required actions foreseen in the nanosafety community to address the ambitions and goals of the CSS focused on the following aspects:

- Improved knowledge and information sharing, e.g. trans-regulatory or outside the nanodomain
- Improved connections to developments in industry, use trusted environments, dialogues
- How to weigh safety, sustainability, functionality (circularity); recognize that addressing all these values well is a transitional process of continuous improvement

Activities already in place to address the abovementioned gaps:

- Activities mentioned reflect new or running European projects creating initiatives to connect different stakeholders (e.g. nano risk governance projects, new network for SSbD of materials)

3.2.3 Reflection and identification of potential risk assessment challenges and research needs in the light of the CSS

In the following part of the session, there was time for reflection and identification of potential risk assessment challenges and research needs and the link with the CSS. The topics considered relevant to put on the agenda of the second RRAS covered:

- Safe and Sustainable by Design (SSbD)
- Non-toxic material cycles
- Endocrine disruptors
- Protection against most harmful chemicals
- Chemical mixtures
- One substance, one assessment

3.2.3.1 Safe and sustainable by Design (SSbD)

- In the 1st RRAS the research on early identification of hazard of nanomaterials was recognized as an important risk assessment challenge.
- Expansion from SbD to SSbD and standardised methods and tools for early hazard assessment are considered necessary but will bring additional challenges.
- Participants were asked about the "by design" aspect and how they envision the role of regulatory risk assessors in this respect? Nineteen out of 25 respondents envision a role of the regulatory risk assessor in the "by design aspect".
- Many suggestions were given by the audience for the type of role of the regulatory risk assessor in this respect (Annex II, Figure A - 3)
- Regarding the role of regulatory risk assessors, input ranged from no role to a very steering and descriptive role. In general involvement of regulatory risk assessors in the role of advising and help to bring SSbD into practice was favoured.
- In order to extend from SbD to SSbD participants stressed (Annex II, Figure A - 4):
  - the need for more clarity on what sustainability should entail,
  - that circularity should be included,
  - that it is too much to address all at the same time, so priorities or weighing are needed
  - to have an eye for feasibility to put it into practice

3.2.3.2 Non-toxic material cycles

In the CSS, the ambition of the Commission is to:

- Minimize the presence of substance of concern in products
- Develop methodologies for chemical risk assessment that take into account the whole life cycle of substances, materials and products.

In the 1st RRAS, two risk assessment challenges for non-toxic material cycles were identified:

1. Identification of nanomaterials (or advanced materials) of concern and
2. A better understanding of the life cycle impacts (form manufacturing to end of life) of nanomaterials or advanced materials in products.

In this 2nd RRAS, the audience has been asked on how to connect the risk assessment of materials and products, but also include the impact of production processes. The CSS explicitly focuses on this connection.
The answers were of diverse nature, merely addressing that improved interconnection from a risk assessment point of view is required, rather than proposing straightforward solutions on how to give shape to such interconnections (Annex II, Figure A - 5).

3.2.3.3 Endocrine disruptors

The CSS describes the ambition of the Commission to establish a legally binding hazard identification of endocrine disruptors, and to ensure that ED are banned in consumer products, as well as to ensure the protection of workers.

During the 2nd RRAS we asked ourselves which nanospecific issues we could add to the already identified risk assessment challenges with respect to ED effects of chemicals. It was also discussed that the use of *in vitro* studies for assessing endocrine disruptive effects is a challenge, while it is a prerequisite in cosmetics where animal testing is banned.

In line with this, the question to the audience was whether they were familiar with a hypothesis that nanomaterials could cause endocrine disruptive effects? And if so, what

could this be? In general, there was no awareness of such a hypothesis (Annex II, Figure A - 6).

3.2.3.4 Protection against most harmful chemicals

This is a very general topic in the CSS covering that consumer products in general should not contain any hazardous chemicals. Therefore, a better understanding on the life cycle impacts (from manufacturing to end of life) of NMs or advanced materials in products is needed.
In addition, an assessment for vulnerable groups is needed in this extended approach (children, elderly, pregnant women).
An integrated risk assessment is needed in which different endpoints are covered: CMR, ED, chemicals (nanomaterials/ advanced materials) affecting the immune, neurological or respiratory systems and distribution to specific organs. One of the issues, already identified in the CSS, is the lack of standardized methods. Nanospecific issues that need awareness in developing such standardized methods were discussed in this part of the session.

Additional Mentimeter questions have been asked on knowledge of and methods for different endpoints and age specific effects. The input is reflected in the Figures 3, 4 and Annex II, A - 7. In summary it was the view of the audience that:

- There is not enough nanospecific knowledge to perform risk assessment for neurotoxicity and ED; for immunotoxicity and distribution to specific organs there seems to be a more ambivalent view (Figure 3).
- A similar answer was derived from the question whether there are sufficient nanospecific analytical methods. During the discussions, it appeared that the word standardized was interpreted in different ways (Figure 4).
- The Mentimeter question regarding vulnerable groups appeared to be challenging, hinting that this topic can be regarded as food for further thought. One of the groups specifically discussed was pregnant women and the unborn child. In analogue to what has been found for micro/nanoplastics, effects on the placenta caused by small particles could be a topic of interest.

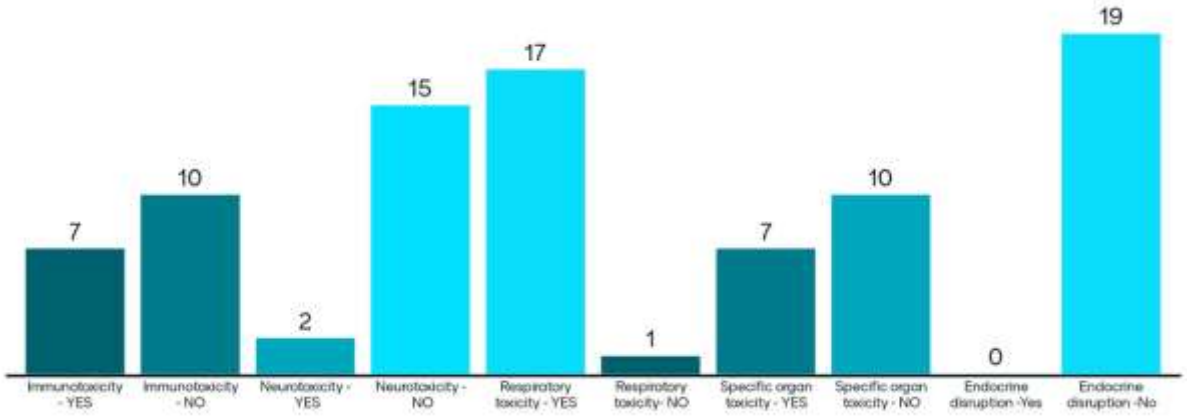


Figure 3: Do we have enough knowledge to perform nanospecific RA for the following endpoints (14 participants answered)

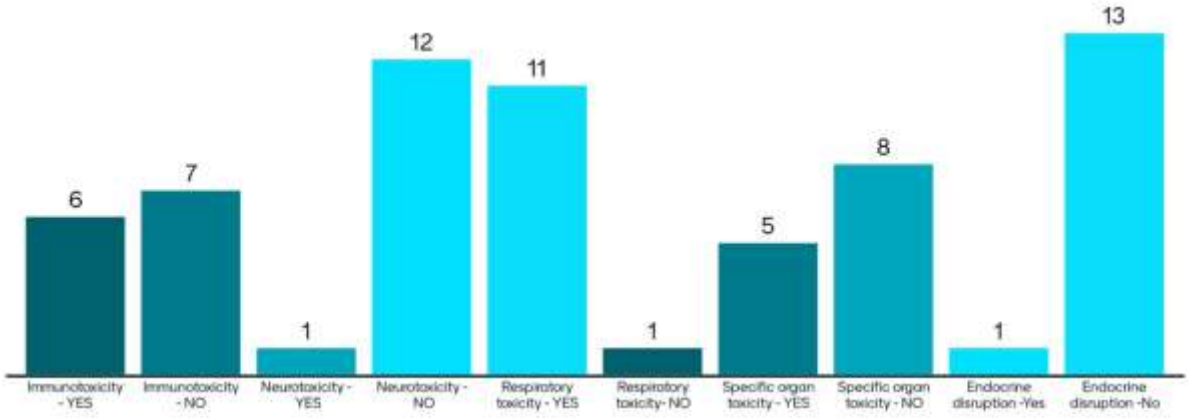


Figure 4: Are there enough nano-specific analytical (standardized) methods to determine the nano-specific toxicity for the following endpoints (14 participants answered)

3.2.3.5 Chemical mixtures

The ambition of the Commission is to assess how to best introduce a mixture assessment factor for the safety assessment of substances. Provisions for the combination effects in other relevant legislations are also further formulated. In the subsequent Mentimeter question participants were asked whether these challenges are also considered relevant for nanomaterials? And how could the nanospecific issues be solved? Would traditional testing methods suffice or are new methods like new approach methodologies (NAMs) and machine learning/AI essential (Annex II, Figure A – 8)?

- There was no uniform answer to this question, but answers leaned towards the application of NAMs, AOPs etc., due to the high complexity caused by the continuum of different forms, sizes, etc., and a lack of knowledge on which physico-chemical characteristics drive nanotoxicity.

3.2.3.6 One substance, one assessment (OSOA)

Proceeding the afternoon session scheduled on this topic, some first reflections were gathered. The link between reflections of the 1st RRAS (as summarized in section 3.2.1) with the OSOA figure (Figure 5) was further discussed.

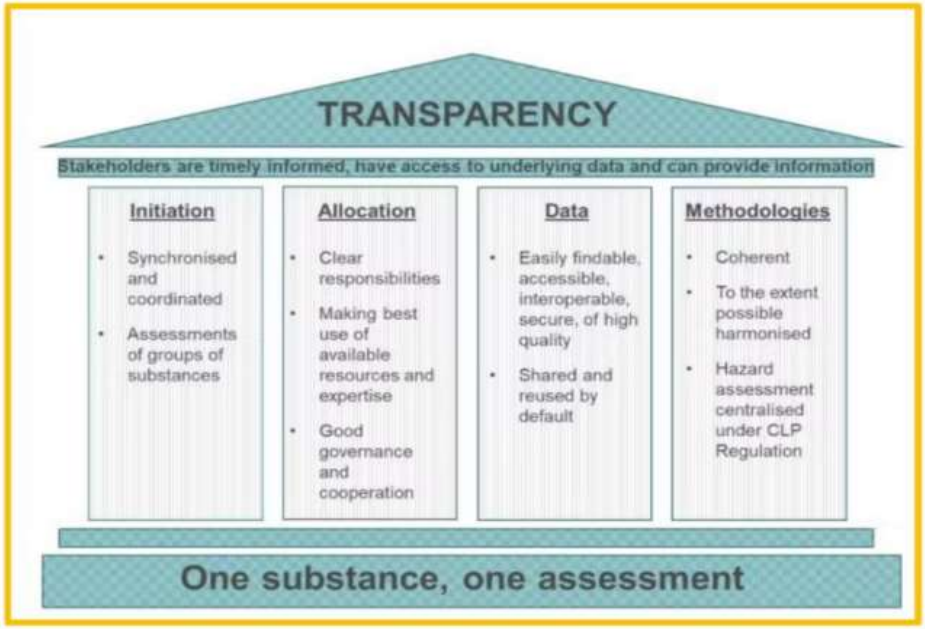


Figure 5: One substance one assessment approach within the CSS with the four different pillars.

During the discussion the following risk assessment challenges were seen:

- How to give shape to trans-regulatory collaboration
- Alignment of the different regulatory frameworks
- Risk assessment of multi-component nanomaterials, advanced materials in products

Participants were asked what would be needed to bring the knowledge together in the search for trans-regulatory input (Annex II, Figure A - 9). Needs concentrated around:

- shared databases with reliable data
- a platform for knowledge and information exchange
- formal and informal supportive arrangements to facilitate exchange

3.3 Plenary Session: One substance one assessment (OSOA)

The subject of "one substance, one assessment" in the CSS has been further elaborated in a keynote lecture by dr. Andrej Kobe (DG Environment, EC). Personal reflections were given by three experts:

1. Dr. Christoph Rousselle (ANSES) as representative of the PARC project
2. Prof. dr. Agnes Oomen (RIVM) as member of the EFSA working group of nanomaterials in food and the RIVM Working Group on nanotechnology covering many regulatory domains
3. Dr. Danail Hristosov (EMERGE) as expert in a variety of European nanosafety projects, and outcomes

A summary of the presentation and the reflections is covered in Figure 6.

