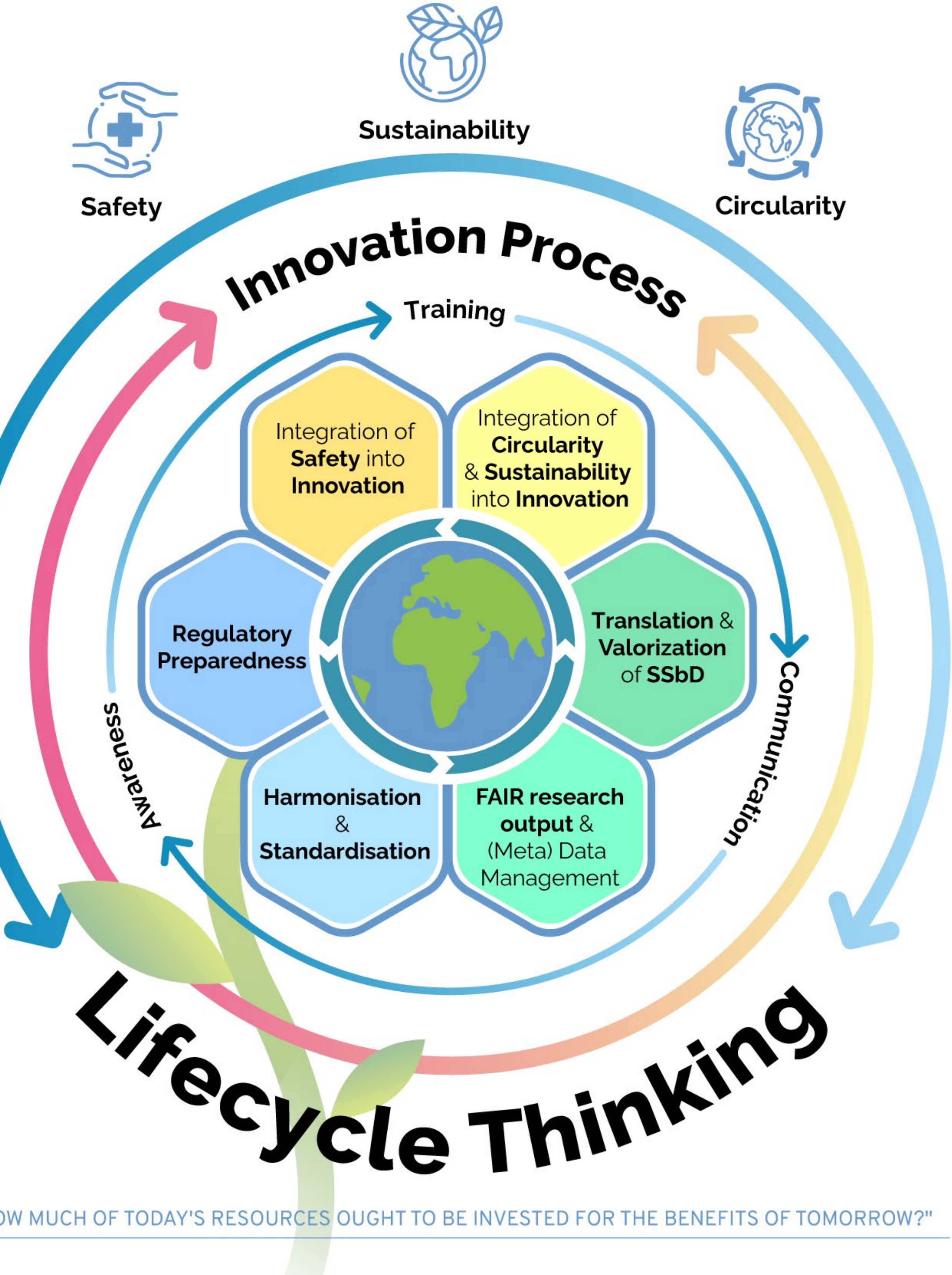
ROADMAP SAFE AND SUSTAINABLE ADVANCED AND INNOVATIVE MATERIALS 2024-2030



"HOW MUCH OF TODAY'S RESOURCES OUGHT TO BE INVESTED FOR THE BENEFITS OF TOMORROW?"

Disclaimer:

This publication “Roadmap Safe and Sustainable Advanced and Innovative Materials 2024-2030” was instigated as an initiative of European members of the NanoSafety Cluster[1] community in response to and to provide input for the European Commission‘s request for a European Partnership[2] on “Innovative Advanced Materials for EU” (“IAM4EU”). An advanced draft of this document has been shared with the Steering Group of the NanoSafety Cluster for review. Great care was taken to integrate feedback from the complete NSC community. However, this is not possible without representing different and partly even conflicting opinion on how to address the complex issues targeted in this roadmap and the views expressed in this document or even parts of it are those of the individual authors and do not necessarily reflect the policy and opinions of their employer, or the projects they are part of.

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PREFACE

The (nano)materials safety community has a long record of accomplishments in fully incorporating and embracing the safety assessment of nanomaterials at an early stage in the material design and innovation process [Figure 1]. In fact, the community was instrumental in introducing and implementing the concept of regulatory relevant method development for characterisation and toxicity testing through its multidisciplinary publicly funded projects, setting milestones with NANoREG (2013 - 2017)[3] , NanoReg-II (2015 – 2019)[4] and PROSAFE (2015-2017)[5] , and branching out too many other nanomaterial projects since then.

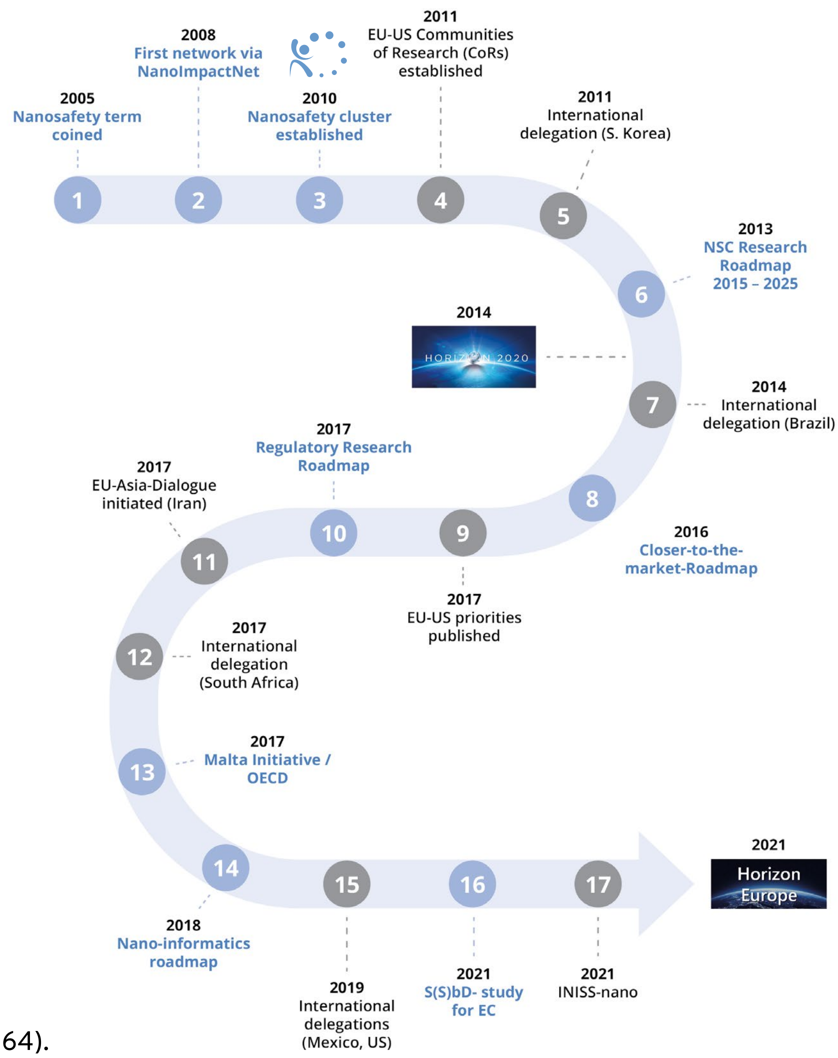

Figure 1:
Key milestones achieved in Nanosafety Cluster (https://doi.org/10.1016/j.nantod.2021.101364).

