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Safe Innovation Approach: Towards an agile system for dealing with innovations

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Graphical Abstract

**Safe Innovation Approach (SIA) Framework**

**Why?** To have safe MNMs and nano-enabled products on the market
Or as a minimum identifying their potential risks in order to take appropriate measures to protect human health and ensure environmental safety

**How?** Safe Innovation Approach
Stimulating companies to integrate safety in the design and throughout the innovation process and regulators to keep up with the pace of innovation

**What?** Change of mind-set for regulators and innovators to be more proactive and interactive
By creating awareness, developing SIA methodology, building Trusted Environment and bringing Trust in the regulatory preparedness concept into an operational level, and by developing and applying new business and governance models

**Highlights**

- The Safe Innovation Approach (SIA) is a framework outlining the necessary elements needed to achieve safe(r) nanomaterials and nano-enabled products.
- SIA consists of the combination of the safe-by-design (SbD) and regulatory preparedness (RP) concept; as both industry/innovators and regulators need to be proactive and vigilant.
- SbD recommends industry to integrate safety considerations as early as possible in the innovation process.
- The RP concept aims to improve anticipation of regulators in order that they can facilitate the development of adaptable (safety) regulation that can keep up with the pace of knowledge generation and innovation of MNMs and MNM-enabled products.
- The SIA framework consists of creating awareness, developing a SIA methodology (SbD scenarios, SbD methodology including information needs, functionality, and grouping, SIA Toolbox and a nano-specific database), bringing the Trusted Environment and regulatory preparedness concept into an operational level, and the development of novel business and governance models.
- The SIA framework is an agile and robust risk assessment system for MNMs and nano-enabled products that is currently being brought to practice internationally.
ABSTRACT

Nanotechnologies are characterized by a growing legacy of already marketed and novel manufactured nanomaterials (MNMs) and nano-enabled products with a lack of a coherent risk governance system to address their safety effectively. In response to this situation, a proactive system is needed to minimize the gap between the pace of innovation and the pace of developing nano-specific risk governance. With the Safe Innovation Approach (SIA), we seek to enhance the ability of all stakeholders to address the safety assessment of innovations in a robust yet agile manner. The SIA is an approach that combines a) the Safe-by-Design (SbD) concept, which recommends industry to integrate safety considerations as early as possible into the innovation process, and b) the Regulatory Preparedness (RP) concept which aims to improve anticipation of regulators in order that they can facilitate the development of adaptable (safety) regulation that can keep up with the pace of knowledge generation and innovation of MNMs and MNM-enabled products. SIA promotes a safe and responsible approach for industry when developing innovative products and materials, and stimulates a proactive attitude amongst policymakers and regulators to minimize the time gap between appearance and approval of innovation and appropriate legislation. Here we introduce a SIA framework consisting of creating SIA awareness, developing a SIA methodology (SbD scenarios, SbD methodology including information needs, functionality, and grouping, SIA Toolbox and a nano-specific database), bringing the Trusted Environment and RP concept into an operational level, and the development of novel business for industry and novel governance models for regulators. The SIA framework once implemented will result in a system for MNMs and nano-enabled products that is agile and robust. Current international efforts such as in the OECD are now trying to bring this concept to practice.
1. Introduction

Nanotechnology offers society economic and technological opportunities, but technological innovations pose a challenge to governance of human and environmental safety due to the large difference in the pace between innovation and the development of suited governance. In order to cope with this change in pace and move towards safe innovations, a system is needed that is pro-active and interactive, that deals with the fast pace of knowledge generation (agile) and adapts to ensure that knowledge is transferred to adaptable safety regulation (robust).

Safe Innovation can be seen as a process to ensure that potential risks of innovations can be timely addressed throughout the R&D process and not only in the later stages before going to market. This process requires improved interaction between innovators and regulators as well as safety assessment throughout the whole innovation process. This results in a focus on nano-specific safety assessment not only aiming at discussing regulatory requirements, but also the necessary information needed to assess nano-specific safety (information needs). In addition, closer collaboration between industry, regulatory authorities and other stakeholders (e.g. research organizations) is needed within a generally accepted overall safe innovation framework to ensure knowledge dissemination.

SIA is a system that is agile and robust. It is agile because it can easily adapt to new challenges. It is also agile in the sense that it creates a more inclusive system that involves more stakeholders in the process and allows for rapid iteration to meet the needs of all stakeholders and society. It is robust because it ensures that SbD and RP are implemented and practiced using a knowledge-sharing platform where lessons learned from all the phases of the innovation process are shared to stimulate continuous improvement to ensure trust is sustained.

The development, manufacture and use of manufactured nanomaterials (MNMs) with novel properties and potentially novel risks are growing at a rapid pace. One possible solution to reduce the uncertainty surrounding nanomaterial safety is to incorporate safety in the design process of MNMs (Safe-by-Design, SbD). SbD was first developed within the European NANOReg project\(^1\) and later complemented in the European ProSafe project [1, 2] with preparation of industry for regulation. Within NanoReg2, the SbD concept was refined in collaboration with industry and regulators.

\(^1\) http://www.nanoreg.eu/
The SbD concept aims at reducing uncertainties and risks of human and environmental safety of nanotechnology, starting as early as possible during the innovation process, on the basis of mandatory and voluntary safety and efficacy compliance requirements\(^1\). The SbD concept implementation was developed to include products, processes, consumers and workers health and environment protection and consists of three main design pillars:

1) Safe materials and products (aiming to be non-hazardous for human and environment);

2) Safe production (aiming to eliminate risks at the workplace and to eliminate waste); and

3) Safe use and recycling (the end-of-life of the considered innovation aiming to prevent exposure during use of the product and to have efficient recycling routes).

This concept, applied to nanotechnology, aims at balancing safety, functionality and costs in an integrated way \([3]\), in order to improve innovation efficiency for the development of better nanotechnology products, considering all life cycle steps, and not only the product development phase. The properties of the MNMs needed to make the materials useful for a specific application are determined in order to identify the possible SbD options. Such a concept maximises the use of resources and expedites the development of products containing MNMs and new MNMs that are SbD. The SbD approach should be based on the state-of-the-art of reliable and routine methods and tools, as well as best available knowledge and practices \([4]\). It is important to note that SbD does not replace any regulatory requirement processes and that industry has the main responsibility and legal liability for the safety of their products.

Regulatory risk assessors and policy makers are very important stakeholders in the translation of knowledge to adaptable (safety) regulation. For this reason, the regulatory preparedness (RP) concept was developed, in complement to SbD, to ensure the development and application of tools and procedures for regulators to prepare for innovations. The RP concept aims to improve anticipation of regulators in order that they can facilitate the development of adaptable (safety) regulation that can keep up with the pace of knowledge generation and innovation of MNMs and MNM-enabled products. In order to achieve this, regulators need to be prepared by being aware of new materials, technologies and innovations in the early stage of the innovation process. Information about the scientific state-of-the-art and about the innovations is needed in order to timely check on whether current regulations cover all aspects of innovation to ensure human and environmental safety. By engaging in dialogue with innovators, regulators can become aware of the latest advances in innovation and
provide innovators with (informal) input on human and environmental safety of emerging technologies such as (novel) MNMs and nano-enabled products.

Together, the SbD and RP concepts form the safe innovation approach. SIA promotes a safe and responsible approach for industry when developing innovative products and materials, and stimulates a proactive attitude amongst policymakers and regulators to minimize the time gap between appearance and approval of innovation and appropriate legislation. This paper focuses on identifying the steps needed to bring SIA to practical implementation, including a change of mind-set for regulators and innovators to be more proactive and interactive. By creating awareness, developing SIA methodologies and providing motivators for industry, building Trusted Environments (TE), and by developing and applying new business and governance models, a practical SIA can be achieved (Figure 1).

2. Methods

2.1 Development of a SIA operational framework
A SIA framework was developed with experts in the NanoReg2 project in order to translate the SbD and RP concepts to practice, for SIA implementation consisting of creating awareness, developing SIA methodologies and providing motivators for industry, building Trusted Environments (TE), and by developing and applying new business and governance models, a practical SIA can be achieved

2.2 Creating awareness
Several factors were identified by NanoReg2 consortium experts as being vital for the creating awareness of SbD, RP and SIA. These included: inform, educate and create acceptance.

2.2.1 Inform
Several dissemination activities were organized to create awareness of SbD for industry to apply and for regulators to accept and promote SbD. Examples of such activities included SbD trainings and workshops with industry (some led by TEMAS AG and others hosted by NIA) which introduced the SbD concept [5].

2.2.2 Education
The concept of SIA is being offered through BIORIMA training courses whose aim is to transfer the State-of-the-Art knowledge on a variety of topics from key experts to the new generation of nano-environmental, health and safety, and biomedicine professionals [6]. Workshops on SIA are also given in the Debye Institute for Nanomaterial Science Spring School and during the school year [7].
2.2.3 **Create acceptance**
Strategies for creating SIA acceptance were discussed among NanoReg2 consortium experts. Creating SIA acceptance from regulators, policy makers, industry and other stakeholders is vital for implementation; particularly creating SIA acceptance by regulators.