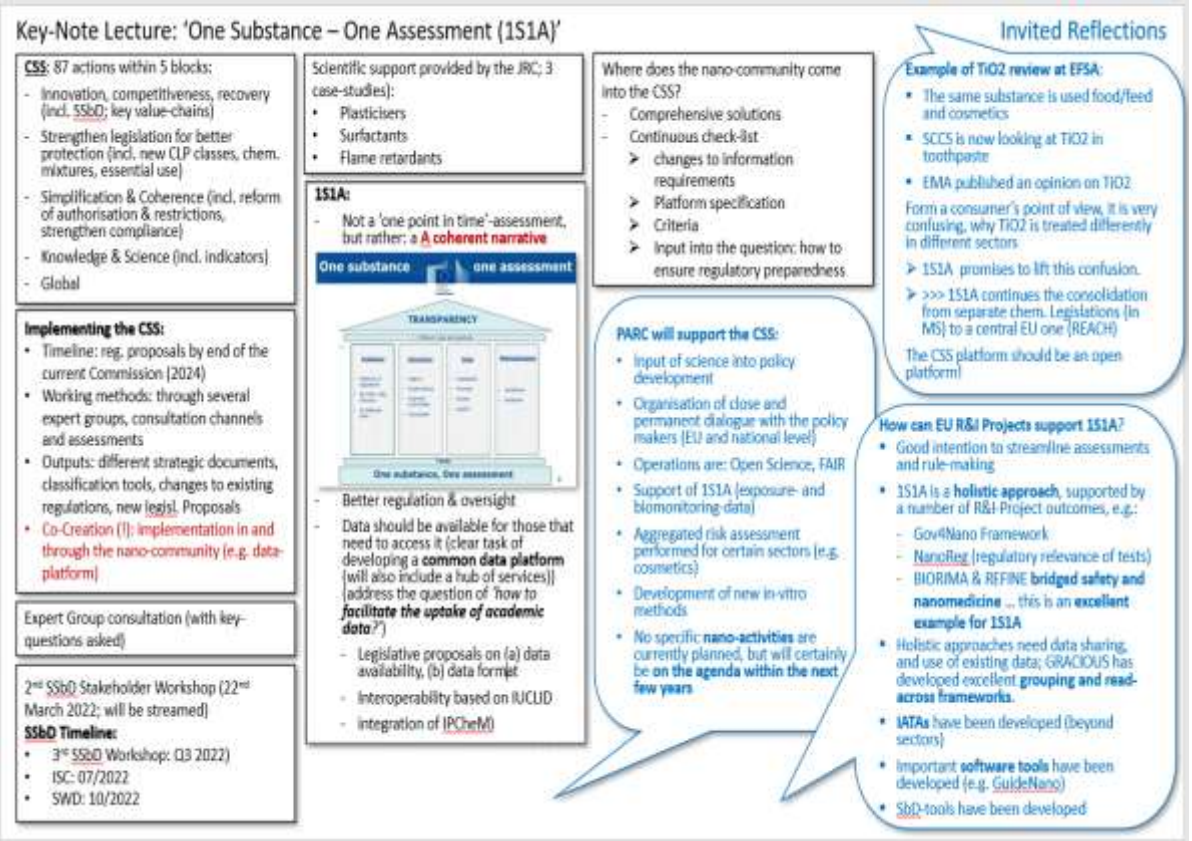


Figure 6: Summary of keynote lecture and reflections of different stakeholders

3.4 Breakout session: Domain specific research needs for RA, recap of old and identification of new research needs

In the following breakout sessions of the workshop, the participants were asked to discuss previous identified research needs from the perspective of the following regulatory domains:

- Chemicals
- Worker
- Environment
- Cosmetics/food
- Medicines/ medical devices

In the different (virtual) breakout rooms, risk assessment issues of the 1st RRAS were presented and discussed. An overview of these issues as identified in the 1st RRAS is described in Table A - 1 and Table A - 2 (Annex III). These tables describe "Issues with respect to toxicity testing: exploratory research or validation of tests of NMs" and "Issues with respect to regulatory risk assessment of NMs", respectively. Per domain and group the specific issue, and any overlap in issues between groups is presented. Most of the issues are potentially relevant for all regulatory domains.

Participants of the 2nd RRAS were invited to identify research needs that should be added to the list of the 1st RRAS. This input has been processed in the subsequent plenary session (see paragraph 3.5).

3.5 Plenary session: Research needs for RA

In the first plenary session on the second day, the goal was to identify potential additional nanospecific issues to address the goals and ambitions of the CSS, and to identify how domain specific regulatory issues could benefit from trans-regulatory approaches (Figure 7).

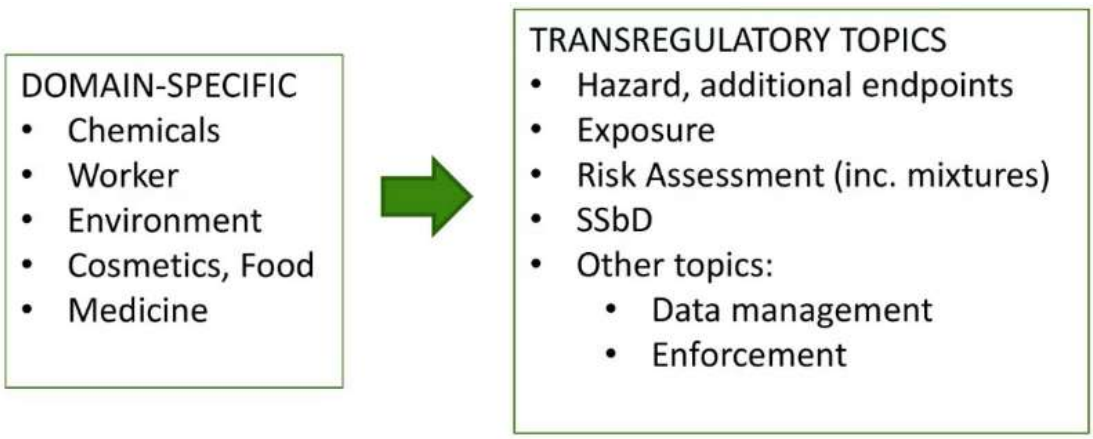


Figure 7: Approach to identify trans-regulatory topics

3.5.1 Inventory of additional research needs per domain

An inventory of the additional research issues per domain was made from the input received in the various breakout sessions at the first day.

An overview of the additional research needs per domain is given in the following list (text box below), distributed in the categories conform Figure 7:

- Hazard, additional endpoints
- Exposure
- Risk assessment (Incl. mixtures)

I. Hazard, Additional endpoints

Chemicals

- The relevance of **ED for ENMs** needs further research
- Is there any needs to study **cardiovascular effects**, air pollution showed that one of the major pb is cardiovascular ultrafine particles
  - There is already done quite some research in this area, suggesting that ENMs may indeed show similar potential to cause **cardiovascular effects**. Is this sufficiently covered on the **regulatory side**?
- JRC has report on dealing with additional endpoints using **New Approach Methodologies** (NAMs); all still in first level of discussion.
- Refine/develop methods/tools for the **measurement/determination of NM** for identification, determination of occurrence and amount. (etc.,)

Environment

- **New Approach Methodologies**: there is limited progress
  - *On **NAMs** some progress for bioaccumulation, first steps on tiered approach from chemical, in vitro, earthworm testing*
- **Uncertainties** of applicability of NM methods for **advanced materials**
  - ***New endpoints** for advanced materials, e.g. release of components (at different environments/points than intended)*
  - ***New functionalities:** Interaction of electromagnetic field with nano (specially with electric /magnetic conducting fibers); Agricultural designed nano can be absorbed by plants*
  - *So far most research still focused on 'simple' metallic nanomaterials, other types of materials are still a main challenge.*

Environment

- There are some advancements in **standards/protocols**
- **Life cycle thinking approach**:
  - *A question is to **how to make end-of life product a no waste any longer**; define best techniques to go ahead*
  - *Recyclability sustainability requires much broader interdisciplianry approaches to come to solutions, including new energy resource/other resoruse and changes of **public's behaviour.***

Worker

- New approaches: Get rid of determining toxicity extrapolation for animals
- Most harmful chemicals
  - *Integrated risk assessment approach*
  - *link with issues related to multi-parameter exposure assessment*
- Unclear CLP, DNELs
- One Substance, One Assessment:
  - *The initiation step ask for assessing groups of substances: key also in OSH activities*
  - *The data step asks for sharing and reuse of data: key to share exposure scenarios as well*
  - *methodologies step: establishment of an EU repository of health-based limits values*

Cosmetics

- **Data availability:** Access to in vivo (and other data) across regulatory frameworks limited, but needed because no in vivo testing allowed→ progress, see e-nano mapper. There is a lot of data from many projects, not accessible to everyone
  - *No access to industrial data and EU project data*

Medical products

- **Additional hazard classes** according to CLP revision: learning from pharmaceuticals e.g. immunotoxicity, neurotoxicity, increased allergenicity of e.g. pollutants, proteins use nanomaterials as carrier

- How can we **harmonise standardisation requirements** and regulatory acceptance deriving from different standardisation bodies (national member body of ISO, CEN nominate experts to write vs ASTM each organisation can be a member). Use of these standards is voluntary. OECD MS, umbrella organisations vs ICH also MS docs are publically available. Do we need research on applicability domains if methods should be accepted for different

II. Exposure

Chemicals

- Development of **accurate environmental exposure measurement** techniques around production industrial sites

Environment

- Need for development of Around industrial site **accurate measurement technique of exposure in air**
  - *Presently, TEM methods are most suitable for ambient air exposure, but quantitative evaluations are still difficult to establish from EM measurements.*
- Improvement of exposure modelling within the context of risk assessment (hazard + exposure). Plus better link outputs of hazard assessment with what is measured at the workplace (including in the context of Regulatory exposure assessment)