Through these projects, leading researchers in both the public and the private sector collaboratively contributed to the standardisation and harmonisation needs identified by official, international bodies, such as the OECD Working Party on Manufactured Nanomaterials (OECD WPMN)[6] (established in 2006) and the ISO/TC 229[7] Nanotechnologies and CEN/TC 352 Nanotechnologies committees[8] (both esta-blished in 2005). In doing so, the wider (nano)-

materials safety community developed and adopted a principle of shared responsibility, based on a recognition that the most knowledge and innovation knowhow in nanomaterials' innovation capacity was held by industries that invested in R&I strategies, while the academic and regulatory communities held unique expertise in identifying and removing limitations of existing test methods and the development of new ones.

Over nearly 20 years, the nanomaterials safety community established strong interdisciplinary, precompetitive collaborations under the above-mentioned principle of shared responsibility, and thereby secured both an ongoing advancement of nanomaterials innovation, whilst simultaneously improving the safety and environmental impact of the resulting products and processes.

As a consequence of the drastically increased demand of new (nano)materials resulting from EU policies as well as changes in geopolitical relationships, the Safe-by-Design (SbD) concept, initially developed by the biotechnology community, and subsequently elaborated, improved, and deployed by the nanomaterials safety community, represents a milestone of the communities' practised principle of shared responsibility. Its adoption and widening to a concept of Safe and Sustainable by Design (SSbD) by the European Commission acknowledges the unprecedented nature and achievements of the nanomaterial's safety community.

This ground-breaking collaborative process uniquely enabled the nanomaterials safety community to bring its expertise and complement the approaches to the wider chemicals and materials community, thereby widening the principle of shared responsibility to the safe and sustainable design of all stages along the value chains of materials in all their market sectors.

Why do we need Safe and Sustainable Design of innovative advanced materials?

The regulation, risk assessment, and decision-making process related to the substitution of harmful substances are always relative and dependent on the underlying data used for the assessments. In the case of advanced materials, the available data today is insufficient, and the relevance of the methods used is unclear. This lack of clarity should prompt us to consider similar historical situations, such as those involving PFAS and microplastics. Presently, we are faced with the challenge of mitigating the effects of these substances, given the absence of clear regulatory guidance and efficient methods capable of addressing the tens of thousands of PFAS substances currently on the market.

The current situation serves as a compelling reason to prioritize activities in accordance with the needs outlined in this roadmap, with the aim of averting a future where we are constantly playing catch-up due to past ignorance. Instead, we should strive to achieve a successful transformation towards a safe and sustainable, toxic-free world.

• NSC AS NEUTRAL COMMUNICATION PLATFORM

The EU Nanosafety Cluster (NSC) has been a strong European focal point for developing knowledge and seeking focus and efficiency for good risk governance of nanomaterials. Over the past 15 years a variety of stakeholders have contributed actively, including representatives from industry, regulators/governments and science that participate(d) in projects initiated and often funded by the European Commission. Effective communication to project partners and a wider audience of stakeholders (e.g., regulators and policymakers) has been fundamental to the success of projects and the translation of project outputs into practice. Members of the NSC were the first to adopt the Safe-by-Design concept for nanomaterials, to drive its optimisation and general adoption, and quickly reacted to the rapidly evolving landscape that required going from SbD to SSbD. This document is prepared by representatives of the NSC also using their 'back office' and the NSC working group Safe and Sustainable by Design, Innovation & Regulation.

Table 1:
The NanoSafety Cluster has been actively involved in publishing roadmaps and reports related to nanosafety. Here are some key documents published by or with contributions from the NanoSafety Cluster.

- **NSC Research Roadmap 2015-2025 (2013)[9]:** This Roadmap outlined the strategic research needs for nanosafety in the coming years. It covered various aspects, including risk assessment, exposure scenarios, toxicology, and standardisation.
- **NSC Closer to the market Roadmap - CTTM (2016)[10]:** The CTTM identifies the key challenges to be tackled immediately and outlines a step-by-step approach to establishing a framework to deliver of nano-enabled products to the market.
- **Regulatory Research Roadmap (2017):** NanoReg2 was a European project under the Horizon 2020 program, focusing on the development of grouping and read-across approaches for nanomaterials. The associated roadmap addressed key challenges and priorities in nanomaterials safety assessment.
- **EU-US Roadmap: Nanoinformatics (2018):** The Nanoinformatics Roadmap 2030 is a compilation of state-of-the-art commentaries from multiple interconnecting scientific fields, combined with issues involving nanomaterial (NM) risk assessment and governance.
- **Safe-by-design for materials and chemicals[11]:** Experts from different stakeholder groups has developed an overview about the main topics for an innovation programme, which could accelerate the design, development, and adoption of safer alternatives to new and existing applications (materials, chemicals, products, and services).
- **Guidance on Safe-By-Design (SbD) (2019):** The NanoSafety Cluster has contributed to guidance documents on Safe-by-Design principles, emphasising the importance of integrating safety considerations at the initial stages of nanomaterial development.
- **Gov4Nano Roadmap to Standardisation (2020):** This Roadmap aimed to provide guidance on the standardisation of nanotechnologies. It outlined the steps necessary for developing standards and integrating them into the regulatory framework.
- **Test Guideline development From Science to Regulation (2023):** EU funded project NanoHarmony published a White Paper that addresses the harmonisation of test methods and the coordination of efforts in nanosafety research.

NSC ROADMAP

In the Chemicals Strategy for Sustainability (CSS)[12] , the plan for a Strategic Research and Innovation Agenda in 2022 was announced[13] . Subsequently, the European Commission developed a Strategic Research and Innovation Plan (SRIP) that highlights areas in research and innovation (R&I) that are crucial for accelerating the transition to chemicals and materials that are safe and sustainable. The Commission refers to this SRIP in the Horizon Europe work programme as an overarching strategy. In addition, the Commission invites research and innovation funders across EU, national and private funding programmes as well as researchers and innovators to support this strategy and to contribute to its implementation. This roadmap is written in response to this invitation and will serve as guidance for, amongst other, the development of the Innovative Advanced Materials for EU (IAM4EU) partnership on materials, as presented by the European Commission in the second Horizon Europe Strategic Plan[14] and in the recent Communication from the EC on Advanced Materials for Industrial Leadership[15].

What do we mean by 'Safe and Sustainable by Design?

One important aspect of nanotechnology entering the market was making safety and sustainability central to technology development, first leading to the Safe(r)-by-Design (SbD), and then expanded to the Safe-and-Sustainable-by-Design (SSbD) concepts. The application of Safe –by-Design (SbD) principles in the development and production of materials, products, or processes can result in both costs and savings. SbD aims to include safety considerations at the earliest possible stage of material development, avoiding/minimizing the use of (very) hazardous chemicals/materials. The intention is to prevent undesired human and environmental risks and to ensure a clean, healthy, and safe living environment. Safe-by-Design forms part of the EC environmental policy. Implementing SbD often requires upfront investments in research and development to identify and integrate safer alternatives, assess potential risks, and design materials with safety considerations in mind. Towards the end of the design phases, comprehensive testing and validation processes may still be necessary to ensure that the materials or products meet safety standards and are compliant with regulations. SbD aims to minimise health and safety risks associated with materials and processes. By proactively addressing safety concerns, companies can potentially reduce the likelihood of accidents, worker health harm, and associated costs. Designing materials with safety in mind can facilitate compliance with regulatory requirements. This may result in lower regulatory hurdles, and help prevent fines, or legal costs associated with non-compliance. SbD principles often involve selecting materials and processes that are environmentally friendly. This can lead to savings through reduced waste disposal costs, energy efficiency gains, and a positive brand image associated with sustainability.