2.3 **Developing SIA methodology**
SIA methodology was developed by RIVM with the help of NanoReg2 consortium experts.

2.3.1 **SbD concept implementation into SbD scenarios**
SbD scenarios were developed by experts at the RIVM as a conceptual illustration to provide guidance and transparency when implementing and communicating with regard to SbD (Table 1). These were tested and adapted after the PRISMA Meeting in November 2017 (Berlin, Germany), the NanoReg 2 consortium meeting with all the partners in March 2018 (Aix en Provence, France), and with the NanoReg2 industrial partners which were active in implementing SbD (Nanogap, Antolin, Avanzare, HIQnano, Nanocomposix and Nanomakers). Table 2 illustrates the concept of *SbD Scenarios* in practice.

2.3.2 **SbD practical methodology**

**Functionality**
The importance and defining functionality was done by NanoReg2 consortium experts, RIVM (National Institute of Public Health and the Environment, The Netherlands) and INM (Leibniz Institute for New Materials, Germany) after several workshop discussions.

**Safety**

*Safety information needs*
Although it is necessary to meet all regulatory information requirements of applicable domains or regulatory frameworks before an MNM and/or nano-enabled product can enter the market, at present, only few regulatory frameworks contain provisions specifically for MNMs, i.e. the regulatory information requirements may not always be adequate to fully address nano-specific risks. Furthermore, the available information and extent to which the safety aspects of an MNM and/or nano-enabled product need to be taken into account differ for the various phases of the innovation process. Within the NanoReg2 project an approach was developed which aims to identify the safety information needed to address nano-specific human health risks in each phase of the innovation process of MNM and/or nano-enabled products.

The safety aspects or safety questions that would support decisions on how to address potential human health risks for each phase of the innovation process was identified. In this selection, not only the potential nano-specific human health risks, but also the expected availability of information and the expected extent to which the product developer wants to
consider the safety aspects were taken into account for each phase of the innovation process. For each safety aspect, the information needed to address that aspect (or answer that questions) was identified (= information need).

The feasibility of the approach, including the relevance and availability of the information needs in the decision-making was investigated with cooperation of most of the companies involved in NanoReg2.

**Tools for SIA implementation**

**SIA Toolbox**
The basis of the SIA Toolbox are tools and guidance documents which aid in balancing risks, benefits and/or costs. A **tool** was defined as an experimental or computerized procedure used to generate, collect and/or store a certain type of output; and 2) a **guidance document** was defined as a document prepared by a regulatory authority with the purpose of communicating official recommendations on how to implement specific regulatory requirement. The SIA Toolbox can be used by innovators and regulators along the innovation chain. A SIA toolbox operational framework was developed (Figure 3) in order to address the risk-benefit-cost balance needed for SbD implementation.

An inventory of tools and guidance documents was made for the identification of tools and guidance documents that can help in SbD implementation.

**Strategies for data gap filling**
Strategies for data gap filling, particularly grouping were gathered in relation to their role in facilitating SbD implementation by NanoReg2 consortium experts and the RIVM.

**The NanoReg2 Database**
The NanoReg2 database\(^2\) is based on a database model developed within the EU FP7 project eNanoMapper \(^8\). Data in the NanoReg2 database abide to FAIR principles (Findable, Accessible, Interoperable, Reusable). eNanoMapper\(^3\) established a computational infrastructure for MNM toxicological data management, based on extensive requirement analysis, review of existing solutions and direct interactions with scientists in the field. In addition to the open source, online accessible, interactive and searchable database\(^4\), a nanosafety-specific ontology\(^5\) (Hastings et al. [9]) and integrated data analysis services\(^6\) (Chomenidis et al. [10]) were developed. Within the NanoReg2 project, data from several

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\(^2\) [https://search.data.enanomapper.net/about_nanoreg2.html](https://search.data.enanomapper.net/about_nanoreg2.html)
\(^3\) [http://www.enanomapper.net/](http://www.enanomapper.net/)
\(^4\) [https://data.enanomapper.net/](https://data.enanomapper.net/)
\(^5\) [http://bioportal.bioontology.org/ontologies/ENM](http://bioportal.bioontology.org/ontologies/ENM)
\(^6\) [http://jaqpot.org/](http://jaqpot.org/)
previous projects has been gathered into the NanoReg2 database, including from the FP7 projects NANoREG, MARINA, NanoTest, and NanoGenotox, as well as the Nano exposure and contextual information database (NECID).

2.3.3 Trusted environment: linking SbD to RP concepts
The working description of a trusted environment was developed by NanoReg2 consortium experts and the RIVM after several workshop discussions. Input was asked from Nanoreg2 Consortium participants, which included innovators, regulators and nanotechnology experts.

2.3.4 Regulatory Preparedness Methodology
The regulatory preparedness concept was developed in a Workshop on Regulatory Preparedness for Innovation in Nanotechnology which was hosted by the European Commission’s Joint Research Centre in 2017 attended by more than 60 regulators and risk assessors from the EU and United States of America (USA), representatives of the industry and NGOs. In this workshop, active discussions were held on how regulators currently deal with innovation, the needs of regulatory risk assessors to prepare for addressing innovations, the tools available and needed to support RP and possible practical barriers.

2.4 Governance: Novel business models incorporating SIA for industry and novel governance models incorporating SIA for regulators
A literature review was performed in search for business models incorporating SIA in industry and governance models incorporating SIA used in a regulatory context.

2.5 Benefits and challenges of SIA
The benefits and challenges of SIA were identified by NanoReg2 consortium experts and the RIVM after many discussions and during NanoReg2 consortium meetings.

3. Results from NanoReg2 activities for implementing SIA

3.1 SIA conceptual and operational frameworks
The conceptual (Figure 1) and operational (Figure 2) framework of SIA was developed and included creating awareness, SIA methodologies (SbD scenarios, SbD methodologies: functionality and grouping, SIA toolbox and database), bringing the Trusted Environment (TE) and regulatory preparedness (RP) concepts to an operational level and the development of new governance and business models incorporating SIA.

7 https://www.nanoreg2.eu/sites/default/files/Trusted%20Environments%20Flyer.pdf
3.2 Creating SIA awareness

Creating SIA awareness among innovators, regulators and other relevant stakeholders is important for the implementation of SbD by industry and acceptance by regulators.

3.2.1 Inform

SbD – for innovator use and acceptance by regulators

Several activities can be performed to inform industry and other stakeholders about SbD to facilitate SIA implementation. SbD trainings and workshops with industry were developed to introduce the SbD concept, including information on regulatory requirements and their alignment into the innovation process, to all stakeholders, to allow for new relationships between Horizon 2020 projects involved in SbD implementation and to bring together industrial companies who can benefit from SbD [5]. Open webinars were also developed introducing the SbD concept, describing tools and frameworks for product development available for SbD can also be an effective way to inform stakeholders about SbD [11].

Courses informing industry and stakeholders of SbD are also needed to create awareness in important settings such as industrial trade shows, conferences and other venues.

SIA - Innovators and regulators

In addition, using media such as a youtube films explaining the SIA helps to inform stakeholders and we made a SIA youtube video⁸ to inform stakeholders.

3.2.2 Educate

Innovators and regulators

Education is an important component of SIA, particularly as we transition to a Learning and Circular Economy and the process of learning is the fundamental driver of the system. Learning fuels innovation and it enables participants in the system to anticipate and easily adapt to change [12]. SIA should therefore be embedded in the curriculum in transdisciplinary programs (for instance toxicology, nanomaterial sciences, nanotechnology, nanoengineering) and should continuously be adapted as new knowledge arises. The development of a SIA Massive Open Online Courses (MOOC) is essential to reach a wide audience (for instance students, industry, researchers, innovators, regulators, policy makers). With a transdisciplinary approach, the understanding of the modes or mechanisms of action of toxicity induced by MNMs might aid in SIA implementation. We find that expanding SIA training will create a new generation of innovators that include safety in the design process.

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⁸ https://www.youtube.com/watch?v=qc9t_iSCpGI
3.2.3 Create SIA acceptance
Innovators and regulators

Creating SIA acceptance requires the combination of creating awareness among innovators, regulators and other stakeholders with education. There is also a need for a new Code of Conduct where industry and regulators can interact in a TE to reduce the uncertainty associated with NMs and nano-enabled products and have inherently safer products. The workshop on TE showed that the major barriers for innovators were lack of trust, honesty and transparency, intellectual property restrictions, cost, time, and lack of opportunities for interactions with regulators. On the other hand, regulators had more issues with how innovators will deal with statements made by regulators, responsibility and liability, quality of information provided by industry, coping with the new role of regulators and the lack of expertise, knowledge and people skills. Public and innovator perception is also an important component for SIA acceptance.