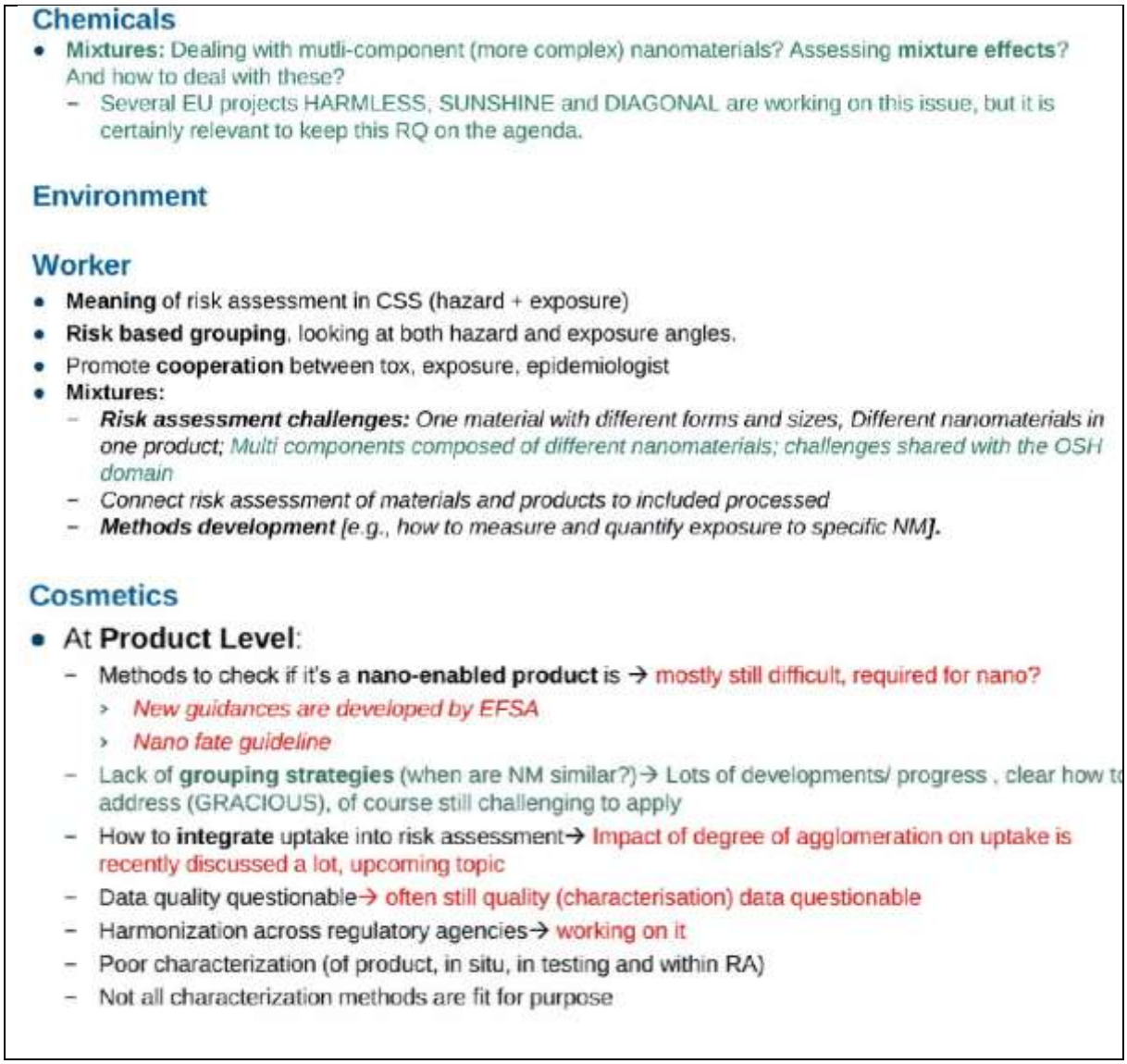
Worker

- Better defining what is needed in terms of **biomonitoring** (and opportunities of **advanced techniques** to improve quality of data from biomonitoring)
- **exposure** should be considered more clearly as part of this CSS. In particular, in the case of **hazardous substances**.

Cosmetics

- **Data availability:** No exposure data→ slight progress

III. Risk assessment



Many of the above-mentioned input from the breakout session is referring to issues that are not nanospecific. However it was mentioned that the nanosafety community might be well equipped (open-minded, open for collaboration, policy and regulatory oriented) to explore how to tackle these more general issues best.

Subsequently, questions were formulated to translate the above-mentioned domain-specific issues into trans-regulatory research questions and solutions. The questions formulated were not a translation of the points raised in the summary of issues, but much more given in by issues that result from the state-of-the-art and the new demands from the CSS.

3.5.2 Mentimeter questions to trans-regulatory issues

Mentimeter questions were formulated for the different categories, first hazard endpoints, and then followed by exposure and risk assessment. The questions were focused on specific trans-regulatory issues and research that needs to be addressed in the future. Additionally, what nano-specific effects are missing in the list of additional endpoints and whether there is a role for NAMs in the risk assessment of nanomaterials:

- Regarding **measurement of physico chemical characteristics** answers were still quite in line with the results of the 1st RRAS (Annex II, Figure A - 10).

- A sound set of **test methods for ED effects** is still under development. It is to be explored whether these tests are valid for testing nanomaterials. Moreover, a hypothesis is required how the particle aspect could contribute to ED effects (Annex II, Figure A - 11).

Answers to the question whether **nanospecific effects** were missed **to the list of additional endpoints** (as given in by the CSS) did bring points of attention rather than additional endpoints. These points of attention covered topics as epigenetic effects, new types of functionality and their relation to other types of endpoints, etc. (Annex II, Figure A - 12).

- **SSbD** has been in several domain-specific breakout groups. Below a summary of the discussions.

Chemicals

- 2 discussions: **marketing and pre-marketing**
  - Mixing ideas and concepts and terms; what is sustainability? What is safe and what is safer? What is the difference between marketing and pre- marketing? Pre-market is surrounded by issues such as IP
  - Pre-marketing: Develop **test beds** to address this in the pre-market stage
    - ***Paradigm shift*** *to allow* ***innovators to discuss with regulators*** *under specific rules and conditions; start* ***working out solutions together to improve safety and sustainability****; you have to get people together to do this.*
- Important is also know how to **incorporate sustainability next to safety into a safe and sustainable by design approach.**
- How can we **connect** all the ongoing H2020, HE, other projects and **initiatives**; create synergies and connect all data and approaches.
  - *Look at regulatory issues in other legislative frameworks and try to find synergies*
  - *Consider changes in the Evaluation in REACH; Do we know if dossiers including NMs?*

Environment

- Concerns in case of **uncontrolled, uncontained environmental release**, especially for advanced materials: how to make it '**sustainable by design**'. What instruments do we have to assess impact and effects?
- **(Screening) tools** to assess/estimate aspects of **sustainability**: e.g. various environmental footprints, resource demand, etc.
- **Incentives:**
  - *Reduce taxes to 0 for products made sustainable and circular by design, and tax everything else; +20% to increase incentives from industry to more towards better compounds*
  - *Some kind of premium*

The role of regulatory risk assessors in SSbD
In subsequent Mentimeter questions participants were of the opinion (22 out of 26) that in the light of SSbD the work of risk assessors should be extended to also include sustainability assessment. Risk assessors should be trained to assess sustainability. The view on who should train risk assessors ranged from experts and consultants on sustainability to learning communities (Annex II, Figure A - 14).

Only a minority of the respondents (5 out of 25) considered that **'by design' activities'** should be part of the regulatory dossier. Reflections whether the criteria for SSbD need to take nanospecific requirements into account ranged from 'not needed' to increased attention for physical characteristics (Annex II, Figure A - 15).

Finally, most of the respondents (17 out of 23) considered AI could be a powerful tool for development of predictive nanotoxicology.

3.6 Plenary session: Regulatory needs within different legislative frameworks

The goal of this session was to inform participants on the regulatory needs within different legislative frameworks and give an overview on new endpoints within the CSS. What are the implications on risk assessment needs? Eric Bleeker (RIVM) presented an overview of nanospecific regulatory knowledge needs. Figure 8 depicts a summary of the presentation.

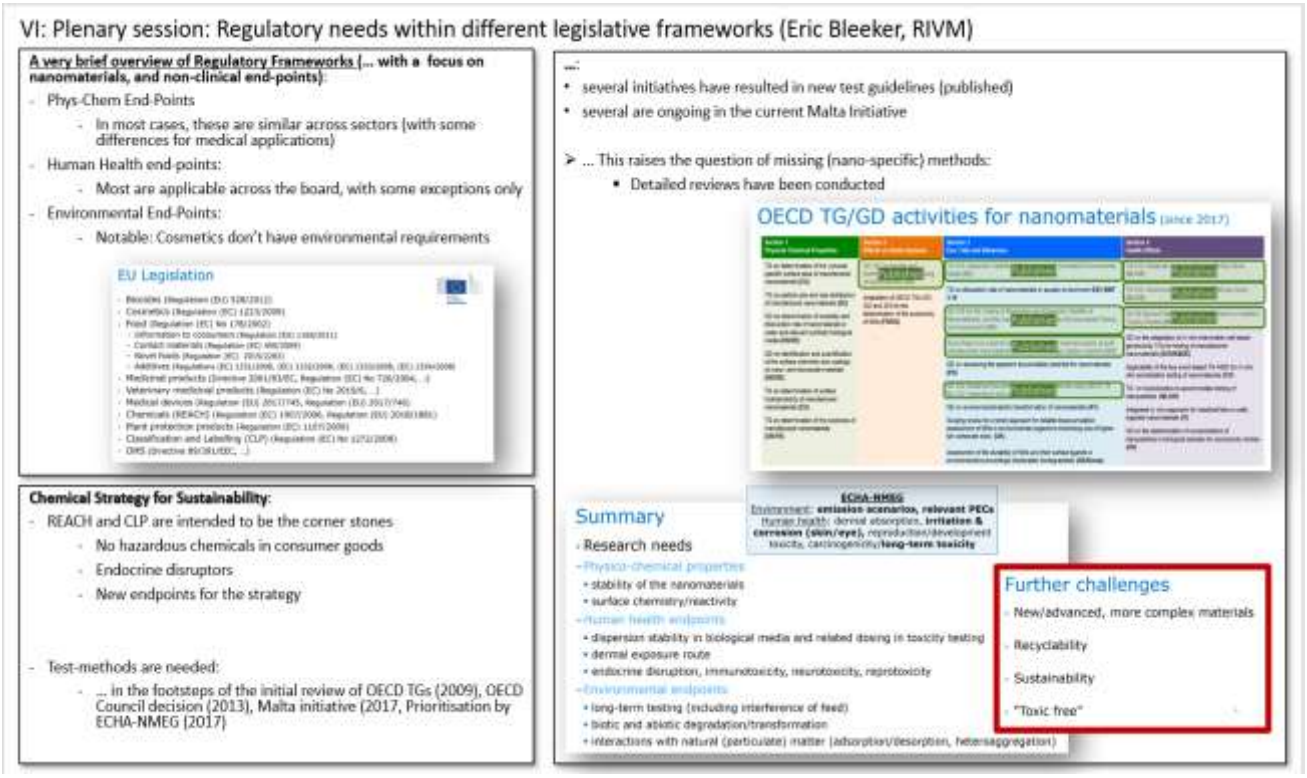


Figure 8: Summary of regulatory needs within different legislative frameworks

3.7 Breakout and plenary session: Implications of New Endpoints in the CSS on risk assessment needs

In the subsequent breakout session, the focus was on the "new endpoints" in the CSS in order to update the outcomes of the first RRAS. The ambition of the Commission is to extend the generic approach for risk assessment to ensure that consumer products do not contain hazardous chemicals. Apart from the well-known endpoints as cancer, gene mutations, effects on reproductive or endocrine system, the focus is on relatively "new endpoints" as the immune, neurological or respiratory systems and chemicals that are toxic to a specific organ.

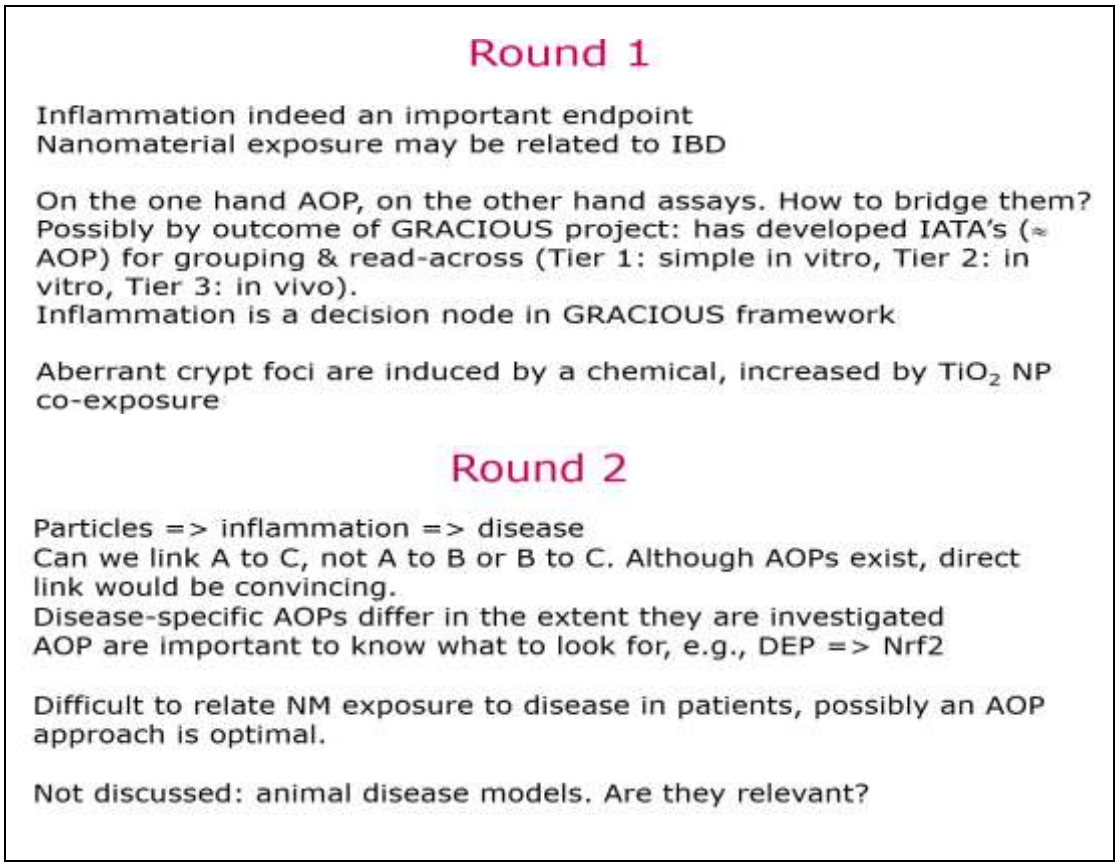
Discussions on some of these new endpoints were introduced by four experts in the field in different breakout rooms.