In recent years SbD is extended to SSbD and in this context, sustainability refers to the integration of ecological, social, and economic considerations into the design and development of materials, products or processes to ensure long-term safety and minimize environmental impact. The goal is to create innovations that not only meet safety requirements but also contribute to broader sustainability objectives. SSbD considers the environmental footprint of materials and processes, aiming to minimize resource consumption, energy use, and waste generation. This includes assessing the life cycle of a product, from raw material extraction to disposal, and identifying ways to reduce negative environmental effects. Safety and sustainability are part of the innovation (should be logical to incorporate it and not see SSbD as a standalone activity that also is perceived as a barrier rather than an opportunity).

Innovative advanced materials[16] possess novel functionalities aimed at addressing key objectives outlined in the Green Deal and the zero-pollution action plan. These materials play a pivotal role in facilitating both the green and digital transitions, fostering a circular and resilient economy, and contributing to a secure and sustainable European society. As nanomaterials constitute a significant subset of advanced materials, others may derive their characteristics from either external nanosized features or internal/associated nanostructures. Leveraging the expertise developed by the nanomaterials community, who have extensively explored the distinctions and commonalities between nano and bulk materials, provides a valuable foundation for implementing Safety and Sustainability by Design (SSbD) principles across various material types. This expertise offers advanced materials a strategic advantage in integrating safety and sustainability seamlessly into the innovation process. Additionally, it underscores the potential risks associated with the uncoordinated handling or lack of handling of advanced materials within the existing regulatory frameworks.

SUMMARY

To take full advantage of the possibilities that innovative advanced materials may bring, addressing safety aspects is crucial, preferably together with sustainability aspects. Incorporating this already in the design phase can smoothen the process and save costs towards market introduction of these materials. To ease this process, the European Commission advocates the use of a framework of Safe and Sustainable by Design (SSbD). The aim is to integrate functionality/innovation with safety and sustainability considerations as early as possible in the innovation process. Within this framework sustainability entails incorporating ecological, social, and economic factors into the design and advancement of materials, products, or processes. If SSbD is implemented broadly in industrial R&I, it can be expected to smoothen the process towards supplying the regulatory requirements necessary for market introduction. The "by-Design" approach acts in a forward-looking manner, based on valid predictive measures. As such this enables anticipation of potential drawbacks any technology could bring eventually.

In this Roadmap, the NanoSafety Cluster (NSC) presents the primary areas relevant to safety and sustainability of both nanomaterials and other innovative advanced materials. For each of these areas a description is provided of the current state-of-the-art, and unresolved aspects and emerging issues are identified, as well as the needs to close the gaps within each area. By providing these issues and needs the NSC aims to supply directions in research to facilitate development of safe and sustainable innovative advanced materials and offers knowledge based on years of nanosafety research. The NSC can help innovation projects and shape the effective and proportionate governance of nanotechnology by EC Member States and promote the societal acceptance of the use of nanomaterials and advanced materials. This requires some investment that can be reached by active participation in newly developed projects in the IAM4EU partnership and projects started thereof.

FAIR Data and Management of (Meta) Data

There is a strong need for data to be FAIR (Findable, Accessible, Interoperable, and Reusable) to maximise the valorisation of data. This requires a FAIR data management plan that integrates SSbD data into the materials' digital ecosystem. The tools and resources used in materials and medical/biological research need alignment. This includes extending, mapping, and complementing existing ontologies, and (further) developing the necessary tools. The data management and interoperability should become a central part of new and updated testing guidelines and guidance documents.

FAIR Data and Management of (Meta) Data

Already existing reliable knowledge and data should be used to inform new work and discoveries. The lack of fundamental research addressing the unique properties of these advanced materials should be solved. This should take regulatory aspects into account as well.

Integration of Circularity and Sustainability into Innovation

While science and innovation should be driving the SSbD process, clear guidance is needed on how to implement SSbD. This should include data needs and tools to be used per innovation stage and identifying the responsible actors.

Translation & Valorisation of SSbD

Innovative advanced materials can propel positive transformation and play a role in shaping a future that is more innovative and accountable. To fulfil this promise, their developments should embrace collaboration among stakeholders from different disciplines, anticipate regulatory requirements, and demonstrate a dedication to sustainability.

Harmonisation and Standardisation

Standards and Test Guidelines should be made available for the safety and sustainability testing of innovative advanced materials, either by testing and/or adapting those that already exist, or developing new ones where needed. This should include New Approach Methodologies (NAMs[17]), in particular where these can assist in early R&I phases for innovative advanced materials. Priorities have been suggested by the Malta Initiative[18].

Regulatory Preparedness and Governance

For governance of safe and sustainable innovative advanced materials an exchange platform should be established to allow regulators to prepare for new developments, while at the same time preparing developers for (changes in) regulatory requirements.

INTRODUCTION & BACKGROUND

To take full advantage of the possibilities that innovative advanced materials[19] may bring, addressing safety aspects is crucial, preferably together with sustainability aspects [Figure 2]. These safety aspects include possible negative impact on humans and the environment, and preferably encompass the entire research, development, and innovation process of chemicals and materials, spanning from the earliest stages of development. Recent years have seen considerable progress in understanding and addressing safety concerns related to nanomaterials. In recent years, next to safety aspects also sustainability aspects became more important, e.g., connected to energy consumption and the (re-)use of raw materials. This accumulated knowledge empowers development and manufacturing sectors to streamline product launches, integrating safety and sustainability into their design processes (Safe-and-Sustainable-by-Design (SSbD)[20,21], (see also Box 2). Several EU-funded projects under H2020 have already addressed these aspects into their activities. Some frontrunner projects that focused on applications or products have integrated sustainability, while others have conducted case studies and initiated discussions on a safe and sustainable innovation approach (SSIA)[22]. Advancing current SSbD tools and models is essential for their future relevance. A critical factor for SSbD implementation is data.