Data sharing while protecting intellectual property is an important issue for creating SIA acceptance by industry. Ensuring confidentiality in a TE is essential to achieving this. Further, industry might be more inclined to apply SIA if regulators provide incentives. Initiatives such as grant/subvention programs or SIA price incentives, reduced time to market, and a SbD index might be useful for SIA implementation. A SbD index might create transparency in the action perspectives (reduced hazard, reduced exposure or both) and for communicating these action perspectives to regulators, consumers and other stakeholders. If regulators and industry come into dialogue (share knowledge, engaging and interacting) on the generation of a SbD index, then through this dialogue regulators can better anticipate for novel MNMs and nano-enabled products, and industry can benefit from incentives such as price incentives, consumer acceptance and shorter time to market. This SbD index needs to be developed as SIA comes to practical implementation.

In addition, it is imperative to generate standards in order to facilitate acceptance. Standardization may improve both the quality of the data and the adherence to existing guidelines or official documents requested by regulators and policy makers by harmonization of methodologies/techniques and reducing reproducibility issues [13, 14]. Current initiatives through the OECD such as the recently started project "Moving Towards a ‘Safer Innovation Approach’ for More Sustainable Nanomaterials and Nano-enabled Products: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations" will support this goal [15].
Figure 1 An agile multifaceted framework and its elements (‘creating SIA awareness’, ‘developing SIA methodology, ‘bringing Trusted Environment (TE) concept into an operational level’, and ‘developing new business and governance models’) needed for the implementation of SIA

**Safe Innovation Approach (SIA) Framework**

*Why?* To have safe MNMs and nano-enabled products on the market
Or as a minimum identify their potential risks in order to take appropriate measures to protect human health and ensure environmental safety

*How? Safe Innovation Approach*
Stimulating companies to integrate safety in their design and throughout the innovation process and regulators to keep up with the pace of innovation

*What? Change of mind-set for regulators and innovators to be more proactive and interactive*
By creating awareness, developing SIA methodology, building Trusted Environments (TE) and a Nano Risk Governance Portal, and by developing and applying new business and governance models

Figure 2 Operational framework of SIA including creating SIA awareness, SIA methodologies (SbD scenarios, SbD methodologies: functionality and grouping, SIA toolbox and database), bringing the Trusted Environment (TE) and regulatory preparedness (RP) concepts to an operational level and the development of new governance and business models incorporating SIA.
3.2 Developing SIA methodology

The SIA methodology consists of: 1) the development of SbD scenarios for SbD concept implementation which can serve as a guidance, communication, and/or management tool; 2) the development of SbD practical methodology consisting of functionality and safety. Safety consists of the identification of specific information needs complementing regulatory requirements, and the development of tools for SIA implementation (SIA Toolbox, strategies for data gap filling and the NanoReg2 database); 3) the development of a Trusted Environment (TE) linking SbD and RP concepts; and 4) development of RP methodology.

3.2.1 SbD concept implementation into SbD Scenarios

The SbD concept aims at reducing uncertainties and risks of human and environmental safety starting at an early stage of the innovation process. With regard to safety, there are three safety elements and maximum ambitions that are regarded as important (Table 1a and Table 1b):

1. Uncertainty: the uncertainties can be reduced by specifically addressing and collecting nano-specific information (maximum ambition is to maximize the amount of nano-specific information for instance full characterization, reactivity and toxicity information). The uncertainties can be also be reduced by improving data quality and applying standardization of methods and techniques that may help to increase adherence to official requests or guidelines and benchmarking. The latter will favor also grouping and indirectly the application of SbD in the various scenarios;

2. Exposure: the risks can be reduced by reduction of MNM exposure over the life-cycle or by preventing release (maximum ambition to reach minimal to zero MNM exposure);

3. Hazard: the risks can be reduced by reduction of hazard properties (e.g. by using coatings or choosing an alternative MNM; maximum ambition is to minimize the risk for toxicity to as non-toxic as possible). Within this safety element, there is mitigation of the intrinsic toxicity of MNMs by careful consideration on the shape, size, and reactivity (surface charge, surface chemistry) without compromising functionality.

Here, we developed the concept of SbD Scenarios. A SbD Scenario is defined as a combination of safety element(s) and a level of ambition on a specific safety element. The level of risk that is acceptable to have the SbD label needs further refinement and it is dependent on how policy makers and regulatory bodies define SbD (Table 1b and 1c).
The scenarios are not designed in a quantitative manner where one is better than the other but rather in a qualitative manner where Scenario 1 is not SbD/only collection of nano-specific information; Scenario 2 focuses on reducing nano-specific exposure, Scenario 3 focuses on reducing nano-specific hazard and Scenario 4 is reducing both nano-specific hazard and exposure.

The SbD scenarios provide a general guide for SbD implementation and provide transparency of action perspectives. They bring the SbD concept of reducing uncertainties, health and environmental risks, and the management of potential risks, into more practical use. The scenarios illustrated here might help guide all the stakeholders involved with SbD (innovators, manufacturers, suppliers, regulators, policy makers, etc) with the application and communication of SbD. The scenarios need to be recognized and accepted in practice.

As a communication tool, SbD scenarios aid in creating SbD awareness to a wide range of stakeholders but also in ensuring that the SbD actions taken by industry are understood and accepted by policy makers, regulators, society and other stakeholders.

As a management/governance tool, SbD scenarios can be used to set safety ambitions by innovators or policy makers, and these can be used to monitor current and future ambitions.

As a guidance tool, SbD scenarios can be used to guide innovators (SMEs, large companies, academia) and regulatory risk assessors in the application of SbD in a transparent way.
3.3 SbD practical methodology

The SbD methodology is based on the application of principles that guide the implementation of SbD early in the innovation process. SbD is not new in itself and has been used in industry for years. Therefore, SbD principles have been developed either independently from MNMs [16, 17], as well as in the context of MNMs [18, 19]. In order to integrate such principles into a structured stage-gate innovation process and to address the whole life-cycle of MNMs and nano-enabled products, specific principles for NanoReg2 are proposed including the determination of the identity and functionality of MNMs and nano-enabled products, the design out of hazardous properties, the preclusion of release and exposure, and the implementation of SbD as early as possible in the innovation process.

The application of these principles demands in depth knowledge of the MNM and product properties (identity) that are linked to their functionality (use-oriented properties and potential applications) as well as the properties that are linked to their safety. This knowledge can be used already in the innovation process to address potential safety issues arising during the whole life-cycle of the nanomaterials or nano-enabled products by modification of the nanomaterials properties or their production process in a way that accommodates and ensures functionality (SbD).

The SbD methodology comprises the integration of the following three interdependent aspects into the innovation process:

1) **Functionality**, comprising the use-oriented properties of the nanomaterial or nanoproduct that are directly derived from the identity of the used nanomaterial and its corresponding application.

2) **Safety** aspects related to potential hazard/risk connected with the envisaged nanomaterial/nanoproduct throughout its whole life cycle including SbD actions taken to maximize safety while maintaining functionality in the context of the target innovation.

SbD should be applied at the very early steps during the innovation process as at these steps, alternative synthesis and production procedures can be implemented or alternative materials can be chosen given the fact that they must maintain the original use-oriented properties of the previous material. The identification of safety information needs, functionality, and grouping are key for the implementation of SbD methodologies.
Functionality

One of the main reasons for the high potential for manifold applications of MNMs is their distinct functionalities, such as magnetic, optical, electronic, mechanical, thermal, and chemical properties compared to their bulk counterparts due to higher surface-to-volume ratio and quantum confinement effects. These unique properties depend not only on the composition and size of the MNM, but also on their shape, surface topography, crystallinity, refractive index and perfection, taken together by the identity of a specific MNM. Furthermore, modification of MNMs or their incorporation into specific matrices influences, or even induces new, use-oriented properties. In parallel, however, these modifications also influence, and change the behavior of the MNMs in biological environments in a complex manner, and thus the safety-related properties of MNM [20]. Functionality defines the relationship between the use-oriented properties, the application of MNMs and their safety. Hence, a clear knowledge of MNMs is necessary, to establish correlations between intrinsic physicochemical parameters, the identity, use-oriented properties, applications and safety. For inclusion of functionality aspects into existing databases a specific ontology is needed. Ontologies allow for unified annotation of information, and supports data integration as well as interpretation across the three related aspects of functionality, application and safety [9]. New analytical methods and tools as well as evaluation of material datasets with systematic variations can be used to overcome knowledge gaps and to expedite the design of novel, tailored MNMs and nano-enabled products. Therefore, SbD necessarily addresses both functionality and safety aspects to achieve or exceed the functional performance of current MNMs and the application they enable, while minimizing inherent hazard potential and avoiding exposure to human and environment at all stages of the life cycle [3]. Depending on the property to be exploited for a distinct application, it might not be possible to maximize both functionality and safety at the same time, therefore only an optimized balance through SbD actions might be possible. Thus, finding the balance to maximize safety while maintaining functionality is required.