- Immunotoxicity (Rob Vandebriel, RIVM)
- Neurological endpoints (Harm Heusinkveld, RIVM)
- Endocrine disruption (Shalenie den Braver, RIVM)
- Respiratory system (Hedwig Braakhuis, RIVM)

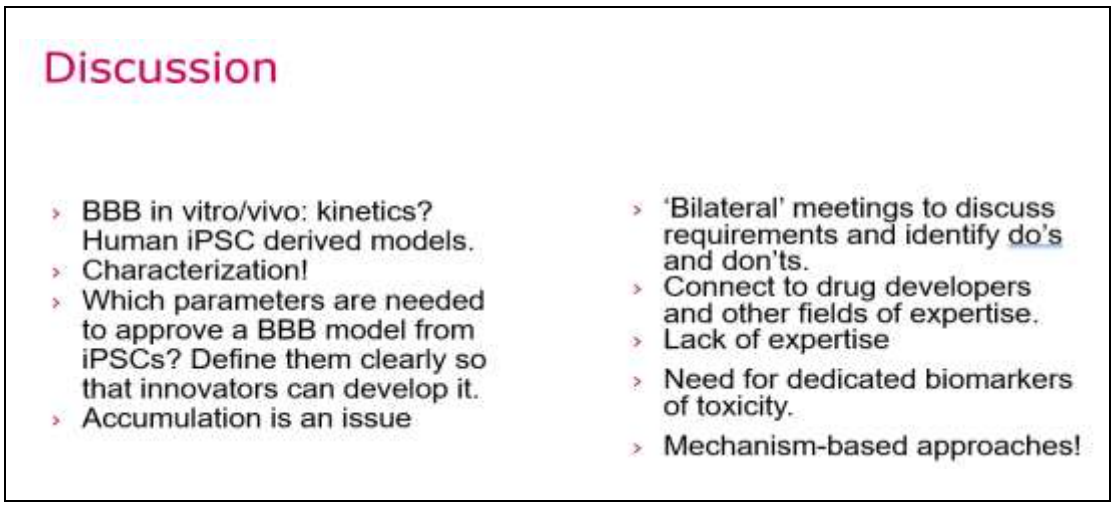
Participants discussed these topics in two rounds, after which the results were summarized in a plenary session.

In the plenary feedback session, the following points of discussion were mentioned (see text boxes per endpoint below).

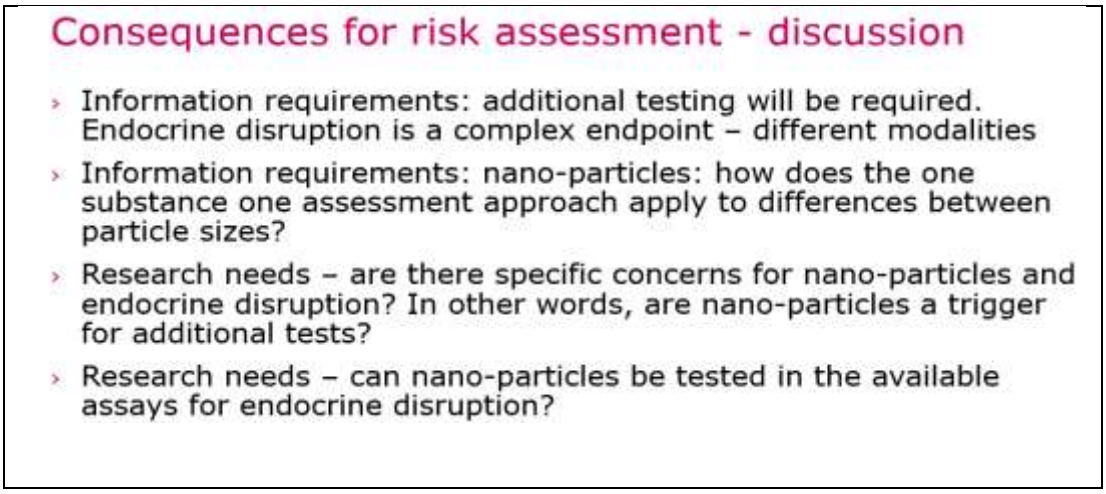
- **Immunotoxicity**



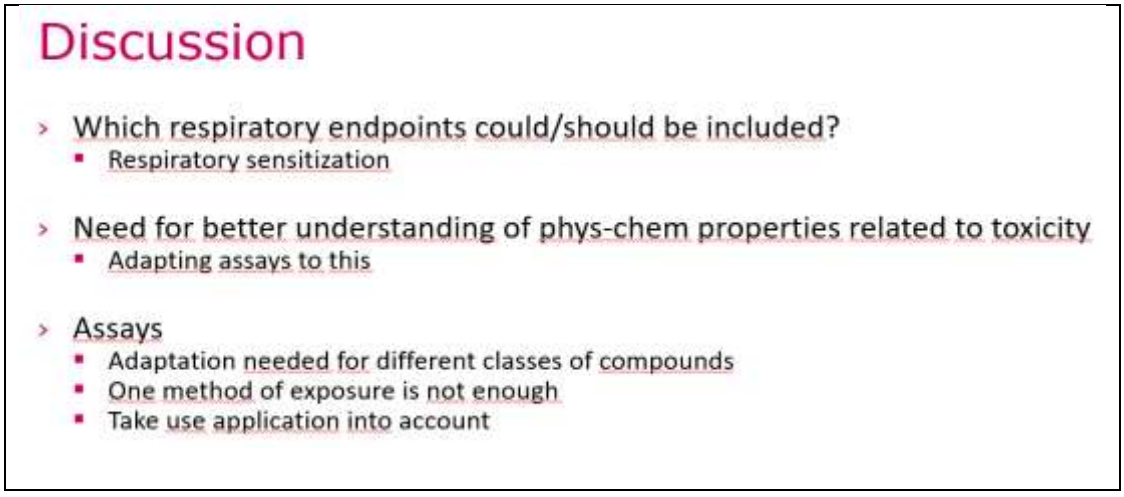
- **Neurotoxicity**



- **Endocrine disruption**



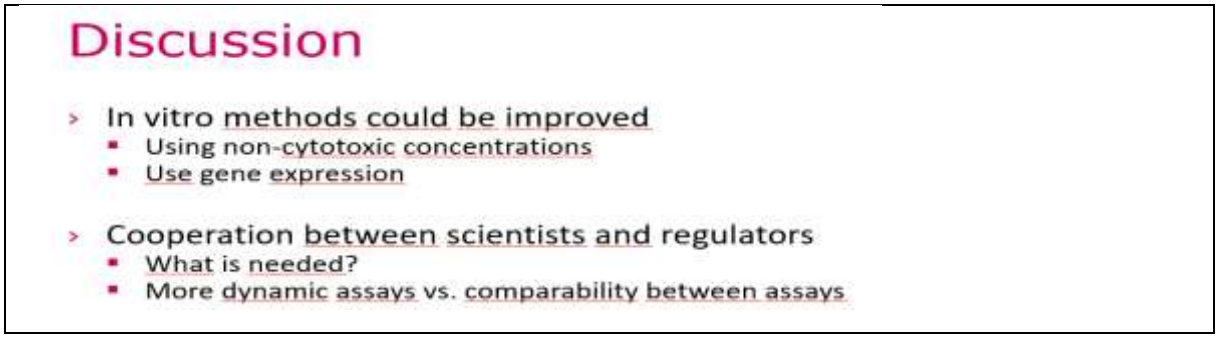
- **Respiratory system**



All discussions supported the need for further identification of nanospecific issues that may arise for these endpoints. Issues range from exploring whether the particle aspect induces these types of effects to validity of tests for nanomaterials.

Some general important remarks are given below:

- **General discussion points**



3.8 Joint Session between the Gov4Nano 2nd Trans-Regulatory Risk Analysis Summit 2022 (RRAS2022) and the 3rd REFINE Knowledge Exchange Conference (KEC3).

The final session of the 2nd RRAS was a coproduction of the H2020 projects Gov4nano and REFINE. The **aim of the joint session** was

- to raise awareness for development and mutual acceptance of test methods to overcome regulatory silos across.

The Joint Session connected two events i.e. the final session of the G4N Trans-Regulatory Summit and the start of the REFINE KEC3 meeting). While the 2nd RRAS aimed to find solutions to address the complexity of risk analysis for nanomaterials and to meet the ambitions of the Green Deal and the new Chemical Strategy for Sustainability, the KEC3 presented a comprehensive and realistic state-of-the-art of the current scientific regulatory framework for the risk-benefit assessment of nano-enabled health products and the existing and to be developed tools to meet the regulatory challenges within this framework.

The Joint Session started with an overview of the new demands to address nanosafety as put forward by the Green Deal and the ambitions of relevant underlying strategies such as the Chemical Strategy for Sustainability (CSS). Presentations were given by Adrienne Sips (RIVM), Susanne Bremer Hoffmann (JRC) and Monique Groenewold (RIVM). This was followed by presentations of the current status of regulations and standardisation regimes by Denis Koltsov focusing on ISO standards and Eric Bleeker (RIVM) focusing on OECD test guidelines.

The core of the joint session consisted of three themes with case studies dealing with

1) Theme A: Iron oxide as example where combining data and knowledge from both regulatory communities could have added value
2) Theme B: Titanium dioxide as showcase how new insights in safety in certain regulatory domains have significant impact in other regulatory domains
3) Theme C: Graphene as an example for a new advanced nanomaterial with a broad spectrum of applications, driven by the demand for innovative solutions to societal challenges

The case studies were discussed in different breakout rooms. The discussions were introduced by one or more pitches on the subject. For iron oxide there were pitches from Virginia Cazzagon (University of Venice), Gerrit Borchard (University of Geneva), and Lisa Pizzol (GreenDecision). TiO_2 pitches were given by Ana Maria Rincon (EFSA), Susan Wijnhoven (RIVM) and Robert Geertsma (RIVM) and Graphene has been introduced by Lya Hernandez (RIVM) and Peter Wick (EMPA).
In the final plenary session, the moderators of the three sessions haven given a summary of the discussions.

Theme A: The consumer safety focus is on risk and exposure assessment while the medical sector focus is on balancing medical benefit with possible risks (side effects). However, the advancement of knowledge in both communities down to the molecular level and mechanistic understanding of toxic effects now calls for better sharing of data and experiences to cross-fertilise the safety assessment in both communities and to synergize efforts.

Theme B: The feedback for the discussion is summarized in Figure 9.