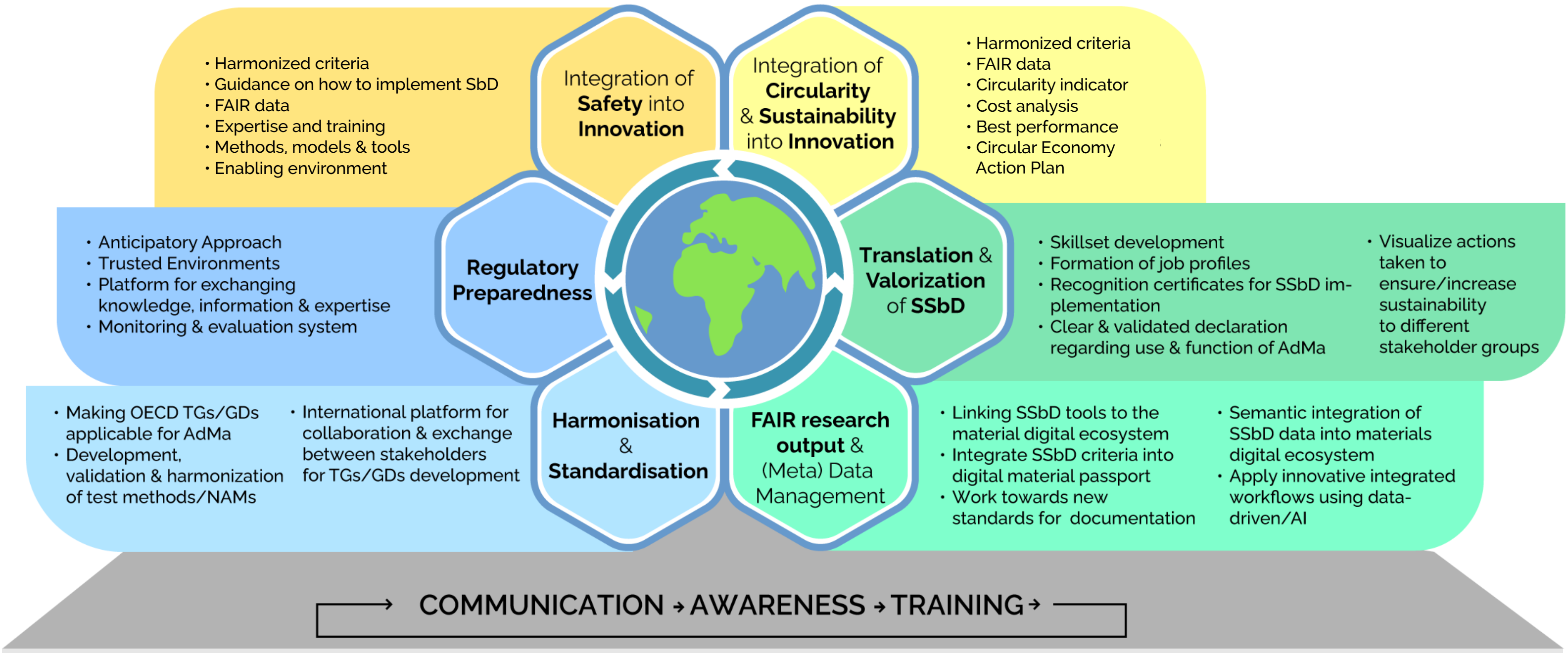

Figure 2: To take full advantage of the possibilities that innovative advanced materials actions are needed in several areas to ensure their safety and sustainability. This is summarised here and further detailed in the different sections of this document.

To facilitate SSbD, all knowledge must adhere to the "FAIR"[23] principles to ensure long-term accessibility and use. This involves connecting with European initiatives and connecting to/ ensuring an umbrella infrastructure as the organisational hub for incorporating or providing access to data from completed and ongoing H2020 projects, as well as those funded under Horizon Europe in the future.

The SSbD framework developed by the JRC represents a significant advancement in the realm of responsible innovation, offering a structured and comprehensive approach to integrating safety considerations into the design and development of new materials and technologies.

Safe and sustainable by design framework

The SSbD (Safe & Sustainable-by-Design) framework[24] developed by the Joint Research Centre (JRC) is a pioneering approach that integrates safety considerations into the design and development of new materials, products, and processes. This framework emphasizes the proactive identification and mitigation of potential risks at the early stages of innovation, thereby promoting the creation of safer and more sustainable technologies.

The SSbD framework developed by the JRC offers a structured methodology for incorporating safety principles into the design phase, aligning with the principles of responsible innovation. By integrating safety considerations from the outset, this approach aims to minimize the likelihood of unintended hazards and ensure that emerging technologies are developed with a strong focus on risk prevention and mitigation.

Furthermore, the SSbD framework provides a systematic approach to evaluating the safety and sustainability implications of new materials and technologies, facilitating informed decision-making, and reducing the likelihood of adverse outcomes. By promoting a proactive and holistic approach to safety, the SSbD framework enables innovators to consider the potential impacts of their creations and make informed choices that prioritize safety and sustainability.

The JRC framework has the potential to drive the development of innovative advanced materials that are not only cutting-edge but also safe and sustainable, aligning with the broader goals of promoting responsible and ethical innovation.

By considering sustainability aspects, the SSbD approach aims to support the development of safer materials and products that not only meet safety standards but also contribute positively to planetary health and societal wellbeing, and promote a holistic and responsible approach to innovation and R&D.

Sustainability supports societal, economical, and environmental UN Sustainable Development Goals (SDGs)[26] for our planet and for present and future generations. It refers to the use of the biosphere by present generations while maintaining its potential yield (benefit) for future generations. The safety concept for humans and the environment is transversal to all sustainability dimensions (environmental, social, and economic). Sustainability relates to / is about minimizing the environmental footprint, regarding climate change, pollution, and resource use, protecting ecosystems and biodiversity (see Box 2). It entails a lifecycle perspective (from raw material extraction, production, use, and end of life) where research and development (R&D) is aligned to a comprehensive approach by integrating human and environmental safety and taking advantage of and promoting circularity and innovation.

Aspects of Sustainability

Sustainability has three main aspects, all of them overlapping and cross linked with safety: planet, people, and prosperity. The Planet/Biosphere/Environment aspect deals with remaining within the planetary boundaries by preserving the environment and natural resources and ensuring biological quality. This should enable providing ecosystem services to society for the present and future generations (maintenance of ecosystem services for humanity). This aspect aims at using green and sustainable chemistry principles to minimize the toxicity and environmental footprint, regarding climate change, pollution, and resource use. The People/Society aspect aims at ensuring beneficial social impact such as social welfare, human health safety, and respect of human rights, including equality and education. The Prosperity/Economy aspect should ensure economic growth and innovation within the planetary boundaries.

In summary, sustainability could be described as the ability of a material or chemical to provide products/services with desired functionalities without exceeding planetary boundaries, while ensuring wellbeing and other socio-economic benefits.

FROM NANO-MATERIALS TO INNOVATIVE ADVANCED MATERIALS

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

Engineered nanomaterials have been produced for over 50 years and are used in every industrial sector (e.g., construction, structural and functional materials, active ingredients, food, healthcare, energy, cosmetics, and electronics). In the last two decades the degree of engineering at the nanoscale has improved. Most recently, the complexity of such materials has further increased. In the last few years, interest in novel materials has expanded beyond nanomaterials, to encompass functionality derived from properties other than size in the nanoscale or from internal nanostructures, which are the criteria of the **EC recommended definition**[27] **of a nanomaterial**. Innovative advanced and materials, although sometimes containing nanosized structures or components, do not necessarily fall under the definition. As with nanomaterials, the definition of which has often been debated, a description of the term advanced materials has also come under scrutiny. In a pragmatic approach[28] , it is accepted that advanced materials comprise a variety of materials for which innovative and novel behaviour may be demonstrated; this implies that there is a comparative element in the definition, either temporal (novel) or relating to innovation (advanced), and in years to come materials currently perceived as advanced will no longer qualify, whereas new materials will be added to the list. There is **no definition of advanced materials existing** yet, although working descriptions exist[29] and work on definition is ongoing e.g., at ISO. However, it is unclear, if such definition will ever be created, that could be used for regulatory aspects. Irrespectively, some examples of advanced materials include multi-component (nano) composites formed by two or more functional components (e.g., nanoparticles, nanocrystals, organic molecules) conjugated by strong molecular bonds, or by a nanomaterial with a unique chemical composition modified by hard or soft coatings. Some of the most widely used components are (combinations of) carbonaceous (e.g., fullerenes, carbon nanotubes, graphene) or metallic (metal or metal oxide) nanomaterials with or without organic coatings (e.g., polymers, macromolecules, and enzymes)[30].

In terms of using nanomaterials to inform the process of driving towards safe and sustainable innovative advanced materials, there is a body of work that can serve as a guide. This applies to both the SSbD assessment of nanomaterials (as members of the innovative advanced materials family), as well as the methods, approaches and roadmaps already established for the former that can serve as recommendations to speed up and streamline innovative advanced materials assessment.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

New innovative advanced materials can offer unprecedented technological benefits as the integration of different components in a unique system can produce new or improved functionalities. However, they also pose substantial design challenges as well as environmental, health and safety (EHS) concerns. The latter are particularly complex due to the differing rates of degradation, solubility, reactivity and associated toxic potencies of the separate and interacting components, and their more complex interactions with biological and environmental systems. These concerns are magnified by the lack of fundamental research and regulatory guidance addressing the unique properties of these advanced materials.

These challenges are not unique for the advanced and innovative materials, although these are complicated by data gaps and the lack of tools to address the toxicity of more complex properties and interactions of these materials. Tackling these challenges is of potentially high societal impact because the purposeful design of these new materials can (potentially) eliminate the environmental and health safety issues posed by standard chemicals (e.g., persistency, mobility, endocrine disrupting properties), while higher sustainability performance may be achieved[31].