Safety

Safety Information Needs

The safety aspects or safety questions that would support decisions on how to address human health risks for each phase of the innovation process were identified. Secondly, the information needed to address these aspects (or answer these questions) were identified (Table 3). It is important to note that the aim of this approach is not to guarantee the safety of an MNM, nor is it intended to be used for regulatory purposes. Rather, the purpose of this approach is to recommend the type of information that supports the consideration of human health risks in
material or product development decision-making for each phase of the innovation process in order to minimize the risk.

**Tools to aid SIA implementation**

There are several tools and strategies that are needed for SIA implementation. We developed the SIA toolbox which provides a collection of tools and guidance documents that can help for the implementation of SbD. Strategies such as grouping are also important for filling risk assessment gaps when information on MNMs is scarce. A platform is needed for data sharing and for this purpose, the NanoReg2 database was built. Trusted environments are essential for SIA implementation because they provide a podium for dialogue between innovators, regulators and other stakeholders.

**SIA Toolbox**

The SIA Toolbox is an important component of SIA methodology because it brings together tools and guidance documents that can aid in maximize safety while maintaining functionality.

The basis of the SIA Toolbox are tools and guidance documents which aid in balancing risks, benefits and/or costs. A SIA toolbox operational framework was developed (Figure 3) in order to address the risk-benefit-cost balance needed for SbD implementation.

Evaluating the risks (Figure 3) from exposure to MNMs by testing the effects that they have on humans and other species requires a lot of time, money, and resources (including costly in vivo experimentation). To minimize the costs and animal use, the existing data for similar substances in an integrated way could be used to fill data gaps. In this regards, keeping up with grouping approaches for MNMs is essential [20-27]. In addition, toxicological methods are advancing rapidly and keeping flexibility towards utilization of new types of non-animal data, such as high-throughput screening, omics and integrated scoring strategies is clearly important [28-30]. Furthermore, within the NanoReg2 project, a user guidance is written that allows users to use the NanoReg2 database to find data on nanomaterial’s physical chemical characterization, toxicity and exposure for use in the SIA toolbox.

In order to gain insight in the benefits (Figure 3) of an MNM or nano-enabled product, information is required about the functionality of the material (see paragraph on functionality above). Functionality aspects have to be derived and considered at each gate (Figure 2), and together with the safety aspects, these can be used to derive potential SbD actions. Benefits could also include economic benefits. A portfolio of concepts and procedures will support the elaboration of potential economic benefits associated with the implementation of SbD concept.
Costs (Figure 3) of measures to reduce uncertainties in every phase of the innovation process may have a direct impact on the uncertainty of the risk assessment. However, the costs of uncertainty reduction have to be balanced with the remaining uncertainty to find the most efficient solutions.

Tools in the SIA Toolbox are nano-specific or nano-applicable, support SbD or RP, and address at least one part of the ‘risk-benefit-cost-triangle. Other types of ‘tools’ like protocols, reports, (computational) models, databases, libraries and SOPs are not included in the SIA Toolbox since these type of tools are not specifically supporting SbD or RP. For more information about these other types of tools we refer to an overview developed within the Prosafe project and the NANoREG Toolbox [1, 2] and the SbD Implementation Platform. In addition, within the EU Horizon 2020 project calIBRAte, other tools covering so called New Approach Methodologies are currently being explored for applicability/integration into the SIA Toolbox tools [31].

The Stage-Gate innovation process model is a conceptual and operational map describing the innovation process from idea-to-launch and beyond [32, 33] and forms the basis for further classifying tools in “Early phase”, “Midterm phase” and “Late phase” (see Figure 3). Although this model is an oversimplification of the real innovation models used by industry, it provides a good logical structure of the innovation process. During the first stages of the innovation (Early phase) process, tools focus on the potential for health risks, followed by indicators for risk at midterm stages of innovation (Midterm phase), and to be finalized by demonstrators for health risks as laid down in regulatory requirements (Late Phase) (see Figure 3). This approach aims at improved insights into human and environmental risks and supports decisions at the various stages of development.

The tools and guidance documents are listed in Table 4. See the SIA Toolbox website [34] for more information on each tool and guidance.

In addition to the SIA Toolbox, a SbD Platform was developed by TEMAS AG, which is a web-based application providing a step-by-step procedure to design and elaborate an innovation project according to the SbD concept following regulatory and non-regulatory (e.g. quality standards) information needs. It is important to highlight that there is a great deal of communication involved in the application of the Platform, because it is not possible to use it without an interdisciplinary team. Different parts of the company, as well as the company with suppliers and customers, and finally in a certain measure also with regulators, are essential to effectively apply the SbD Platform.

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9 www.temas.ch
10 www.nanocalibrate.eu
11 https://temas.taglab.ch/SbDimplementation/
The SbD Platform is composed of 4 elements.

The workflow for the implementation of SbD in industrial innovation projects
It is the starting point of the whole process, allowing the user to define its project according to her/his needs, approach and method, following a structure based on Phases, which are not necessarily related to Stages. This approach allows for a better flexibility in its application to industry reality, accommodating different processes in parallel or in sequence, as well as outside contributions and cooperation of different actors inside the same company.

The Safety Dossier for the SbD to define for each project and each Phase the regulatory and “soft law” requirements, etc. as well as actor specific information.
The SbD Platform is based on regulatory requirements, with information needs templates for each specific regulation. For example, if for a specific Phase the relevant regulation is the occupational safety regulation or the REACH regulation, the user will find a subset of parameters limited to the specific regulations. However, the user has the possibility to select hers/his own suite of parameters to measure, even outside the specific regulation. In addition, a part of soft law, i.e. voluntary approaches, is also included, to account for other elements besides the regulation. In general, it is possible to easily create a specific user-tailored version of the SbD Platform, including important parameters which are not specifically included in the regulation requirement list. For each parameter it is possible to assign the information to a specific target/s, managing in this way the communication and information flow.

The Safety Profiles as graphical representation and overview of the closeness to Phase-related safety specifications, for the innovation under development.
Once the data are collected and included in the Platform, it is possible to evaluate how close the measured value is to a defined benchmark. The benchmark can be defined by regulators (e.g. environmental release limits or water concentration, CLP classification), or by the innovator (e.g. functionality level higher than X, or toxicity below concentration Y). A benchmark can also be an SbD indicator or index. In either case, personalized spider graphs allow to compare the measurement against the benchmark, and the scope is to support the decision making on uncertainty and risk reduction on specific parameters, and in general on the actions to be taken (e.g. carry on, go back, terminate) of the overall innovation project.

A harmonized inventory to support SbD with protocols, tools, procedures and data sources, etc.
The inventory is a collection of approaches, guidelines, methods, SOPs, and other documents that can be used to measure and quantify the parameters necessary to fulfill the regulatory and non-regulatory requirements of a specific innovation project. The inventory core is curated (as for now by TEMAS AG) taking into account inputs from this and other research projects,
standards, expected developments, accepted methods, etc. To this core curated inventory, the user can add hers/his own methods, SOPs, and guidelines. Of course, these other added inventory items are marked as such and are not guaranteed for reliability for nanomaterials. There is a very good correspondence and complementarity between the SbD Platform and the other elements of this chapter. For example, the SIA Toolbox can provide indication to the SbD Platform user about what kind of method is better suited to address a specific parameter in a specific development Phase of the innovation project. The database is essential to collect available information and avoid testing or design a better testing strategy, and the functionality measurement is necessary to balance the decision making with the Safety Profile results.

**Strategies for data gap filling**

Grouping strategies can be used in all stages of the innovation process to fill gaps in the risk assessment of MNMs. For a new material under development, information available on similar materials or relationships with e.g. physicochemical properties can provide an indication of potential issues with exposure, fate, kinetic behaviour, or hazard. This provides an opportunity to exploit this information to steer SbD actions. Especially in the early phases of product or material development, existing knowledge can be used to select MNMs for which grouping for regulatory use is expected to be possible at a later stage. This can highly increase the efficiency in gathering the information needed to comply with a regulation. The use grouping strategies is relevant, as targeted testing and read-across approaches will likely reduce resources and be less time-consuming than case-by-case testing. Grouping can also provide insights relevant for decisions at each stage of the innovation process [36]. A system biology approach has been recently proposed where adverse outcome pathways are generated using transcriptomics, proteomics and metabolomics for the possible identification of novel biomarkers and biological pathways involved mode or mechanism of toxicity data and physico-chemical data provide crucial information on the toxicity induced by MNMs [37]. A recent approach combined read-across and AOP for understanding MNM- and chemical-induced liver toxicity by first linking molecular initiating events to adverse outcome by following a sequential path of connected key events at different levels of biological organization. The reported differences between MNM and chemically-induced toxicity were proposed to be primarily related to toxicokinetic differences and the nature of the initial key events in the AOP [38].