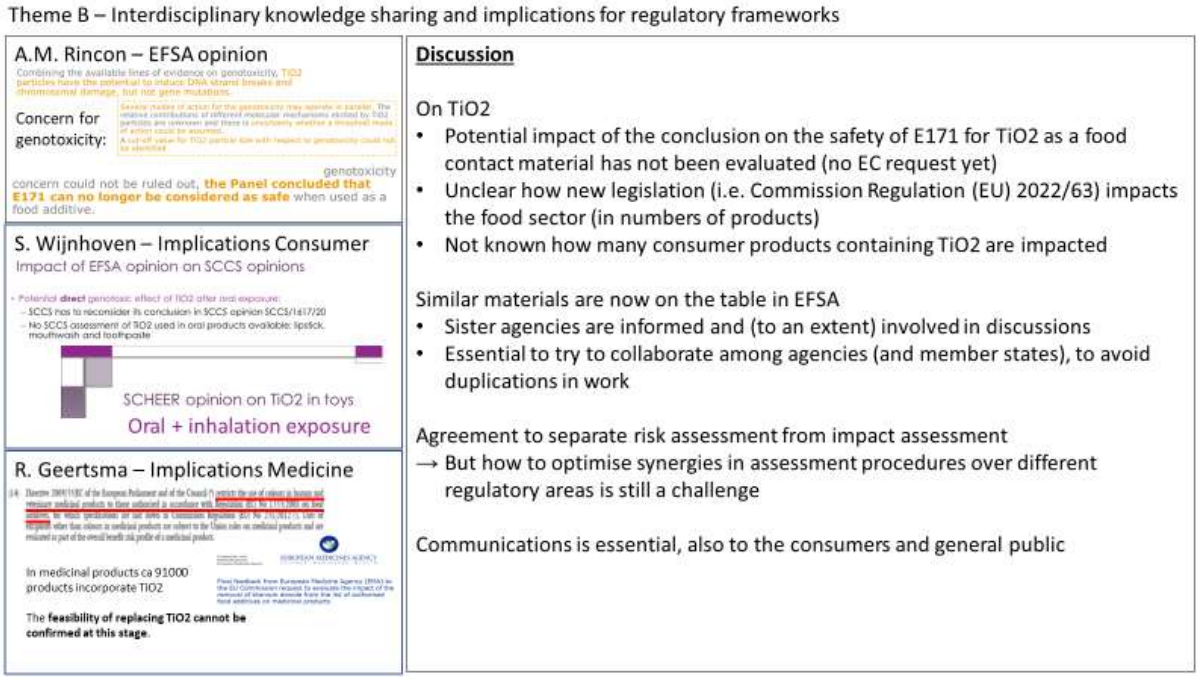


Figure 9: Summary of Theme B: Interdisciplinary knowledge sharing and implications for regulatory frameworks

Theme C: Graphene exists in many forms. A classification system is developed under the regime of the European Graphene Flagship activities. Moreover, elaborate in vitro studies on biological responses have been performed. Nevertheless, there still are many unknowns about safe use, application and production of graphene. Graphene is targeting more and more different markets, so increasing the demand for clarity on how to handle this material in a regulatory context. To that end, a working group has been established by the Graphene Flagship (the name REACH/ECHA WG is a misleading name; this WG is not an ECHA WG - (Figure 10).

Graphene flagship: Graphene research, innovation and collaboration | Graphene Flagship (graphene-flagship.eu)

REGULATORY: - REACH-ECHA Working Group
Graphene Flagship establishes a new REACH-ECHA Working Group | Graphene Flagship (graphene-flagship.eu)

INNOVATION/STATE-OF-THE-ART

1. Life cycle graphene-related materials determines dose, exposure, fate and risk scenarios. Modelling of structural activity relationships with biological response. Model physico-chemical properties with biological responses. Several compartments:

   - Skin barrier
   - Intestinal barrier
   - Air-blood barrier
   - Immune system
   - Placenta barrier
   - Neuronal barrier
   - Lungs

2. Human airway epithelium (HAE) from biopsies for determining AOP via transcriptomics to model more chronic effects.

3. In silico approaches in NANORIGO for the determination of human effect factor (HEF) for NM subgroups focusing on inhalation
4. Data gaps:
   a. Batch-to-batch variations and reproducible production. Ageing of graphene-related materials.
   b. Degradation studies to ensure that graphene-related-materials are not persistent (ensuring circularity and no environmental toxicity)
5. Need for exchange of state-of-the-art knowledge with regulators. Need for community of innovators and regulators. Create synergies and complementarities with existing activities.

Figure 10: Summary of Theme C: Keeping pace with innovation.

The 2nd RRAS was finalized with questions addressing a previously identified need for a trans-regulatory platform to exchange knowledge and information. The platform is still considered as a good idea, but also continuation of organizing RRAS meetings was considered helpful (Annex II, Figure A - 16 and Figure A - 17).

Access of scientific data and methods for an informed (trans)regulatory decision making was regarded useful. This would on one hand require sound data management and data curation (like FAIR data, a supportive platform) and on the other hand enhanced connectivity between scientists and regulators (risk assessors) in order to tune knowledge generation to the needs of regulatory risk assessment (Annex II, Figure A - 18).

Harmonization of method development is regarded supportive to address one substance, one assessment. However, how to align knowledge generation and trans-regulatory approaches from the perspective of different standardization bodies remained a point of discussion (ANNEX II, Figure A - 19).

In summary, the presentations and discussions in the three thematic breakout groups and the comments from the audience clearly showed the need, but also the interest of all stakeholders to exchange knowledge, information and experience.

Annex I

Registration list for Gov4nano 2nd RRAS (participants in green are speakers)

ANNEX II Mentimeter inputs

Figure A - 1: List of input of the participants on what is needed to meet the EU policy ambitions (42 respondents)

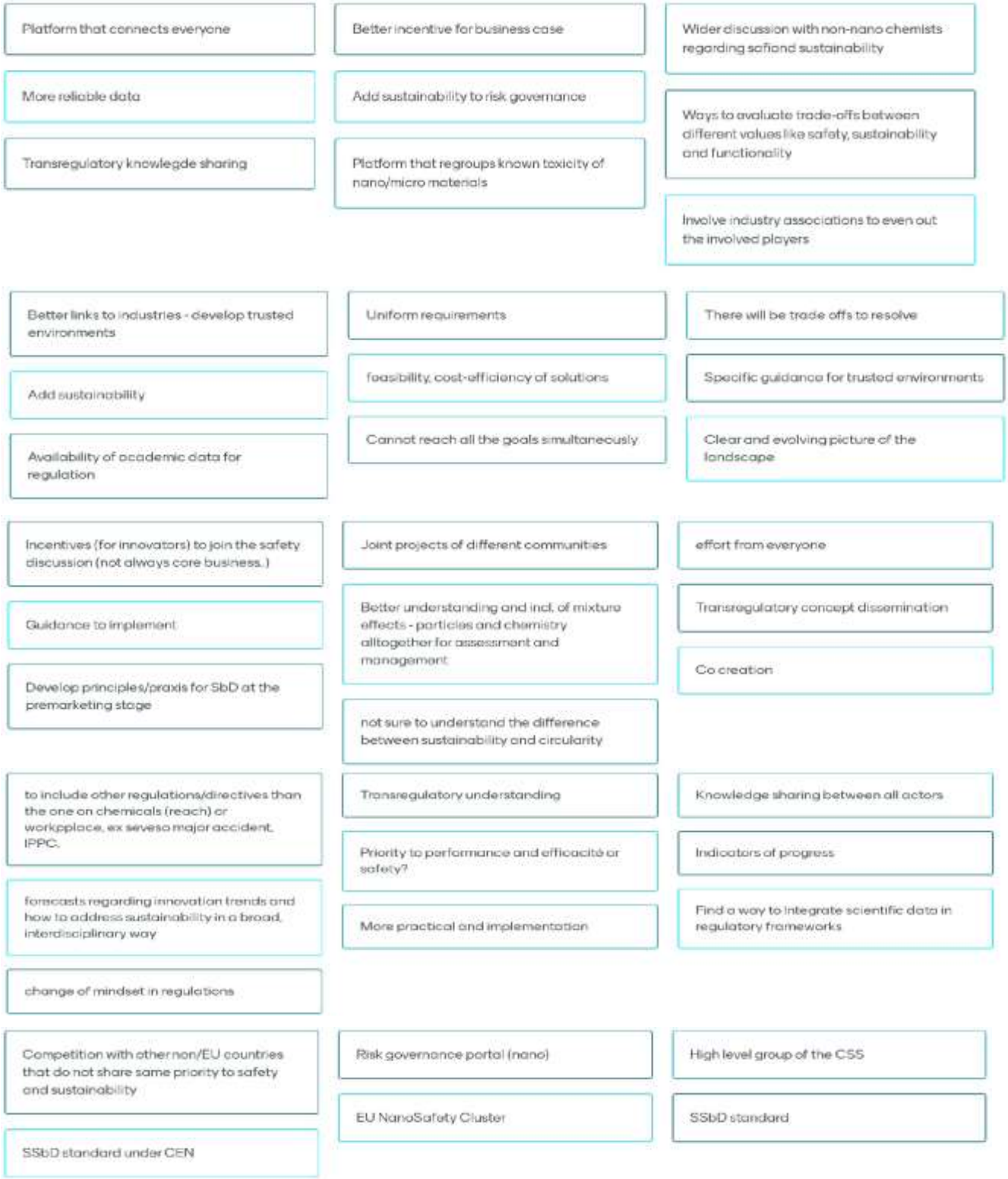


Figure A - 2: Input of the participants on the activities to fill the gaps mentioned (16 respondents)