HOW TO CLOSE THE GAPS?

- **Increase efficiency, predictivity and robustness of toxicity testing**

  To be able to address the rate of their development, as well as uncertainties arising from the more complex properties and interactions of innovative advanced materials in safety assessment we need to increase the efficiency of testing. This requires a safety assessment framework, which makes maximum use of any existing information, and optimal use of integrated approaches to testing and assessment (IATA) and 'new approach methodologies' (NAMs), also to minimise animal testing in an efficient and strategic manner. At the same time, this requires an increase in the acceptance of NAM derived data by regulatory authorities for risk assessment, including applying replacement, reduction, and refinement of animal experiments. This clearly requires a demonstration of the predictive power of in vitro methods.

- **Methods development, revision, validation, and standardisation / harmonisation**

  Improve and adapt existing Standard Operating Procedures (SOPs) and experimental methods for materials and chemicals so they can address the unique and more complex properties and interactions of innovative advanced materials. Where necessary new methods should be developed and advanced into Standards or Test Guidelines for regulatory use. This should include simple and practical approaches, as well as more complex methods for characterisation of (i) their physical identity (including transformations and life cycle releases), (ii) their environmental fate, human biodistribution and exposure, and (iii) their human and environmental toxicity.

INTEGRATION OF SAFETY IN INNOVATION: SAFE-BY-DESIGN & (GROUPING) APPROACHES

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

SbD refers to identification of risks concerning adverse effects on humans and the environment including environmental species at an early phase of the innovation process to minimise uncertainties, potential hazard(s) and/or exposure. As such it can provide an opportunity in lowering (perceived) legal barriers on safety. The nanosafety community initiated the development of the concept, in a response to the growing development of complex nanomaterials and (other) advanced materials and the need to be regulatory prepared for addressing emerging features/ characteristics. Developments initiated a decade ago, building on principles from green chemistry and green toxicology. These are still highly active through projects such as SAbyNA, SABYDOMA, ASINA, SbD4Nano, SUNRISE, SUNSHINE, HARMLESS, PINK and many more[32].

For SbD, three pillars of design can be specified:

1. Safe(r) material/product: minimising, in the R&D phase, possible hazardous properties of the nanomaterial or nano-enabled product while maintaining function.

2. Safe(r) production: ensuring industrial safety during the production of advanced materials and advanced material-enabled products, more specifically occupational, environmental and process safety aspects

3. Safe(r) use and end-of-life: minimising exposure and associated adverse effects through the entire use life, recycling and disposal of the advanced material or advanced material-enabled product. This can also support a circular economy.

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

Safety to human health and the environment is a relative concept rather than an absolute value. Especially during the initial stages different options may be compared for their safety in a relative way. For the later stages, however, more absolute values are needed to perform the necessary regulatory risk assessment. SbD strives for negligible human and environmental safety risks through an acceptable balance between safety, product functionality, and, as far as possible, costs. At the same time, it aims to meet any applicable regulatory requirements for human and environmental safety and consider how the specific aspects of the innovative advancded material/product may affect safety. As such, the SbD approach can help industry to produce the safety-related information and data needed to comply with regulatory requirements in a cost-effective way, and effectively communicate on any remaining risks[33]. A practical example on how to use the SbD approach has been described for graphene[34].

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

Within nanosafety several knowledge gaps have been identified since the initiation of developments relating to SbD. These can be summarized in the following set of needs.

- **Harmonized criteria (potentially grounded in regulation)**

  A first insight into the criteria to implement Safe by Design per innovation stage was gathered initially through NANoREG and NanoReg2 projects. This latter project provided insights into the 5 distinct stages and gates needed to implement SbD in six case studies. The NanoReg2 project followed the Cooper Stage gate model[35] based on a rigid and linear structure, and indicated data needs and corresponding tools/methods for safety and sustainability assessment following a life cycle assessment exercise, with increasing data demanding approaches[36,37]. Due to the particulars of nanomaterials, only methods adapted and harmonised for nanomaterials were used (NANOSOLUTIONS, NANoREG), moreover, NanoReg2 highlighted the need of data harmonisation, and an extensive data curation exercise in the eNanoMapper database was performed during the project. Regarding Life Cycle Assessment, and in the particular case of nanomaterials, needs for harmonised approaches regarding how to use proxies to cover data gaps have been highlighted in NanoReg2 and other EU projects. In 2022 the European Commission published their SSbD Framework based on a stepwise approach[38]. Based on this publication, several Nanosafety Cluster Projects have been implementing the current Framework to case studies on nanomaterials and advanced materials.

  While the implementation of the EU Framework to the nanosized shares all the challenges found with standard chemicals, nanomaterials, and advanced materials both require harmonised approaches on the following:

  1. Toxicity may not necessarily be driven by mass but by physicochemical parameters (this challenges the current Step 1 of the Framework which collects CLP information based initially on CAS numbers), hence an adapted harmonised approach is required.

2. Lack of harmonised strategies regarding key end points leading to classification for substances of very high concern (SVHC) are currently not adapted to nanomaterials, representing a challenge to proceed from Step 1 to Step 2 of the Framework.

3. Regarding end of life (Steps 3 and Step 4), information on the behaviour and forms in which AdMa are released during their lifecycle is currently lacking, hampering data gathering regarding fate, exposure and/or effects of AdMa in the environment, hence harmonised approaches to characterise materials in complex matrices will need to be developed.

4. Following on the above, harmonisation of Life Cycle Impact Assessment methodologies (LCIA) will need to be adapted too once knowledge on the transformed materials becomes available.

A 2-year testing period is currently in place where the European Commission is open to feedback and discussion from individual companies (large industries), industry associations and European initiatives. The criteria should also consider expected new REACH hazard criteria for new endpoints such as endocrine disrupters; persistent, mobile, and toxic (PMT) and very persistent and very mobile substances; toxicity to terrestrial organisms; immunotoxicity and developmental neurotoxicity; and persistent, bio accumulative and toxic (PBT) and very persistent, very bio accumulative substances.

At present NMBP15 and NMBP16[39] EU projects have been developing harmonisation approaches on how to categorise nanomaterials and advanced materials as a first step to SSbD, to avoid case by case approaches (due to the unlimited number of possibilities). In a recent publication by Di Battista et al. 2024[40]), the development of multi-dimensional similarity assessment methods applied to multicomponent nanomaterials is reported as an initial step to SSbD for the particular case of core-shell quantum dots (QD). The choice of properties for similarity assessment was guided by the Integrated Approaches to Testing and Assessment (IATA) for the inhalation hazard of simple nanomaterials. Descriptors such as leachable mass (%) and mass based biological oxidative damage were selected based on expert knowledge and used as input data for generation of similarity matrices.

An approach based on the InnoMat.Life project[41] findings is currently under review and represents a simple approach to categorise nanomaterials and AdMa based on three simple dimensions, as a pre-step to implement SSbD, which is subsequently guided by questions prompted from the allocated category (Wohlleben et al, 2024 under review).

The Early4AdMa approach developed by RIVM, UBA, BfR and BAuA[42] as a regulatory preparedness tool was tested for its applicability as an early warning tool with inorganic aerogel mats[21,43] at a joined workshop between the OECD and the EU Project HARMLESS. The tool was further improved following lessons learnt from the workshop and has been further proposed as a first step in a SSbD approach for inorganic aerogels mats21, . On-going strategies to implement the Step 1 of the SSbD are based on questionnaires developed to anticipate safety and sustainability issues based on very limited amount of data., however evaluation of data collection still needs to be harmonised to avoid subjective evaluations[44].

- ## Guidance on how to implement SbD

This includes data needs and tools to be used per innovation stage and actors responsible to implement the approach (including data providers from upstream users). At present it is not clear which of the relevant actors in the product life cycle will bear responsibility for implementing SbD (manufacturer's, upstream users). A selection of tools to implement SbD needs to be allocated to the different innovation stages and should be adapted to availability of data per stage, or lack of data in case of novel materials.