**The NanoReg2 Database**

The NanoReg2 database was developed with a structure that allows for the inclusion of a wide variety of information, including material identity, measured properties (both physicochemical and hazard), as well as contextual information, such as protocols (e.g. SOPs or test guidance documents) and other types of descriptive metadata. In addition, the database structure
enables linkage to other information sites, such as external databases for high-throughput and omics data, exposure information, and product details/webpages. Currently, measured data in the database include physicochemical characterization, toxicological assay results and exposure data. Approximately 100 MNMs are currently represented by various levels of data and information (database accessed August 2018), which is being curated and coupled to quality aspects in line with recent efforts on how to address these issues [39, 40]. A user guidance for how to use the database during SIA is currently being developed and will be linked to the SIA Toolbox. The tools and guidance documents in the SIA Toolbox require specific data input (parameters), which have been defined within the NanoReg2 project, and a link between the tool input parameters and the database is being established through the eNanoMapper ontology. This forms the basis of the NanoReg2 database user guidance for the SIA Toolbox, and the implementation (i.e. annotation) of ontology eventually allows for the development of automatic search interfaces and integration of data into the SIA Toolbox.
Figure 3 Safe Innovation Approach in relation to the Stage-Gate innovation process and including a risk-benefit-cost evaluation per phase of the innovation process. Blocks indicate “Early phase” (Potential), “Midterm phase” (Indicator) and “Late phase” (Demonstrator).

3.3.3 Building a TE to link the SbD and RP concepts

A Trusted Environment (TE) is a physical or virtual space in which industry, innovators and governmental institutions can share and exchange knowledge, information and views on new technologies, such as for innovative nanomaterials and nano-enabled products. A TE can facilitate SbD by providing a podium for dialogue with regulatory risk assessors and/or other stakeholders to reduce the uncertainty in the safety assessment of MNMs and/or discuss relevant issues surrounding MNMs. It can also aid RP by providing regulatory risk assessors a podium for contact with innovators and stakeholders for the awareness of novel MNMs. A TE could also be applied to unite stakeholders to discuss functionality and cost issues faced when implementing SbD.
A TE invites trust by ensuring confidentiality and protecting intellectual property. Information-sharing through a TE is motivated by mutual benefit (e.g. reduced uncertainty), and entails some pre-requisites:

a) appropriate technical conditions that give organisations control over the process of information sharing (anonymity, logging of actions etc.)

b) juridical certainty to safeguard the information exchange process (non-disclosure agreements, regulations etc.),

c) clarity and agreement about rules of behaviour on dealing with the obtained information (Code of Conduct).

When these requirements are complied with, maintaining confidentiality as far as requested by the participants, TE stimulates transparency and openness on the exchanged information.

TE provides requirements in all three aspects, thereby stimulating transparency on the information exchanged but at the same time maintaining confidentiality as far as requested by the participants. In order to implement the TE principle, an independent organization might be established to define and supervise the technical, juridical and behavioral aspects of the TE (including mediation in situations of conflict) and facilitate the organizational aspects including setting up (virtual) meeting points for the related actors along the innovation process. The European Medicines Agency (EMA), for instance, has an Innovation Task Force and a pre-consultation process which allows the agency to anticipate the regulatory challenges posed by innovations, provides an entry point for promoting innovative technology and methods, contributes towards preparing for regulatory processes and provides a platform for exchange of information between innovators and regulators for the benefit of public health [41]. The Food Safety Authority of Ireland also has a working TE where innovators are often in dialogue with regulators for ensuring the safety and clarifying legal uncertainty surrounding the innovative product [42]. Engagement of various stakeholders, including fundamental researchers, market players, regulators and policy makers [43, 44] is advantageous for knowledge sharing and exchanging information about recent developments. Information can be gathered from a wide range of experts along the nanomaterial’s life-cycle, from upstream research to downstream management, which results in increased awareness and preparation for nanotechnologies [45, 46]. Similar engagement activities include integration, which creates close collaboration between natural scientists and social scientists [47], and boundary spanning, which links different stakeholders and thus bridges gaps between different actors and communities while simultaneously allowing “divergent interests and unique social norms to persist” [48, 49]. The European Food Safety Authority’s (EFSA) Emerging Risks Exchange Network (EREN), for instance, exchanges information between EFSA and Member States on possible emerging risks concerning food and feed [50]. Further boundary spanning is done via EFSA’s Stakeholder Consultative Group on Emerging Risks. Other examples include Finland which has regular
meetings involving all stakeholders at the Ministry level, and foresight workshops and stakeholder dialogs (e.g. Nanodialog [51]) being organised in Germany. The present H2020 NMBP-14 call “Risk governance of nanotechnology” is foreseen to bring the TE concept to an operational level.

3.3.4 Bringing the regulatory preparedness concept to practice

The Regulatory Preparedness (RP) concept aims to improve the anticipatory capabilities of regulators and to facilitate the development of (safety) regulation that can adapt to the pace of knowledge generation and innovation regarding new technologies such as MNMs and MNM-containing products. Results from the RP workshop hosted by JRC showed that achieving RP for innovations requires a continuous proactive combination of interconnected activities: awareness of innovations, dialogue and stakeholder engagement, knowledge building, soft regulation and reflection, and possibly dedicated organizations or task forces to deal with innovations and disseminate information across domains and among stakeholders [52].

3.4 Governance

3.4.1 Novel business models incorporating SIA for industry

Industry needs to develop business models that allow for SbD implementation and dialogue with regulatory risk assessors for the reduction of uncertainty of MNMs and nano-enabled products. Ideally, these business models would allow for safety to be incorporated in the design process of the MNM or nano-enabled product. To the best of our knowledge, there are no business models available incorporating SbD to MNMs or nano-enabled products. A business model describes the rationale of how an organization creates, delivers, and captures value, in economic, social, cultural or other contexts. The process of business model construction and modification is sometimes also called business model innovation and forms part of business strategy [53]. It is beyond the scope of this article to generate novel business models incorporating SbD but consideration needs to be taken in aligning the organization's strategy with the organization's structure, operations, and the environmental factors in achieving competitive advantage in varying combination of cost, quality, time, flexibility, innovation and attitudes [53]. Cooper has published a new version of the Stage-Gate model for progressive companies to develop a new generation of idea-to-launch processes [33]. In this next generation idea-to-launch system, each stage is adaptive, flexible, agile and accelerated to meet customers’ and users’ needs. This next-generation model can form the basis for the generation of suitable business models with intrinsic SbD phases embedded in them.

3.4.2 Novel governance models incorporating SIA for regulators

Regulatory risk assessors and policy makers need to develop novel governance models that are more anticipatory and that allow dialogue with innovators and other stakeholders. The current
European Union’s Horizon 2020 Research and Innovation Programme projects Gov4Nano, NANORIGO, and RiskGONE are currently working to develop an agile operational Nano Risk Governance system. The IRGC has developed a comprehensive framework for risk governance to provide guidance for early identification and handling of risks, involving multiple stakeholders. An inclusive approach is recommended to frame, assess, evaluate, manage and communicate important risk issues, often marked by complexity, uncertainty and ambiguity [54]. This framework could be adapted to MNMs and nano-enabled products to include tools and guidance for risk assessment, risk management, concern assessment and risk communication, as well as providing guidance for building trust among stakeholders or for leading effective dialogue. In addition, a database is generated to aid in information standardization and sharing. Future work is needed in bringing this conceptual framework into practice.

3.5 Benefits of SIA
The benefits of SIA implementation as identified by NanoReg2 consortium experts and the RIVM and included:

1. Economic viability by facilitating information acquisition of alternative opinions and the evaluation and the decision-making process along innovation- and R&D-projects,
2. Consumers trust by identifying safety uncertainties and potential risks in early phases of an innovation- or R&D-project,
3. Responsible innovation by providing several tools and information supporting the precautionary approach,
4. A better reputation by supporting sustainable development and focus on risk governance aspects, including socio-economic aspects which are key elements for reputation of an enterprise,
5. Interdisciplinary collaborations by stimulating TEs for dialogue between industry, regulators and other stakeholders

3.6 Challenges for SIA implementation
The challenges of SIA implementation as identified by NanoReg2 consortium experts and the RIVM are summarized here. Implementing a system (SIA) where innovators address safety from the early stages of the innovation process and where regulators are more aware and prepared for innovations is challenging because it requires a change of mindset from both innovators and regulators. We recommend the following activities for further development: i) raising awareness among innovators and safety regulators/risk assessors for each other’s questions and needs; ii) stimulate dialogue among innovators and safety regulators/risk assessors on a general level and per case to exchange views, knowledge and information in order to help all stakeholders deal with uncertainties about safety; iii) set boundary conditions to secure a
trustful environment for dialogues; and iv) integrate nano-specific safety from early phases of innovation onwards in business cases.

For industry/innovators, there are several challenges and possible barriers for SIA implementation: i) limited resources of SME such as time, money, management processes, equipment, availability of the right personnel, commitment by higher management or in bigger companies of local higher management; ii) lack of business plans with detailed guidance on how to implement SbD at the operative and strategic processual level including training; iii) lack of guidance on how to proceed with operative SbD implementation on the project level; iv) lack of information from supplier, academia or unknown applications/uses, dealers and information availability; and v) lack of trust for information sharing.