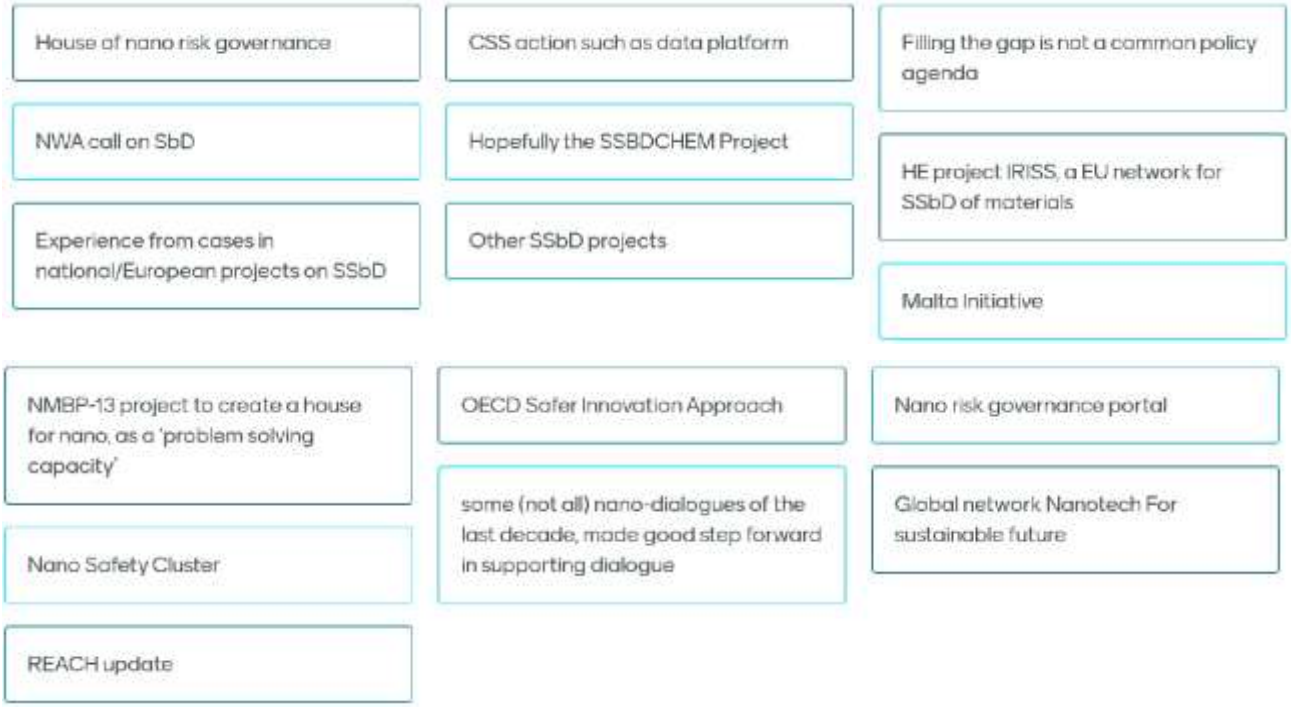
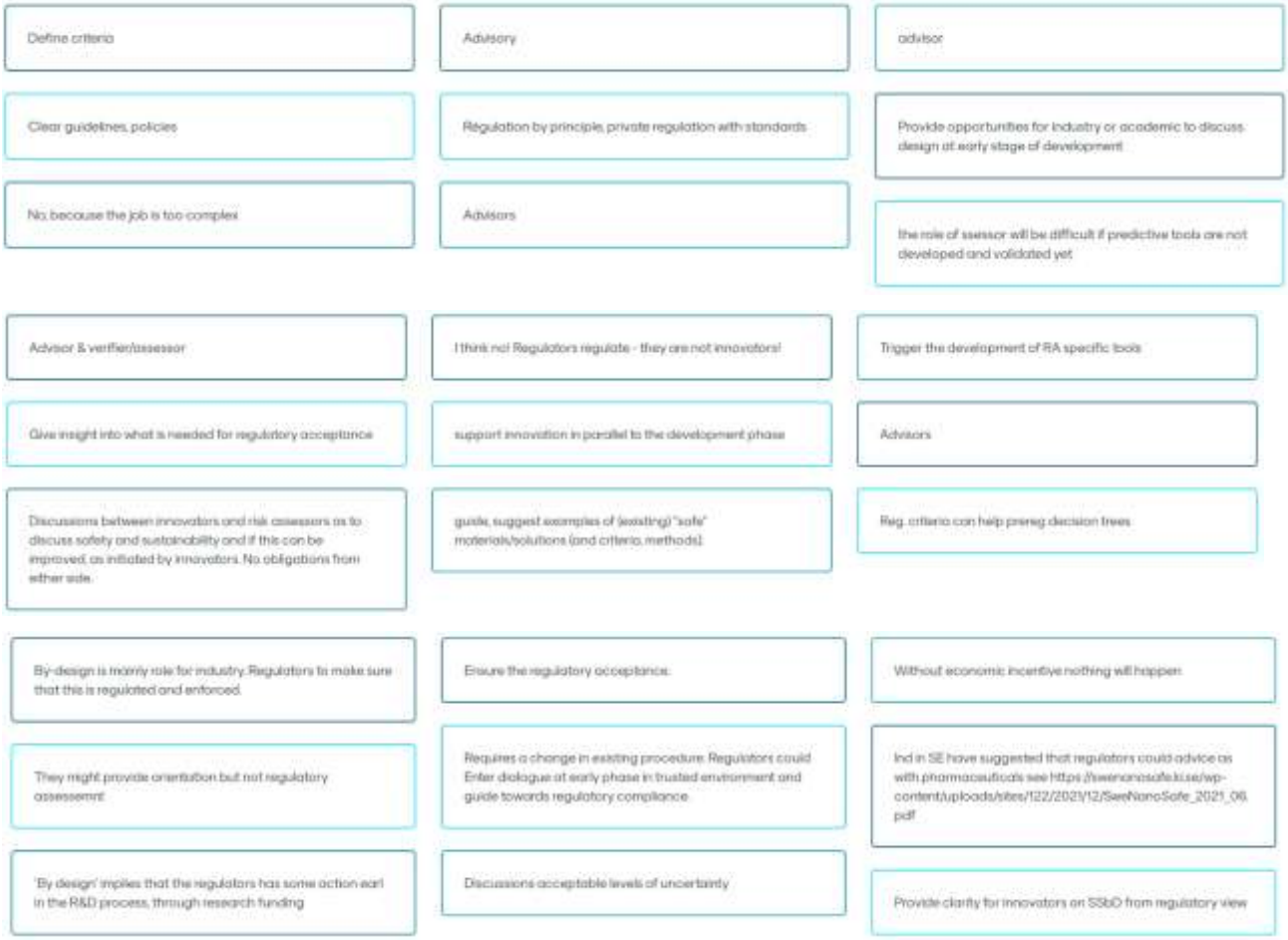


Figure A - 3: Do you have suggestions to the role of regulatory risk assessors in the 'by-design' aspect? Input of participants (35 respondents)



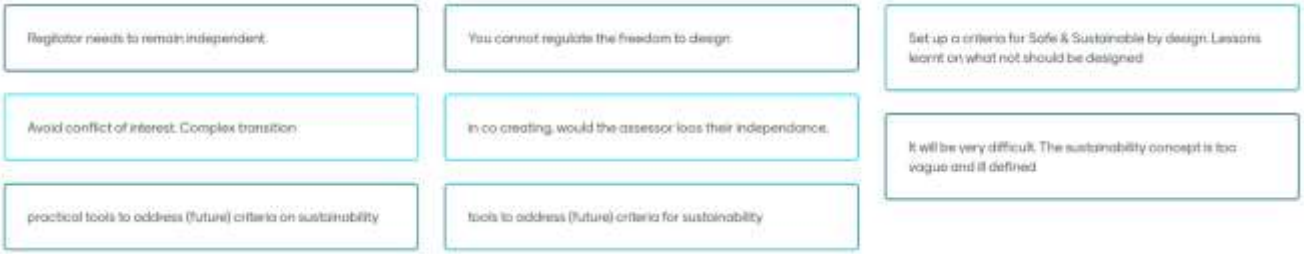


Figure A - 4: What is needed to bring SbD to SSbD? Input of participants (23 respondents)

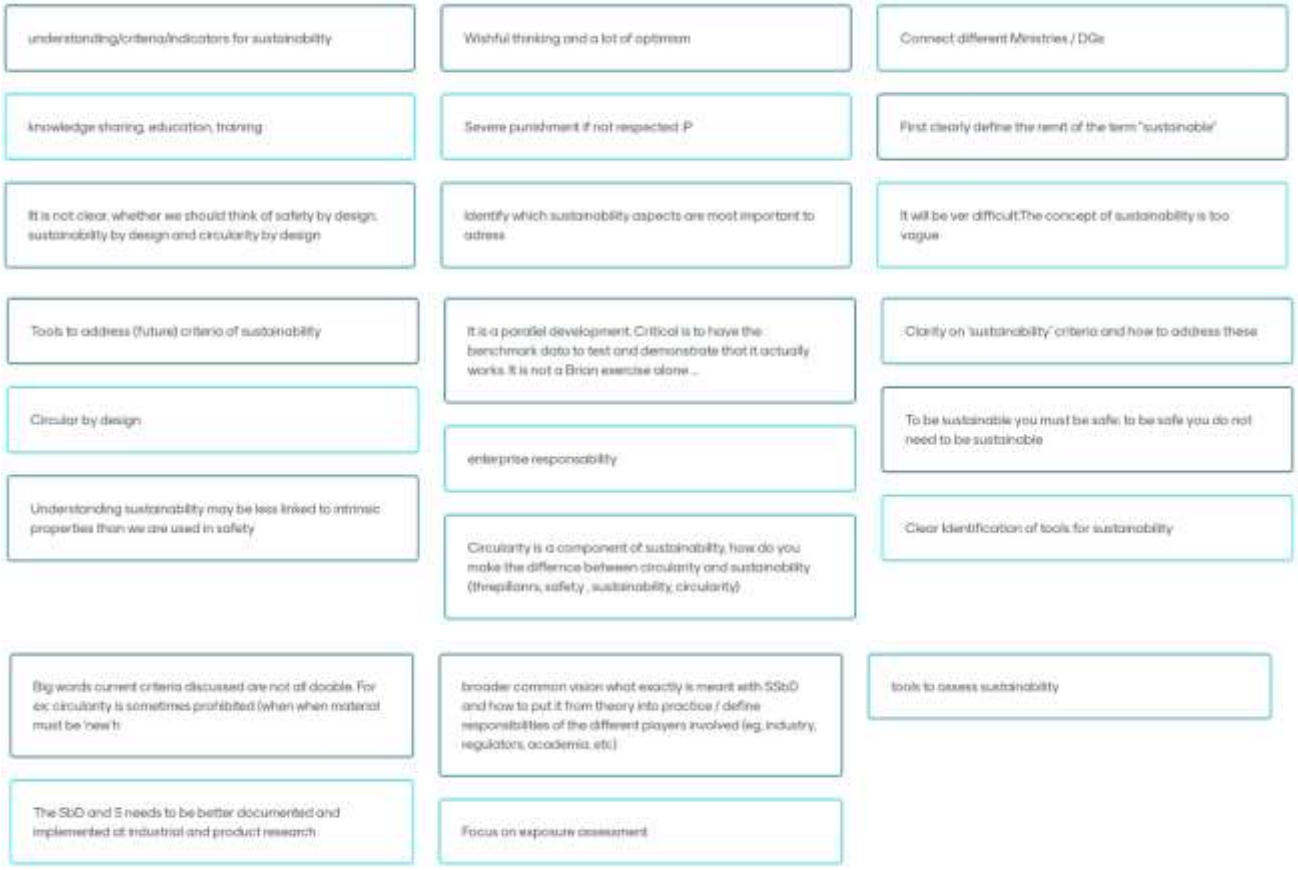


Figure A - 5: How can we connect the risk assessment of materials and products to also include processes?

Figure A - 6: Can nanomaterials cause endocrine disruptive effects?

Figure A - 7: Are you aware of any age-specific effects of nanomaterials to vulnerable groups such as children/ elderly? (20 respondents)

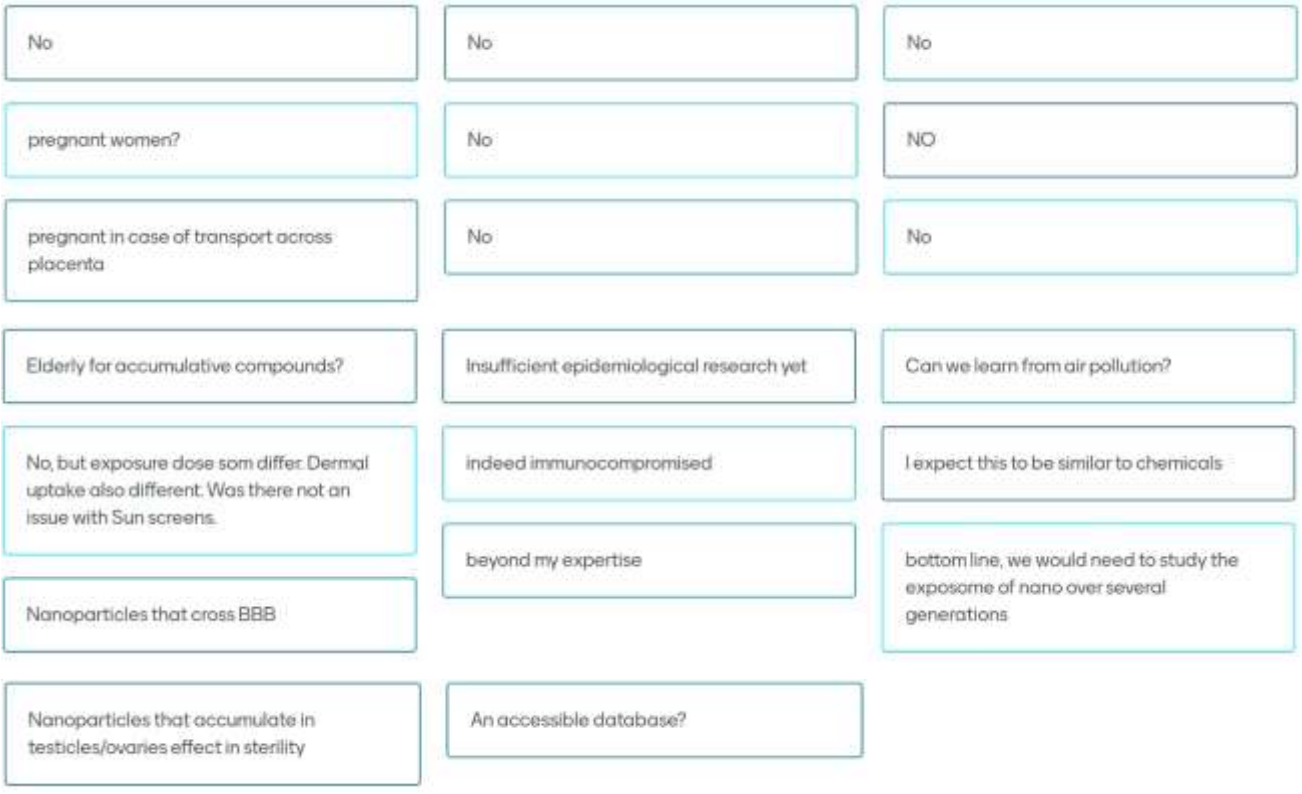


Figure A - 8: Input on the role of new tests on the solution of the challenges with respect to mixtures assessment (16 respondents)