- ## FAIR data (see details below)

A corner stone for SbD is the iterative reuse and integration of both existing data that allows for cost efficient data- and machine/AI-driven safety assessments. This is further elaborated below in the section on "Digitalisation of research outcome."

- ## Expertise and training

This can be done through either training staff in industry (in particular SMEs) or encouraging service providers (CROs) to take up strategies to implement SbD. It is important that CROs facilitate SbD implementation through internalisation of these approaches, so industry can rely on experts on the different topics overarching SbD (impossible to implement all of them in SMEs). Training issues are further elaborated below in a dedicated section.

- ## Test methods and New Approach Methodologies

At later stages of R&I, new generation of data becomes relevant. However, testing needs to be cost-efficient while preferably also accepted within the boundaries of regulatory requirements, to be worthwhile. New Approach Methodologies (NAMs)[45] become especially attractive[46]. The inclusion of information from the exposure of materials that is suitable for innovative advanced materials can make NAMs even more useful. NAMs can be used to perform probabilistic hazard assessments useful for relative ranking of the least to the most harmful material. These can be coupled to prioritization approaches aligned with the "by design" concept. Over the past decades some work has been performed to develop and refine NAMs for nanomaterials[30,47,48]. Nevertheless, further standardisation and validation efforts are often still needed (see section on "Harmonisation / Standardisation").

- ## An enabling environment

Two overarching needs for supplying an enabling environment to implement SbD includes i) the acceptance of a focus on hazard and ii) the notion that NAMs do not aim to reproduce animal data. The "inherent" hazard of a substance drives the innovation to minimize the use of potentially hazardous substances in innovation. This is regardless of the assessment that exposure can be contained. Rather than reproducing animal data, NAMs aim to supply a next-generation safety assessment during innovation that is protective and precautionary. Next-generation safety assessment aims to minimize the uncertainties about risk through e.g., ranking and prioritising in terms of the probability for relative risks, i.e., compared to well-studied high and minimal risk reference chemicals/materials. Current political movements have been set in motion about changing the views on NAMs, leading the European Commission to prioritise NAMs in their agenda.

HOW TO CLOSE THE GAPS?

Overall, to close the gaps relating to the issues shown, extensive communication is needed to establish a mutual understanding and to promote agreed policies and procedures. Discussions should focus on setting a basis for criteria and guidance development, while engaging in broader ongoing discussions and developments around data curation/management and NAMs implementation policies. Such discussions include, but are not limited to, the FAIR data policy discussions (see below), and the EC developments of a roadmap towards phasing out animal experiments. These initiatives contribute to the needed enabling environment to promote FAIRification of data and software needed for the initial stages of SbD, and mutual acceptance of NAMs needed to cost-effectively advance the later stages of SbD30.2020).

- Further methodological updates will be necessary to make the SSbD Framework operational for the industry, and potentially deviations from the idealistic view mentioned above will have to be taken. It will be an aim of governance (see Section on "Organisation of Governance") how to produce community-based acceptance criteria for the trade-offs taken today as future generations will have to pay the price for them.

- A few specifics worth mentioning include the methodological updates necessary to make SbD operational for the industry, and potentially deviations from the idealistic view mentioned above will have to be taken. Such aims are included in the approaches taken within governance (see Section on "Organisation of Governance") regarding how to establish community-based acceptance criteria for the trade-offs taken today (between safety and functionality of the material/product/service) as future generations will live to see the results of unbalanced trade-offs. The operationalization of e.g., grouping tools, in vitro, in chemico and in silico methods, including advanced 3D organoids, QSARs, big data generating high-throughput screening bioassays, omics, micro physiological systems, as well as machine learning models and AI, will be crucial and need to mature to reach higher states of regulatory readiness.

The overall goal will be to enable tiered approaches for increased speed and decreased cost of testing, while avoiding the use of animal experiments when generating data required for regulatory approval of new nano-enabled or other innovative advanced products. In addition to promising faster and more efficient toxicity testing, NAMs have the potential to fundamentally transform the current regulatory landscape by allowing more human-relevant decision-making in terms of both hazard and exposure assessment.

FROM SBD TO SSBD: INTEGRATION OF SUSTAINABILITY IN THE INNOVATION PROCESS

STATE OF THE ART - WHAT DO WE ALREADY HAVE OR KNOW?

In November 2022, the Commission introduced the SSbD framework[49], as an extension of the SbD, aiming to steer the innovation process of chemicals and materials towards the sustainable industry transition. The SSbD framework is composed of a (re-)design phase and an assessment phase that are applied iteratively as data become available. This framework provides guidance to the industry to design safer and more sustainable chemicals or materials. The assessment phase comprises 4 steps: (i) hazard, (ii) workers exposure during production, (iii) consumers and environment exposure during use, and (iv) life-cycle assessment or safe and sustainable by design.

As outlined for SbD, three pillars of design can be specified (see section "Integration of safety in innovation: Safe-by-design & (Grouping) approaches"). Apart from the safety aspects outlined for SbD, additional attention is needed for sustainability aspects in each of these pillars:

- Safe and Sustainable material/ chemical/ product: minimising, in the R&D phase, possible sustainability issues (promoting traceability, sustainable sources of raw materials/natural resources, minimising resource consumption and sources, promoting social responsibility) of the designed material/chemical/product.
- Safe and Sustainable production: this pillar should ensure processes to produce materials /chemical/ products minimise emissions (to air, water, and soil) and resource consumption (e.g., energy, water), and optimising waste management.
- Safe and Sustainable use and end-of-life: Materials/chemicals/products should be designed in a way that demand of resources is minimised during the use phase as well as during recycling, and that the material/ chemical/product supports the waste hierarchy and circular economy.

Aspects of the Critical Materials Act[50], the Ecodesign Sustainable Product Regulation (ESPR) and the related Digital Product Passport (DPP)[51], and the Corporate Sustainability Reporting Directive (CSRD)[52] provide directions for the sustainability aspects. The Critical Materials Act sets clear benchmarks for domestic capacities along the strategic raw material supply chain and to diversify EU supply by 2030. The ESPR and DPP includes aspects of product durability, reusability, reparability, etc., as well as aspects of energy and resource efficiency, and expected generation of waste materials. The CSRD sets further requirements, e.g., an obligation for companies to publish carbon footprint and on the strategy to reduce greenhouse gas (GHG) emissions.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

- ### Lack of sustainability harmonised criteria

  The European Commission JRC publication on the Framework for the definition of criteria and evaluation procedure for chemicals and materials put forth a 5-step SSbD framework[53], where environmental sustainability is covered in step 4 and social sustainability is covered in step 5. Criteria will be developed after the 2-year testing period which ends in 2024. The current framework needs to integrate socio-economic aspects, and (further) guidance is needed on how to implement SSbD. Further clarity is needed on which actors are responsible when to implement SSbD (including data providers from upstream users).

- ### Data management and FAIR data is lacking for sustainability.

  This is needed to allow for iterative reuse and integration of both existing data (during early innovation stages) and newly generated data (along later innovation stages) allowing for cost efficient data- and machine/AI-driven safety assessments. Data ontologies for sustainability are needed covering all sustainability aspects.

- ### Multi-disciplinary expertise

  This is needed to be able to assess all dimensions of sustainability (including safety) early in the innovation process and throughout the innovation process and lifecycle.

- ### Methods and tools

  Methods and tools are needed to be used per innovation stage to support a comprehensive approach to assess all sustainability dimensions (environmental, social, and economic) and integrate those with the safety dimensions.

HOW TO CLOSE THE GAPS?

- ### Risk and sustainability governance

In terms of risk and sustainability governance, harmonized and validated safety and sustainability assessment methodologies are needed, as well as integrative tools combining LCA approaches and risk assessment for analysis early in the innovation process and throughout. This lifecycle thinking approach is urgently needed in order to minimise safety and sustainability impacts and avoid unintended consequences. Incentives such as certification schemes and SSbD label should be created to support marketing and consumer choice[54]. In addition, a coordinated inventory of tools, methods and lessons learned from case studies is needed.