For regulators, the biggest challenge is to transition from a passive to an active role where the RP concept is put in action. Being up-to-date with innovations and engaging with innovators to also means that even though in many instances industry is responsible for the safety of their products, regulators need to be pro-active in keeping up-to-date with new innovations and via TEs engage with industry for knowledge sharing with regards to how to deal with new developments and limited insight on how nano-specific characteristics influence human and environmental toxicity. Regulators should act proactively and in a timely manner and engage with innovators and policy makers working on innovations.

4. Practical recommendations and next steps for SIA

4.1 SIA in practice

4.1.1 SIA in the early phase

Safe nanomaterials and products (aiming to be non-hazardous for human and environment).

SbD actions

When an innovator is in the early stage of the innovation process, actions can be taken with regard to all safety elements: awareness, hazard and exposure.

There are a number of options for action:

- Reduction of the nano-specific uncertainty by obtaining more nano-specific information (go to scenario 1)
- Reduction of nano-specific exposure (go to scenario 2)
- Reduction of the nano-specific hazard (go to scenario 3)
- Reduction of the nanospecific uncertainty by knowing the nanospecific hazard and reduction of both nano-specific exposure and nano-specific hazard (go to scenario 4)
RP actions

Regulators come into dialogue in a TE with industry in order to discuss how to reduce the uncertainty, nano-specific hazard and/or exposure.

4.1.2 SIA in the midterm phase

Safe production (aiming to eliminate risks at the workplace and to eliminate waste).

SbD actions

In this stage it is not realistic to reduce the hazard properties of the NM or to choose another NM. The NM and its application in a product is already too far in the production process. The options that remain are:
  - Reduction of the nano-specific uncertainty by obtaining more nano-specific information (go to scenario 1)
  - Reduction of nano-specific exposure (go to scenario 2)

RP actions

Regulators come into dialogue in a TE with industry in order to discuss how to reduce the uncertainty and/or nano-specific exposure.

4.1.3 SIA in the late phase and post-market

Safe use and recycling (the end-of-life of the considered innovation aiming to prevent exposure during use of the product and to have efficient recycling routes).

Provide necessary information to consumers or users for safe use and recycling. When the product or nanomaterial is already introduced on the market reduction of exposure and hazard is not an option anymore. However, nano-specific information needs to be monitored, especially when there is a vast amount of information on a specific nanomaterial. It is important to exchange actual, new information. Therefore the action in this cluster is
  - Share lessons learned if surveillance system detects any nano-specific hazard.

In order for knowledge to be circulated within the innovation process and post-marketing, a knowledge-sharing platform is needed that collects safety information in a secure environment and makes the knowledge accessible to all stakeholders for input and retrieval of information. Figure 4 represents a conceptual illustration on how knowledge of nano-specific hazard, nano-specific exposure and surveillance information is collected in the early, mid and late stages of the innovation process, respectively. ECHA’s Observatory for nanomaterials is one independent action towards a platform for information sharing. The Observatory for Nanomaterials is not only much cheaper and less burdensome to implement than the registry options, but also more
flexible to focus on relevant information, including information on hazards and risks. Nevertheless, a more general platform is needed for innovators and other stakeholders to share safety knowledge, for researchers to share their findings and for regulators to have access to up-to-date knowledge.

![Diagram of Safe Innovations Approach]

**Figure 4** Conceptual illustration on how information and knowledge from nano-specific hazard, exposure and post-marketing lessons learned can be circulated through the innovation process and within SIA (blue and red-blue-green arrows represent information circulation; TRL, technology readiness level).

**RP actions**

Multi-stakeholder dialogue for sharing lessons learned and for discussing issues relevant for reducing nano-specific uncertainty, hazard and/or exposure.

**4.2 Further steps toward SIA implementation**

Moving forward requires many actions and these are highlighted for future progress in the practical implementation of SIA.

**4.2.1 Creating SIA awareness**
As SIA is a relatively new concept, creating SIA awareness is needed by informing, educating and creating acceptance among stakeholders. In addition, a change of mind-set is needed in key stakeholders such as funding agencies, investors and industry. Funding agencies and investors need to focus not only on the impact of innovations on employment and competitiveness, but also on safety and knowing the health and environmental risks of innovations. Industry needs to keep in mind that there are huge costs associated with not knowing the health and environmental risks of innovations in products and supply chains including fines due to non-compliance, product recalls loss of sales, market shares and valuation, high costs for product reformulation, supply chain disruption, lost time and money going through product development for products that never reach the market because of safety issues, and tarnished brand reputation [55]. It is also important to train the new generation of innovators and regulators by embedding SIA in the curriculum of nano-related academic programs, through workshops and training courses.

4.2.2 SIA methodology

The SbD scenarios need to be disseminated by all stakeholders to be used for SIA implementation. The SIA Toolbox has tools and guidance documents for SbD and the users (innovators, regulators or other stakeholders) can select these on the basis of elements of benefit-risk-cost triangle, the phase(s) of the innovation process, population, output and domain of interest. Special attention needs to be made for newly developed tools and guidance documents for SIA Toolbox to stay up to date. With regards to the NanoReg2 database, additional data on MNM needs to be FAIR (Findable, Accessible, Interoperable, Reusable). This database provides a computational infrastructure for MNM toxicological data management with a nano-specific ontology. Work is needed to consolidate newly generate data in the database.

Generating a TE for information sharing is essential for the implementation of SIA. The timely exchange of views between innovators and regulatory risk assessors is essential. The knowledge gap leading to uncertainty on the safety of MNMs and nano-enabled products can be addressed most appropriately and most efficiently by having innovators and regulators share their views, expertise, and ideas on how innovative aspects, such as nano-specific physicochemical characteristics, influence (eco)toxicity. Here, it is vital that input from both regulators and innovators is gathered and the concept of ‘learning while doing’ to be applied and adapting the process to maintain the information flow. Finding common grounds to address the needs of both innovators and regulations is essential for a successful TE that does not restrict innovation.

In order to achieve RP for MNMs and nano-enabled products, a continuous proactive combination of interconnected activities is required. These include being aware of innovations, facilitating dialogue and engagement with stakeholders in a TE, developing knowledge building
strategies which include the applicability of soft regulation and setting a New Code of Conduct which supports SIA. Dedicated organizations or task forces are needed to assess how to deal with innovations and disseminate information across domains and among stakeholders.

4.2.3 Governance

New business models for industry that support SIA implementation are needed. Industry needs to move towards a proactive business model where there is an investment in knowing the risks of innovations in products and production chain, training suppliers and testing products. Strategic options for managing the risks of chemicals in product and supply chain and creating long-term value by implementing systems to know the risks innovations in products and supply chains are needed [55].

New governance models for regulators that support SIA implementation are also needed. Regulatory risk assessors and policy makers need also to transition to more agile governance models that can easily adapt to new challenges. These models need to be more inclusive involving more stakeholders in the process and allowing for rapid iteration to meet the needs of all stakeholders and society.

An information-sharing platform needs to developed for efficient knowledge sharing. Information is being generated at a dynamic speed but an information-sharing platform is needed for innovators and regulators to have access to up-to-date information. This will ensure partly for robustness of SIA where lessons learned from all the phases of the innovation process are shared to stimulate continuous improvement and ensure trust is sustained. This information-sharing platform would also ensure that information is consolidated in one port of reference. The second component to ensure robustness of SIA is oversight because it ensures that SbD and RP are implemented and practiced.
5. Conclusion

Here we present an agile system, the SIA approach, which not only addresses the safety of nanotechnologies in a timely and efficient manner but also aims at reducing the gap between the pace of innovation and the pace of developing nano-specific risk governance. SIA promotes a safer and responsible approach for industry when developing innovative products and materials, and stimulates a proactive attitude amongst policymakers and regulators to minimize the time gap between appearance of innovation and appropriate legislation. The SIA framework involves creating SIA awareness, developing SIA methodology (SbD scenarios, SbD methodologies (safety information needs, functionality and grouping), SIA Toolbox and the NanoReg2 database), bringing the TE and RP concept into an operational level, and developing novel business and governance models. The SIA framework is a system for MNMs and nano-enabled products that applies functionality-application-safety aspects. This system is agile and robust because it is easily adaptable to new MNMs and products as well as safety test developments including new methods implemented through the integration of tools and guidance documents in the SIA Toolbox. The database, which currently has around 100 MNMs and associated characterization, functionality and toxicity data, is currently being curated and it is constantly being updated. A major critical issue with a unified database is to have harmonized terminology (i.e. ontology) which is also (computationally) implemented into both the database and the SIA Toolbox through proper annotation. Building TEs for the dialogue between regulators and innovators (industry) remains a challenge but efforts are being made to bring this concept to an operational level. In order to bring RP to practical implementation requires a continuous proactive combination of interconnected activities: awareness of innovations, dialogue and stakeholder engagement, knowledge building, soft regulation and reflection, and possibly dedicated organizations or task forces to deal with innovations and disseminate information across domains and among stakeholders. The safety elements (uncertainty, hazard and exposure) are the core of the SbD scenarios and these scenarios provide a transparent basis for communication, management/governance and guidance with regard to SbD. Finally, the development of new governance and business models incorporating SIA for nanotechnologies will facilitate the transition to SIA implementation and towards an agile system.
Disclaimer
The content expressed in this paper is solely the opinion of the authors and does not necessarily reflect the opinion of their institutions.