Figure A - 9: Input from participants on what is needed to bring the knowledge of different frameworks together (27 respondents)

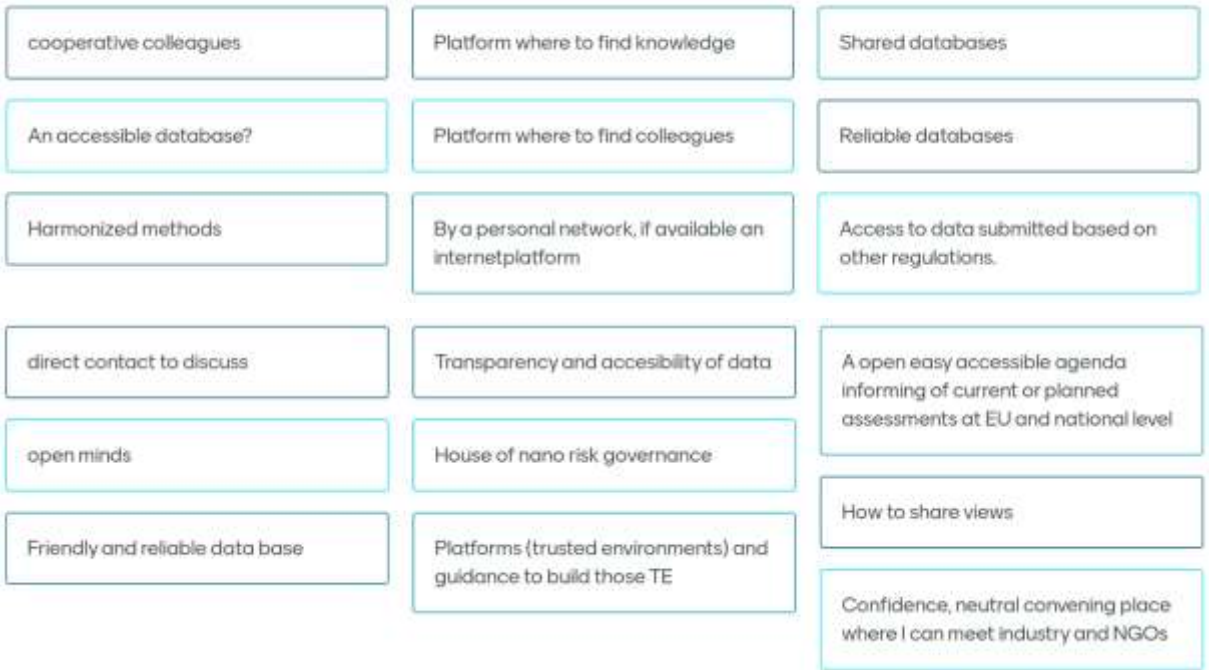


Figure A - 10: In the 1st RRAS a lack of relevant physico-chemical measurement methods was identified. What is (still) open to be addressed?

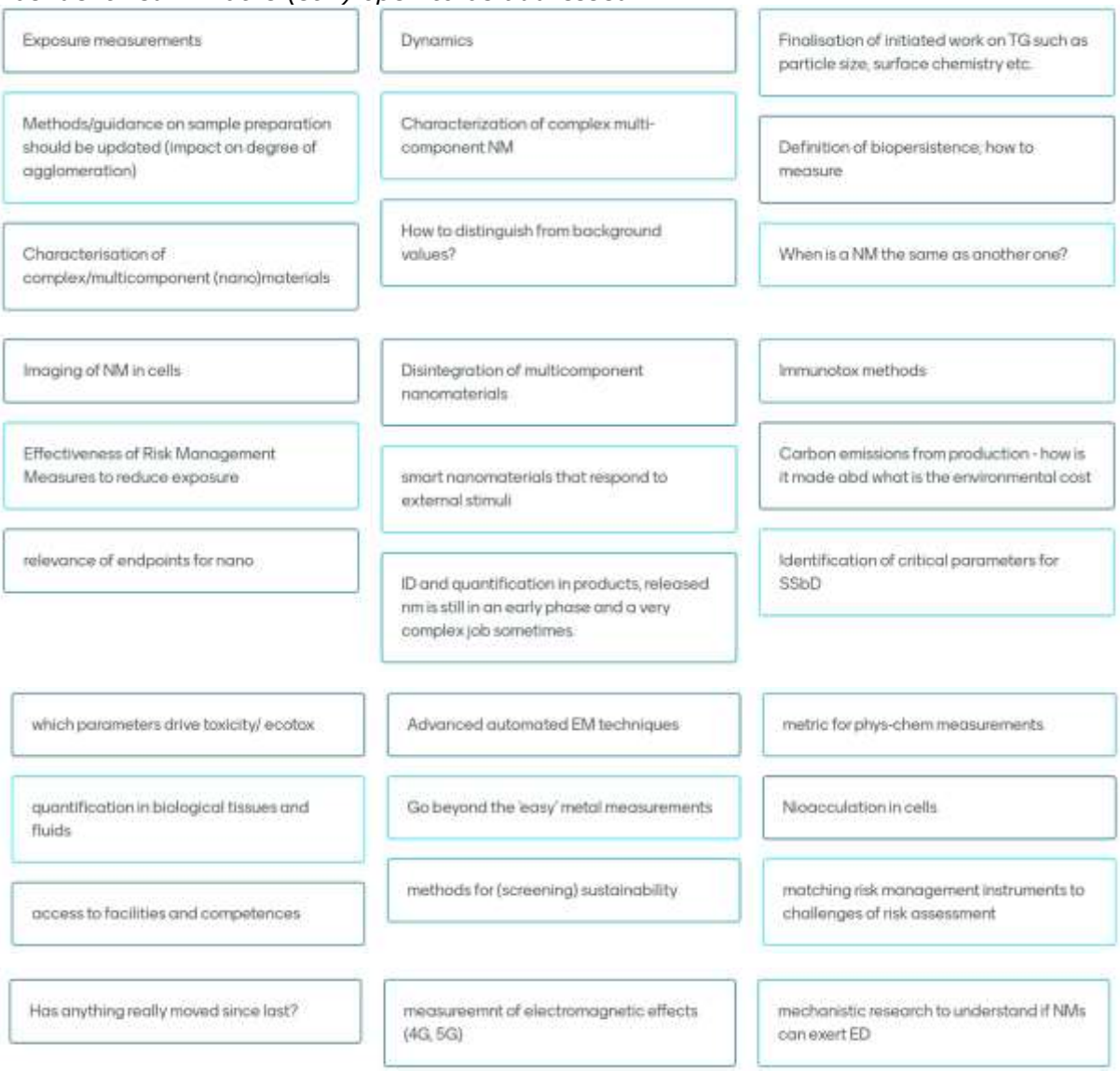


Figure A - 11: Which type of further research on nano-specific ED effects is needed for risk assessment?

Figure A - 12: What nano-specific effects are missed in the list of additional end-points.

Figure A - 13: Do you envisage nano-specific issues for the applications of NAMs for risk assessment?

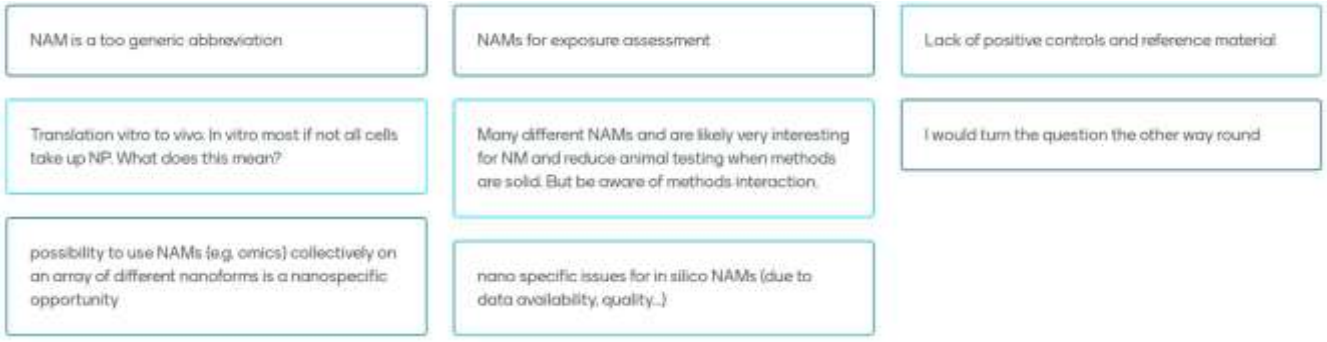


Figure A - 14: Who should train the regulatory risk assessors in the assessment of sustainability (17 respondents)

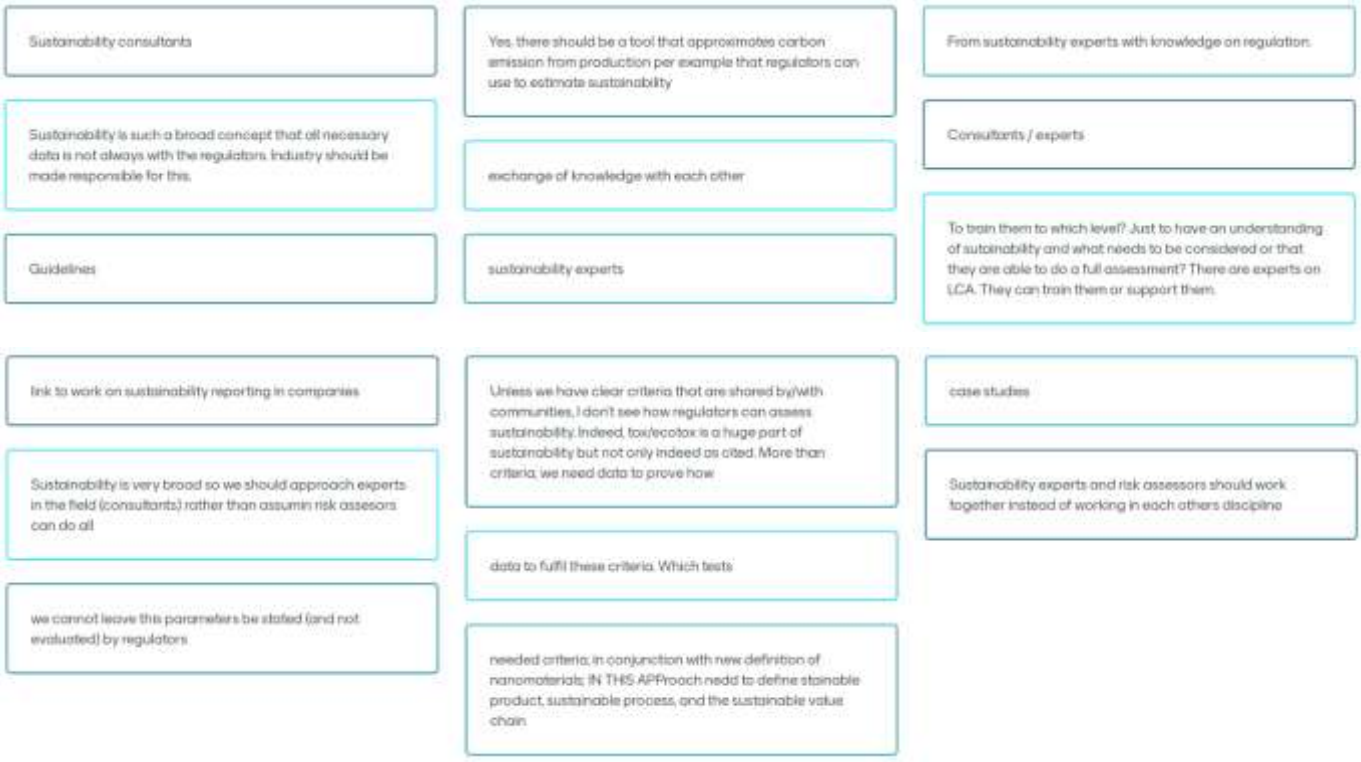


Figure A - 15: What would be your advice to include in the criteria for SSbD in order to cover nanomaterials?