- ### Harmonized SSbD criteria implementable early in the innovation process

Harmonized SSbD criteria should be implementable early in the innovation process and integrated in the design (potentially grounded in regulation).
In terms of design, there is an urgent need for establishing criteria and guiding principles for SSbD driven by the application of life cycle thinking in chemicals, materials, and product design. For SSbD, it is essential to integrate functionality, circularity, climate neutrality, and safety of chemicals, materials, products, and processes throughout their entire lifecycle in an iterative way, while at the same time promoting social responsibility and ensuring economic growth and innovation[20].
SSbD guidance on how to implement the concept, including data needs and tools to be used per innovation stage and actors responsible to implement SSbD are being developed in many Horizon2020 and Horizon Europe Projects; for instance, projects such as PARC[55], SUNSHINE and IRISS. A SSbD guidance is also expected from the EC JRC, once the SSbD criteria have been set.

- ### Communications channels along and across value chain

Communications channels along and across value chain and an information-sharing ecosystem is needed to share and discuss challenges on safety and sustainability issues of chemicals, materials, products, and processes. Industry-driven knowledge-sharing hubs might connect the value chain and provide a value chain-specific SSbD ecosystem that is supportive for the uptake and utilisation of SSbD strategies by industry, especially small and medium-sized enterprises. There is a need for an EU-led SSbD international network of experts to share their knowledge and expertise to support industry in the operationalisation of SSbD in practice[20].

- ### Develop and refine data management (tools) and FAIR data for sustainability

Guidance on how to do this can be obtained in the GoFAIR initiative[56], and from EU projects such as NanoCommons, and OntoCommons. Although these initiatives are more related to safety, lessons learned can be used for the development of sustainability data ontologies. Experts in environmental life cycle assessment (E-LCA), social-LCA (S-LCA), lifecycle costing (LCC) and socio-economic analysis (SEA) need to develop data ontologies to support FAIR principles. From the EU US Roadmap Nanoinformatics 2030[57], several recommendations have been provided.
In terms of data, the development of ontologies for safety and sustainability data is needed to ensure the data is FAIR and maximise data valorisation for machine learning analysis. Given the many data gaps in chemical safety and sustainability assessment, it is essential to obtain or generate data (e.g., through modelling) in

the design phase. Funding agencies should demand dissemination using FAIR data. Industry R&D should also include FAIR data as a good practice. The research community can support the development of SSbD tools which will assist in identification of red flags at an early stage of chemical, material, or product development, guiding the selections towards most safe and sustainable candidate. A further step would be the compilation and harmonisation of the tools into a toolbox and its standardisation to ensure its legitimised use throughout[20].

- **Multi-disciplinary expertise and training for industry** (in particular SMEs)

Training can be provided through programs such as SSbD-related Professional Master Programmes (for instance, Professional Master in Sustainable Chemistry, Master of Business Administration Sustainable Chemistry Management) and Certificate Courses. Targeted and accessible SSbD training is necessary for instance industry, SMEs, service providers (CROs), and value chain actors. SSbD training should also be embedded in university curricula of technical and related nano- or advanced material science programs.
Therefore, in terms of skills, competencies, and education, SSbD aspects need to be integrated into vocational training and university programmes to equip future SSbD actors with the necessary skill profile to apply SSbD in practice. Just as important are training courses for professionals, which need to be open to everyone (e.g., free-of-charge online courses or training schools). An SSbD directory compiling all SSbD courses and events could support the visibility and accessibility of such education offers. As consumer acceptance was identified as an important aspect to accelerate the transition to SSbD, societal education and awareness raising are equally important aspects (e.g., consumer education through product marketing) [20].

- **Develop and apply methods and tools**

This refers to supporting a comprehensive approach to assess all sustainability dimensions (environmental, social, and economic) and integrate those with the safety dimensions. A selection of integrated methods is currently being developed for assessing environmental, social, and economic impacts to implement SSbD in a holistic way using a lifecycle thinking perspective (resources, material production, product manufacturing, distribution, use and end-of-life) in Horizon Europe SSbD projects such as EU funded project SUNRISE. These tools need to be allocated to the different innovation stages and should be adapted to availability of data per stage, or lack of data in case of novel materials. This however cannot be a technocratic task: it should involve key actors along entire value chains in a co-creative process that balances the perspectives and interests of stakeholders from industry (including SMEs), regulation, policy, consultants (and CROs), academia, and the civil society. The NSC and EU funded projects such as IRISS can play a significant role in disseminating the results of these approaches to the broader SSbD community.

- **Social and corporate strategic needs**

SSbD-supportive business models and regenerative leadership are needed to embed SSbD thinking in business strategies for the development of safe, sustainable, and circular chemicals, materials, products and processes. This could be through the support and facilitation of safety and sustainability assessment during R&D, or by looking at services as a business model. CEOs and innovation managers need to embrace SSbD in their daily corporate activities and enable the company culture to become supportive of SSbD and therefore, driving the industry towards a more sustainable future[20]. Culture change in companies is crucial for implementing SSbD. Large companies might have more resources to embed SSbD in their corporate strategies while this might be more challenging for SMEs. Especially in large companies where they embed SSbD as a critical element of innovation, R&D pathway, method, or ideology, it is much easier to extend this into company practices, culture, and ways of working. It is also essential to have direct link between a company's innovation process and SSbD, to for instance link R&D with regulatory affairs and sustainability expertise.

SSBD AS A PRE-REQUISITE FOR A CIRCULAR ECONOMY

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

When the new Circular Economy action plan was adopted in 2020, the EU presented a vision for sustainable growth in the EU and beyond. This action plan targets how products are designed, promotes Circular Economy processes, encourages sustainable consumption, and aims to ensure that waste is prevented, and the resources used are kept in the EU economy for as long as possible. Then, many legislative and non-legislative measures provided directions for the design, production, and end of life of many mass products in sectors such as packaging, vehicles, or electronics.

The SSbD innovation process aims at delivering products design that contributes to the three principles of the Circular Economy: designing out waste and pollution (including enhancing circularity in a toxic free environment), keeping safe products and materials in use, and regenerating natural systems, while providing consumers with cost saving opportunities and trustworthy and relevant information at the point of sales.

Sustainability should prevent waste in the first place (zero waste) and include material loops and processes that support the "waste hierarchy" which ranks waste management options according to what is best for the environment, giving top priority to durability and repairability. When a material, product or process is developed, efforts should be made for re-use, recycling, recovery, waste reduction, and lastly ensure minimal disposal. Circular economy and industrial responsibility are means that contribute to sustainability.

When it comes to designing a product for Circular Economy, industry has limited guidance in their innovation process. The SSbD approach has the potential to be a comprehensive data-driven methodology that the industry could apply in their Research and Innovation process. It will be even more critical as the industry will need to comply with an increasing number of EU Circular Economy related legislations in multiple sectors (e.g., Packaging and packaging waste, End of Life vehicles, Strategy for sustainable and circular textiles, Waste from electronics and electrical equipment).

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

- ### Guidance for industry

Several issues must be considered for the SSbD approach to be the methodological support the industry uses to develop suitable products for the circular economy:

A product (re)designed by the SSbD approach should be assessed with a circularity score to compare its circularity performance with the "old" product or a product from the same competitive environment. However, in the current SSbD framework no multi-criteria scores or metrics can assess the circularity of the product. For example:

- Although the Product Environmental Footprint methodology is included in SSbD and provides sustainability scoring, it does not include metrics on key aspects of the circular economy such as durability, reusability, and recyclability.

- The circular economy can significantly reduce the negative impacts of resource extraction and use on the environment and contribute to restoring biodiversity and natural capital in Europe. However, in the SSbD, impacts on biodiversity and ecosystem functions are not part of the Product Environmental Footprint guidance in a state-of-the-art, LCA compatible methodology. Considering that the current loss of biodiversity is one of those environmental impact categories where we are already exceeding planetary boundaries, Product Environmental Footprint should be complemented with a distinct indicator for it.