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References

**Table 1a** Description of safety elements along with level of ambition

<table>
<thead>
<tr>
<th>Safety element</th>
<th>Ambition</th>
<th>Maximum Ambition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Level</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Minimal, ++ Medium, +++ Complete</td>
<td></td>
</tr>
<tr>
<td>Uncertainty (nano-specific information)</td>
<td></td>
<td>Complete nanospecific information</td>
</tr>
<tr>
<td>Nano-specific Exposure</td>
<td></td>
<td>Zero exposure</td>
</tr>
<tr>
<td>Nano-specific Hazard</td>
<td></td>
<td>Non-toxic</td>
</tr>
</tbody>
</table>

**Table 1b** Schematic representation of Scenario development

![Scenario Development Diagram](image-url)
### Table 1c Scenario description and level of awareness of nano-specific uncertainties, hazard and/or exposure

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Safety Element</th>
<th>Awareness</th>
</tr>
</thead>
</table>
| 0        | Regulatory compliance  
  - MNMs are considered as chemicals  
  - Absence of nano-specific information on hazard, nano-specific exposure protection measures and nano-specific waste handling | **High uncertainty**  
  due to lack of nano-specific environmental and health hazard and exposure information | No nano-specific awareness |
| 1        | Nano-specific information  
  - Regulatory compliance  
  - Knowledge on nano-specific information  
  - Ambition: minimal to maximum depending on available information  
  - Challenge to translate information such as the physical characterization of the MNMs (e.g. particle size, aspect ratio, charge, coating, crystallinity, refractive index, surface topography, etc.) to a complete toxicological profile of MNM  
  - No action to reduce hazard or exposure | **Uncertainty**  
  High $\rightarrow$ Low | Awareness about the discussions surrounding nano-specific information needs |
| 2        | Nano-specific exposure reduction  
  - Regulatory compliance  
  - Knowledge on nano-specific information  
  - Ambition: minimal to maximum (exposure conform regulatory compliance to minimal or no exposure)  
  - **SbD action taken to reduce exposure**  | **Uncertainty**  
  High $\rightarrow$ Low  
  **Exposure**  
  High $\rightarrow$ Low | Awareness about the discussions surrounding nano-specific information needs  
  + Depending on the level of ambition with regards to exposure reduction, exposure is controlled for workers, consumers and/or the environment, resulting |
| 3 | Reduction of nano-specific hazardous properties | Regulatory compliance  
Knowledge on nano-specific information  
Ambition: minimal to maximum depending on available information  
SbD action taken to reduce hazard | Uncertainty  
High $\rightarrow$ Low  
Hazard  
High $\rightarrow$ Low  
Exposure  
High $\rightarrow$ Low | Awareness about the discussions surrounding nano-specific information needs  
+  
Depending on the level of ambition with regards to hazard reduction and economic considerations to determine the level of MNM toxicity |
| 4 | Addressing all SbD Safety Elements | Regulatory compliance  
Knowledge on nano-specific information  
Ambition: minimal to maximum depending on available information  
SbD action taken to reduce hazard and exposure | Uncertainty  
High $\rightarrow$ Low  
Hazard  
High $\rightarrow$ Low  
Exposure  
High $\rightarrow$ Low | Awareness about the discussions surrounding nano-specific information needs  
+  
Depending on the level of ambition with regards to hazard and exposure reduction |
Table 2 Case studies illustrating the SbD Scenario concept (See Figure 3 for innovation stage information). Companies modified their NMs, choose alternative NMs with a less toxic profile, or changed their production process to reduce exposure or minimize waste.

<table>
<thead>
<tr>
<th>Case Study</th>
<th>MNM</th>
<th>Scope of Case</th>
<th>Start Level</th>
<th>Innovation Stage</th>
<th>Safety Element: Uncertainty</th>
<th>Safety Element: Hazard</th>
<th>Safety Element: Exposure</th>
<th>Safety Element: Exposure Information Collected?</th>
<th>Safety Element: Exposure Information Controlled?</th>
<th>End Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avanza re Pristin e Graphe ne</td>
<td>Upscaling of productions</td>
<td>Scenari o 0: Regulatory compliance</td>
<td>Early stage</td>
<td>Yes</td>
<td>Yes, but no measures for reduction</td>
<td>Yes</td>
<td>SbD action: change in synthesis to wet phase with no liquid waste</td>
<td>Scenari o 2 SbD actions taken to reduce exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NANO GAP Nano Ag fibres</td>
<td>Modification of process to reduce liquid waste</td>
<td>Scenari o 0: Regulatory compliance</td>
<td>On-market</td>
<td>Yes</td>
<td>Yes, but no measures for reduction</td>
<td>Yes</td>
<td>SbD action: change in synthesis to increase efficacy and reduce fibres in waste</td>
<td>Scenari o 2 SbD actions taken to reduce exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grupo Antolin Carbon nanofi bres</td>
<td>Upscaling of productions</td>
<td>Scenari o 0: Regulatory compliance</td>
<td>On-market</td>
<td>Yes</td>
<td>Yes, but no measures for reduction</td>
<td>Yes</td>
<td>SbD action: measures taken for reduction. Automatization of the</td>
<td>Scenari o 2 SbD actions taken to reduce exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NANO MAKERS</td>
<td>Silicon-based MNMs</td>
<td>Production of materials used in Li-ion batteries (coating of silicon MNMs with amorphous carbon)</td>
<td>Scenario 1: Information already collected with regard to MNM toxicity</td>
<td>On-market</td>
<td>Yes</td>
<td>Yes SbD action: selected MNM with different coating to reduce MNM toxicity</td>
<td>Yes</td>
<td>No</td>
<td>Scenario 3 SbD action: selected MNM with different coating to reduce MNM toxicity</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>-------------</td>
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<td>-----------------------------</td>
<td>---</td>
<td>---</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>HiQ-nano</td>
<td>Quantum dots and dye-doped silica nanoparticles</td>
<td>Development of safe fluorescent MNMs (substitution of Cadmium for a less toxic material (dye))</td>
<td>Scenario 0: Regulatory compliance</td>
<td>On-market</td>
<td>Yes</td>
<td>Yes SbD action: selection of alternative MNM with lower toxicity</td>
<td>Yes</td>
<td>No</td>
<td>Scenario 3 SbD action: selected MNM with different coating to reduce MNM toxicity</td>
<td></td>
</tr>
<tr>
<td>NANO-COMP OSIX</td>
<td>Nano silver</td>
<td>Application in non-food contact trolleys</td>
<td>Scenario 0: Regulatory compliance</td>
<td>On-market</td>
<td>Yes</td>
<td>Yes SbD action: measures taken for reduction</td>
<td>Yes</td>
<td>No</td>
<td>Scenario 3 SbD action: selected MNM with different coating to reduce MNM toxicity</td>
<td></td>
</tr>
</tbody>
</table>
Scenario 1: reduced uncertainty by collecting nano-specific information; Scenario 2: reduced nano-specific exposure; Scenario 3: reduced nano-specific hazard; Scenario 4: reduced nano-specific hazard and exposure
Table 3: Safety aspects needed for decision-making and SbD actions in the various stages of the innovation process (see Figure 3 for details on Stages and Gates)

<table>
<thead>
<tr>
<th>Stage 1 (Gate 2)</th>
<th>Stage 2 (Gate 3)</th>
<th>Stage 3 (Gate 4)</th>
<th>Stage 4 (Gate 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine if it is a NM</td>
<td>Think about how possible transformation throughout the life cycle (focus on dissolution, aggregation, agglomeration) may affect the toxicity of NM</td>
<td>Determine the expected doses or concentrations for the relevant exposure scenarios</td>
<td>Determine if the occupational exposure increases during the upscaling process</td>
</tr>
<tr>
<td>Determine if High Aspect Ratio Nanomaterial (HARN)</td>
<td>Search for information on reactivity, accumulation, immunotoxicity and/or genotoxicity of the pristine or similar (N)Ms depending on relevant route of exposure</td>
<td>Search for information on reactivity, accumulation, immunotoxicity and/or genotoxicity of the (transformed) nanoforms (or similar nanoforms) for the most relevant exposure scenarios</td>
<td>Perform a risk assessment of the relevant nanoforms for relevant exposure scenarios and identify uncertainties. Use read across or grouping of relevant forms to fill remaining data gaps for risk assessment. If uncertainties remain unresolved, consider further testing.</td>
</tr>
<tr>
<td>Determine if NM is persistent</td>
<td>Identify most relevant exposure and release scenarios and exposure reduction measures that can be applied throughout the life-cycle</td>
<td>Think about SbD actions that can reduce or eliminate risk at the workplace and/or eliminate waste throughout the life-cycle</td>
<td>Assess the quality of the production process</td>
</tr>
<tr>
<td>Think about possible routes of exposure and release scenarios</td>
<td>If functionalization is applied such as doping, coating or surface treatment, search for available safety information on these chemical components.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search for available information on the chemical components, the (pristine) NM and/or similar NMs</td>
<td>Search also for safety information of the different crystalline forms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Think of SbD actions to design out hazard or to</td>
<td>Think about SbD actions by choosing the most</td>
<td></td>
<td></td>
</tr>
<tr>
<td>avoid release and exposure</td>
<td>suitable alternative materials and manufacturing processes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4 List of Tools and Guidance documents used in the SIA Toolbox: the applicability of the tools with regards to the elements of benefit-risk-cost triangle, which phase(s) of the innovation process the tool can be used (early, midterm or late phase), population (Consumer, Environment, General population, Worker), Exposure route (Dermal, Oral, Inhalation), Output (qualitative and/or quantitative) and domain (Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices)