Figure A - 16: How to organise a transregulatory discussion on a continuous basis between different sectors (input of 34 respondents)?

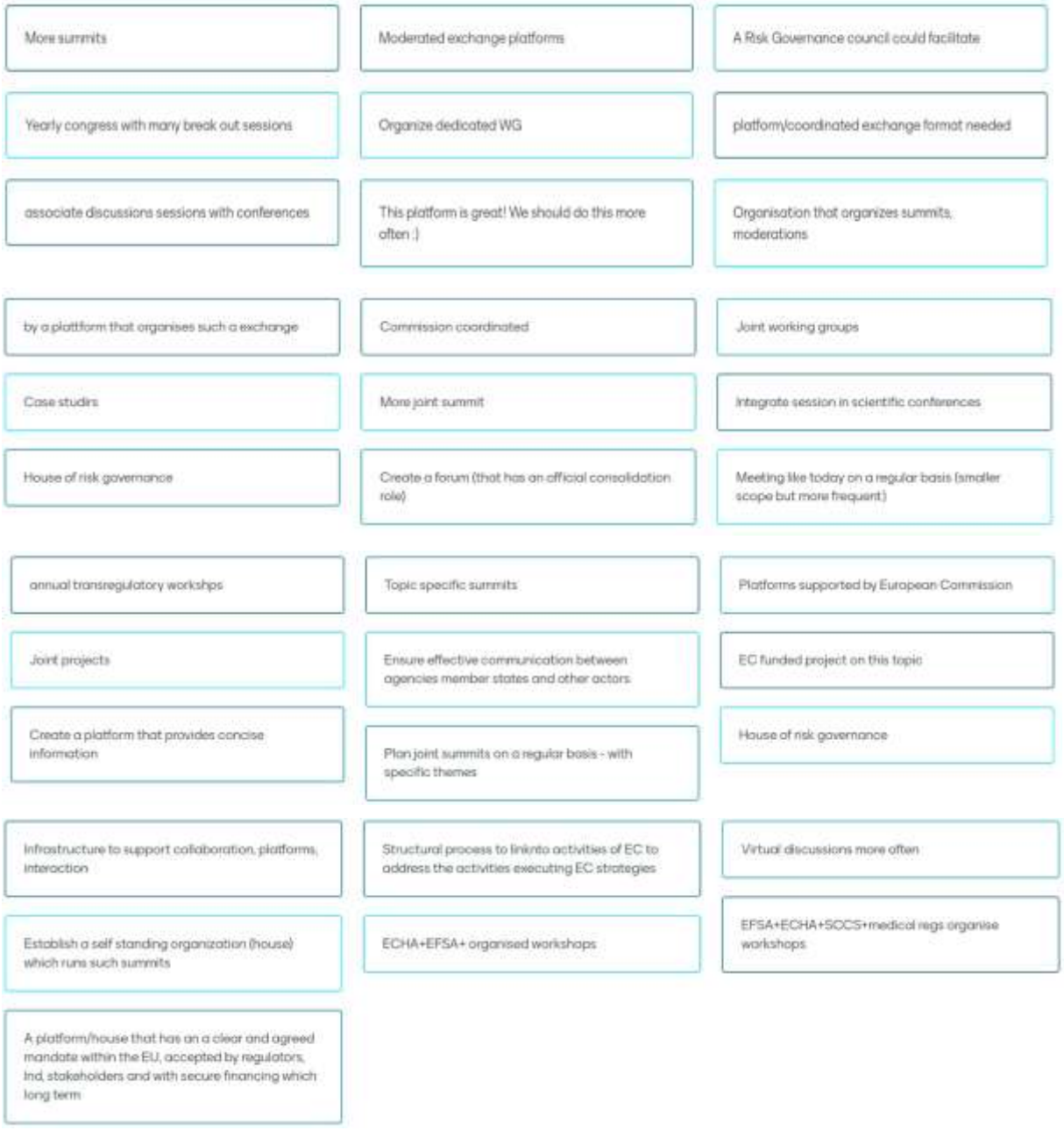
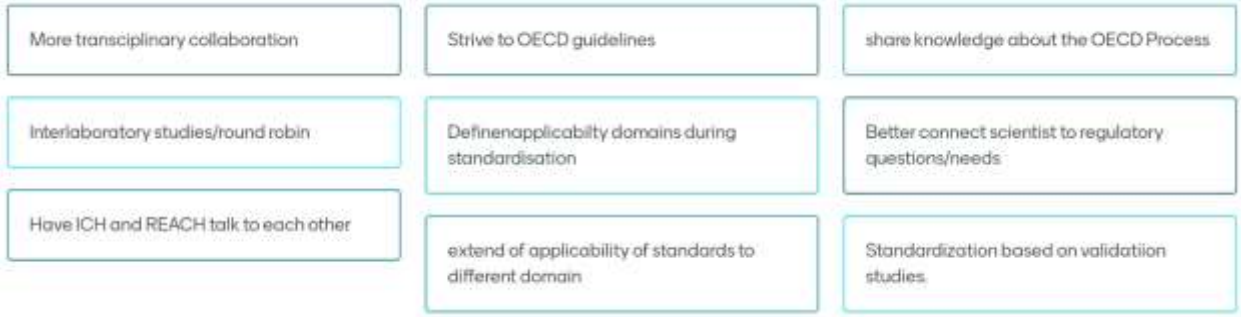
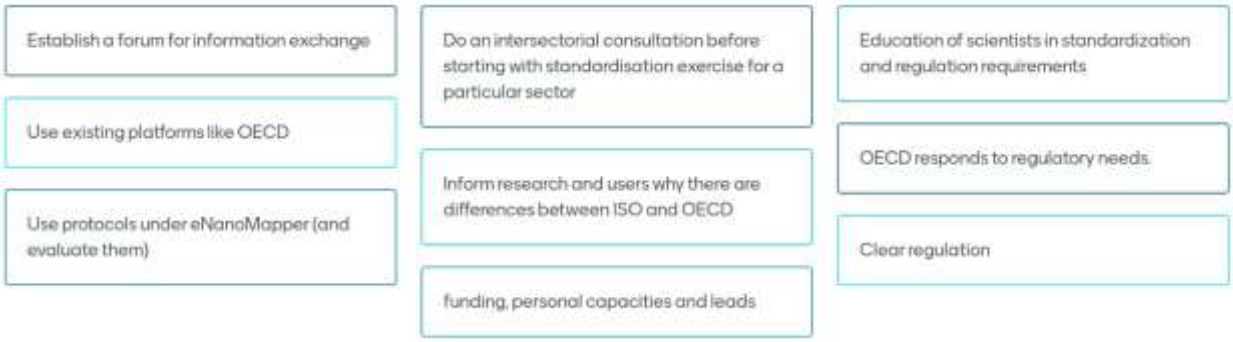


Figure A - 17: Input to the question how to facilitate trans-regulatory collaboration (24 *respondents*)

Figure A - 18: How can access of scientific data & methods for an informed (trans)regulatory decision making be improved? (17 respondents)

Figure A - 19: How can we harmonize method development? (18 respondents)




Establish a forum for information exchange
Use existing platforms like OECD
Use protocols under eNanoMapper (and evaluate them)
Do an intersectorial consultation before starting with standardisation exercise for a particular sector
Inform research and users why there are differences between ISO and OECD
funding, personal capacities and leads
Education of scientists in standardization and regulation requirements
OECD responds to regulatory needs
Clear regulation

Annex III - Domain specific research needs RRAS I (2019) where in the current meeting has been added on

Table A - 1: Issues with respect to toxicity testing: exploratory research or validation of tests of NMs

	Chemicals	Worker	Cosmetics	Environment	Medical devices/ medicines	Food*
Reliability of animal model in predicting NM toxicity; lack of golden standards; relevance to humans	x	x				
How to standardise in vitro models/ setting better standards; Are validated in vitro tests sufficiently predictive (be critical on new tests); role of ADME	x					
Sample preparation (testing NM relevant to exposure)	x					
ADME information is needed in different organs? Particles in brain, pancreas; these should be taken into account, system approach (where and what kind of form?)	x					
Do we know enough about particle toxicity?	x					
Determining toxicity in absence of animal testing (e.g. cosmetics)		x	X			
How toxicity testing can be used to establish safe exposure levels (Occupational exposure limits OELs)		X				
Lack of workplace exposure levels/knowledge of safe levels (methods on how to accurate estimate exposure; development of devices to measure exposure)		x				
Understanding the effectiveness of exposure models (current models are conservative; improved multi-parametric approaches are needed)		x				
Reference, standard and positive control nanomaterials			x		x	
Reliable, validated, protocols/assays/guidelines applicable to NMs			x		x	
Access to protocols			x			
Methods for uptake (cells, in vitro, in vivo and humans) Complexity, interactions with matrix Instability (dissolution/ dispersion)			x	x	x	
Poor characterization (of product, in situ, in testing and within RA)			x			
Characterization methods not fit for purpose			x		x	
Concentration measurements in test system				x		
Other endpoints (electromagnetic fields)				X		
Which toxicity tests are needed under which conditions					x	
How are the methods validated \ which positive controls					x	
What kind of information is needed for toxicity tests \ which organ					x	
How to validate ICHQ2R1/ ISO 17025 requirements					X	
Relevance of tested particle due to possible changes					x	
Development of a new framework						X
Risk management paradigm						X
Enforcement of standards, better communication with enforcers						X
New knowledge needed = new approaches !?						X

X: issue mentioned by the specific discipline-specific group(s) but also potential relevant for other disciplines
X: discipline-specific issue only relevant for one of the disciplines
*The food group had a different type of discussion focusing more on development of a new framework

Table A - 2: Issues with respect to regulatory risk assessment of NMs

	Chemicals	Worker	Cosmetics	Environment	Medical devices/ medicines	Food
Aggregation and agglomeration is often overlooked	x					
Read-across, range of applicability of test results for similar materials?	x					
In silico vs reality?	x					
Lack of measured exposure?	x		x			
Gather sources of uncertainty →comparative uncertainty	x					
Proper methods for testing physico-chem properties	x					
Lack of toxicokinetic data and guidance	x					
Learn from NMs where we have sufficient data and show them	x					
Transformation of materials in life-cycle (aggregation/agglomeration)	x					
How to deal with combined exposures and advanced materials?	x					
Knowing what is a 'realistic' exposure level to do 'realistic' toxicity testing		x				
Are workers exposed to single nano's or only to agglomerates Workers are often exposed to aggregates not single NPs		x				
Libraries and databases to feed into control banding		x				
DNELs are not specified whether it refers to respirable or inhalable particle		x				
How CLP should be implemented when NM hazards change along the supply chain		x				
Communication along supply chain		x				
Nanodefinition is not clear (aggregates/ agglomerates)			x			
Methods to check if a product is nano-enabled			x			
Lack of grouping strategies (when are NM similar?)			x			
How to integrate uptake into risk assessment			x			

	Chemicals	Worker	Cosmetics	Environment	Medical devices/ medicines	Food
Access to in vivo (and other) data across regulatory frameworks limited but needed because no in vivo testing allowed			x	x		
No access to industrial and EU project data			x	x		
Data quality questionable			x	x		
Harmonization across regulatory agencies			x			
Poor characterization (of product, in situ, in testing and within RA)			x			
Not all characterization methods are fit for purpose			x			
Environmental releases: Modelling, Measurements lacking				x		
Reference materials				x		
How is equivalence of different nanomaterials tested with unclear requirements also taking into account food and cosmetics					x	
No accredited labs for testing nanomaterials					x	
No test methods for the Quantification of exposure to nanomaterials from medical devices					x	
Development of a new framework						x

X: issue mentioned by the specific discipline-specific group(s) but also potential relevant for other disciplines
X: discipline-specific issue only relevant for one of the disciplines