<table>
<thead>
<tr>
<th>Tools</th>
<th>Guidance Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENARIOS® Risks management and monitoring system</td>
<td>Australian guidance on regulation impact statement (RIS) cost-benefit analysis</td>
</tr>
<tr>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Benefit-Cost</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Midterm and Late phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Consumer, Environment, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
</tr>
<tr>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Output:</strong> Qualitative</td>
<td><strong>Output:</strong> Quantitative, Semi-quantitative</td>
</tr>
<tr>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
<tr>
<td>GUIDEnano</td>
<td>NanoRisksCat: A Conceptual Decision Support Tool for Nanomaterials</td>
</tr>
<tr>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Risk</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early and Midterm phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population</td>
</tr>
<tr>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Output:</strong> Quantitative</td>
<td><strong>Output:</strong> Qualitative, Semi-quantitative</td>
</tr>
<tr>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
</tr>
<tr>
<td>NanoFASE: SimpleBox4Nano screening fate assessment model</td>
<td>ECHA Socio-Economic Analysis for the analysis of Restrictions or Authorisations under REACH</td>
</tr>
<tr>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Benefit-Cost</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Midterm and Late phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Environment</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
</tr>
<tr>
<td><strong>Output:</strong> Semi-quantitative</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Domain:</strong> Chemical substances</td>
<td><strong>Output:</strong> Qualitative, Quantitative</td>
</tr>
<tr>
<td>Lean Business Canvas, safety and society check</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
<tr>
<td><strong>Element:</strong> Benefit-Risk-Cost</td>
<td><strong>Element:</strong> Benefit-Cost</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early and Midterm phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population</td>
</tr>
<tr>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Output:</strong> Quantitative</td>
<td><strong>Output:</strong> Qualitative, Semi-quantitative</td>
</tr>
<tr>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
</tbody>
</table>

Consexpo Nano Tool | ECHA Socio-Economic Analysis for the analysis of Restrictions or Authorisations under REACH |
<p>| <strong>Element:</strong> Risk | <strong>Element:</strong> Benefit-Cost |
| <strong>Innovation Phase:</strong> Early, Midterm and Late phase | <strong>Innovation Phase:</strong> Midterm and Late phase |
| <strong>Population:</strong> Consumer | <strong>Population:</strong> Consumer, Environment, General population |
| <strong>Route of exposure:</strong> Inhalation | <strong>Route of exposure:</strong> Dermal, Oral, Inhalation |
| <strong>Output:</strong> Quantitative | <strong>Output:</strong> Qualitative, Quantitative |
| <strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products | <strong>Domain:</strong> Chemical substances |</p>
<table>
<thead>
<tr>
<th>Control Banding Nanotool</th>
<th>LICARA NanoScan</th>
<th>Societal incubator</th>
<th>ECHA Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals [35]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Benefit-Risk-Cost</td>
<td><strong>Element:</strong> Benefit-Risk-Cost</td>
<td><strong>Element:</strong> Risk</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early phase</td>
<td><strong>Innovation Phase:</strong> Early and Midterm phase</td>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
</tr>
<tr>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Output:</strong> Qualitative, Semi-quantitative</td>
<td><strong>Output:</strong> Quantitative, Semi-quantitative</td>
<td><strong>Output:</strong> Quantitative</td>
<td><strong>Output:</strong> Qualitative and Semi-Quantitative</td>
</tr>
<tr>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FNN-Bayesian Belief Network (BBN) model</th>
<th>MARINA Risks Assessment Strategy</th>
<th>Stoffenmanager Nano</th>
<th>Health Impact Assessment (HIA) under REACH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Cost-Risk</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Midterm and Late phase</td>
</tr>
<tr>
<td><strong>Population:</strong> Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
<td><strong>Population:</strong> Consumer, Environment, General population, Worker</td>
</tr>
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<td><strong>Route of exposure:</strong> Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
</tr>
<tr>
<td><strong>Output:</strong> Quantitative</td>
<td><strong>Output:</strong> Qualitative, Quantitative</td>
<td><strong>Output:</strong> Qualitative, Quantitative</td>
<td><strong>Output:</strong> Qualitative, Quantitative</td>
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<td><strong>Domain:</strong> Medical Devices</td>
<td><strong>Domain:</strong> Medical Devices</td>
<td><strong>Domain:</strong> Medical Devices</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Golden Egg Check</th>
<th>Nanosafer tool</th>
<th>The Swiss precautionary matrix for synthetic nanomaterials</th>
<th>NanoCRED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Element:</strong> Benefit-cost</td>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Risk</td>
<td><strong>Element:</strong> Risk</td>
</tr>
<tr>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
<td><strong>Innovation Phase:</strong> Early, Midterm and Late phase</td>
</tr>
<tr>
<td><strong>Population:</strong></td>
<td><strong>Population:</strong> Environment</td>
<td><strong>Population:</strong> Consumer, Environment, General Population</td>
<td><strong>Population:</strong> Environment</td>
</tr>
<tr>
<td><strong>Output:</strong> Qualitative</td>
<td><strong>Route of exposure:</strong> Oral</td>
<td><strong>Route of exposure:</strong> Dermal, Oral, Inhalation</td>
<td><strong>Route of exposure:</strong> Oral</td>
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<tr>
<td><strong>Domain:</strong></td>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td><strong>Domain:</strong> Chemical substances</td>
</tr>
</tbody>
</table>

- **Control Banding Nanotool**
  - **Element:** Risk
  - **Innovation Phase:** Early phase
  - **Population:** Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Qualitative, Semi-quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **LICARA NanoScan**
  - **Element:** Benefit-Risk-Cost
  - **Innovation Phase:** Early and Midterm phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Quantitative, Semi-quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **Societal incubator**
  - **Element:** Benefit-Risk-Cost
  - **Innovation Phase:** Early, Midterm and Late phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **ECHA Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals [35]**
  - **Element:** Risk
  - **Innovation Phase:** Early phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Qualitative and Semi-Quantitative
  - **Domain:** Chemical substances

- **FNN-Bayesian Belief Network (BBN) model**
  - **Element:** Risk
  - **Innovation Phase:** Early, Midterm and Late phase
  - **Population:** Worker
  - **Route of exposure:** Inhalation
  - **Output:** Quantitative
  - **Domain:** Medical Devices

- **MARINA Risks Assessment Strategy**
  - **Element:** Risk
  - **Innovation Phase:** Early, Midterm and Late phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Qualitative, Quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **Stoffenmanager Nano**
  - **Element:** Risk
  - **Innovation Phase:** Early and Midterm phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Inhilation
  - **Output:** Semi-quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **Health Impact Assessment (HIA) under REACH**
  - **Element:** Cost-Risk
  - **Innovation Phase:** Midterm and Late phase
  - **Population:** Consumer, Environment, General population, Worker
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Qualitative, Quantitative
  - **Domain:** Chemical substances

- **Golden Egg Check**
  - **Element:** Benefit-cost
  - **Innovation Phase:** Early, Midterm and Late phase
  - **Output:** Qualitative

- **Nanosafer tool**
  - **Element:** Risk
  - **Innovation Phase:** Midterm and Late phase
  - **Population:** Environment
  - **Route of exposure:** Oral
  - **Output:** Quantitative
  - **Domain:** Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices

- **The Swiss precautionary matrix for synthetic nanomaterials**
  - **Element:** Risk
  - **Innovation Phase:** Early and Midterm phase
  - **Population:** Consumer, Environment, General Population
  - **Route of exposure:** Dermal, Oral, Inhalation
  - **Output:** Qualitative, Semi-quantitative
  - **Domain:** Medical devices
<table>
<thead>
<tr>
<th>devices</th>
<th>quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain:</strong> Biocide products, Chemical substances, Cosmetic products, Drugs, Food contact materials, Food labelling, Medical devices</td>
<td>One box-model for accident situations in laboratories (Walser et al. 2012)</td>
</tr>
</tbody>
</table>

**Element:** Risk  
**Innovation Phase:** Early, Midterm and Late phase  
**Population:** Worker  
**Route of exposure:** Dermal, Oral, Inhalation  
**Output:** Quantitative  
**Domain:** Chemical substances