The transition to the circular economy will also be enabled by empowering consumers to purchase and consume goods with better circularity performance. The outcome of the SSbD should result in a group of meaningful information that can be digitalized and communicated to consumers. Information that needs to be defined, would transit in the Business-to-Consumers value chain, and inform EU Citizens on product safety and sustainability performance as indicator of circularity score.

The Business-to-Business value chain, especially stakeholders involved in the product end of life, need to access SSbD information such as the product composition, the presence of hazardous substances or substances that inhibit circularity.

- ### Cost analysis

Designing circular products that are not affordable to consumers will slow down the transition to the Circular Economy. The SSbD currently includes a socio-economic assessment that should be adapted with better guidance on LCC.

HOW TO CLOSE THE GAPS?

Closing the gaps to step-up the SSbD as a prerequisite for the Circular Economy would need to take initiatives on multiple fronts:

- ### Guidance for industry

There are multiple EU policies related to product design such as Eco-design for sustainable products, Eco-labelling, and the future Digital Product Passport. To ensure the industry will follow unique guidance on product design with the SSbD, these policies must be harmonised.

- ### Cost analysis

The SSbD approach as currently implemented in several EU projects includes a cost analysis of the (re)designed product to validate that it is cost competitive compared to a linear economy product. Adapt the socio-economic assessment with a Life cycle costing (LCC) that focuses on comparative cost analysis with other products being sold on the market. Complement the Product Environmental Footprint with Biodiversity metrics. Add circularity assessment aspects such as durability, recyclability, or reusability.

- ### Circularity indicator of SSbD product

Provide an approach to score the circularity of a product developed by the SSbD methodology by upgrading product circularity modelling tools to include other complementary safety and sustainability aspects assessed in the SSbD. Currently the circularity indicators provided by the World Business Council of Sustainable Development (WBCSD[58]) are too data demanding and only implementation at later stages of the innovation process.

- ### Best perform in a circular economy

Standardize the SSbD as a unique methodology to design safe and sustainable products and materials that best perform in a circular economy and to feed trustworthy and science-based information for Marketing claim, Eco-labelling, or Digital Product Passport. Ultimately, the product adherence to the SSbD standards could be the conditions for "a licence to operate" the product in the EU market. At present, as SSbD standard is being developed under CEN/352 Nanotechnologies to support and harmonise SSbD approaches in the industrial setting.

- ### A Circular Economy Action Plan

Promote strengthening the role of SSbD as a methodology to (re)-design circular products in future revisions of the Circular Economy Action Plan.

Overall, some argue that the implementation of circular economy may involve an economic cost for European companies at a time when they are already struggling with high resource prices, leading into a potential drain of companies outside Europe. However, an effort into this direction may help re-directing resources in the already highly wasteful European economy, largely based on take-make-dispose systems. Circularity also represents the creation of new business niches and business models based on collaborations through the value chain, while benefiting the environment. So overall, while the implementation of circularity will bear large costs, it will also create opportunities for economic and industrial renewal. In the meantime, European policies should be implemented in a way to assure European industries and citizens do not loose competitiveness against third countries by protecting the European space against practices not supported by a future Circular Economy Plan.

DIGITALISATION OF RESEARCH OUTCOME: FAIR PRINCIPLES & DATA MANAGEMENT

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

A corner stone for the development of safe and sustainable materials, is the iterative reuse and integration of both existing data (during early innovation stages) and newly generated data (along later innovation stages). This reuse allows for cost efficient data- and machine/AI-driven safety assessments[59,60,61,62]. In parallel, increased reuse of data also supports development of iteratively improved SSbD tools coupled to increasingly big safety data and reference databases, which contribute to improved understanding of safety and sustainability aspects and refinement of criteria and guidance for SSbD.

Nanosafety has a long history of providing concepts and tools for data management, (public) sharing and semantic integration. This is now also entering other areas as part of projects such as the PARC, IRISS and WorldFAIR. Besides increased ontological coverage and semantic integration of and mapping across different semantic frameworks, this included building a mutual understanding of the need for rich metadata, minimum information requirements. This also resulted in development of metadata completeness checklists and corresponding (meta)data templates to make data understandable, reproducible and build trust in the provided data and its applicability to guide SSbD. Due to the importance of describing bio-nano-interactions, these are based on and adopt solutions from the biological and medical fields and are designed to be interoperable. One example is the eNanoMapper ontology developed by the EU funded project of the same name and extended by many other projects, which integrates terms from many biological and chemical ontologies and is aligned with the Open Biological and Biomedical Ontology Foundry (OBO[63]) universe of interoperable ontologies. The SSbD framework now requires a much larger cross-domain interoperability, including data integration from the complete material value chain and lifecycle.

The generated data ecosystem, therefore, has to be combined with solutions from other communities. of particular relevance here are the materials modelling and characterisation ecosystem developed by the European Materials Modelling Council (EMMC[64]) and European Materials Characterisation Council (EMCC) that use the Elementary Multiperspective Material Ontology (EMMO[65]) as their semantic environment. EU funded projects like OntoCommons are trying to merge these two ecosystems. However, the current solutions are limited to very specific applications. To achieve the global materials data ecosystem requested by AMI2030, an overarching concept is needed to achieve high-level cross-domain interoperability and, at the same time, profit from all the achievements of the last years. Achievements in data digitalisation, data documentation, data/knowledge sharing (with clear rules for access and re-use), and ontology development (that combines domain-specific and cross-domain interoperability elements).

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

SSbD advanced materials need to provide the high functionality required for their advanced applications, whilst simultaneously exhibiting improved safety and sustainability performances considering the complete value chain and life cycle. To enable industry to develop new innovative and, at the same time, SSbD materials, they need to have access to tools and data for the evaluation and prediction of all these criteria. These data need to be interoperable and seamlessly integrated with the characterisation and process optimisation approaches. The tools need to scale with respect to throughput and costs with the development stage of the material (design idea, lab-scale, pilot plant, production) and need to support exploratory and prospective (ex-ante) investigations. Tools need to enable evaluation of SSbD, based on extrapolations from small scale productions, or even based on virtual materials that are not synthesised yet. This should enable and guide decision making from the earliest time onwards.

To achieve this integration and interoperability of all current and especially new data as well as data-related and -producing tools, this needs to become part of the common materials data and software ecosystem. This requires two interconnected activities:

Combining the two until now often independently developed semantic and technological frameworks. For materials modelling, characterisation, and production these are frameworks driven by the EMMC, EMCC, Industry Commons[66] and corresponding projects. For safety, sustainability, and circularity these frameworks are based on medical and biological semantic approaches (e.g., from the OBO foundry[67]) driven by NSC, PARC, the ASPIS cluster[68] and corresponding projects. Combining these will need adaptations from both sides to make the tools interoperable across domains and make the data understandable to the level needed for specific applications like the digital material/product passports. Tool development and adaptation needs to be structured in a way that they all work towards this common goal and complement each other. This is not meant to push for one specific solutions for all areas but to agree on (meta)data harmonisation priorities on a high, project-overarching level required for decisions making to guide SSbD materials and processes development. This includes but is not limited to ontology mappings for making data available in multiple semantic environments and ontology developments focusing on main aspects improving understandability and trust on a high level. In this way, harmonised high-level metadata for all datasets will be available at the earliest possible time. The semantic enrichment of the data can be then continued adopting more domain-specific aspects to support experts in these fields.

Data providers need to be constantly supported to adapt their experimental and computational workflows to these new requirements. This should enable them to create (meta)data and data documentation on-the-fly, i.e., FAIRification and quality-assurance and -documentation steps will be performed as part of the daily work. Not as additional tasks performed when data is prepared for sharing and integration. This will only be possible if support and guidance are customised for data providers in a stepwise personal roadmap to improve data management quality over (a short) time. In the same way, data users also need to be supported by collecting (meta)data and quality-ensuring requirements. This should build the trust for reuse and guarantee that all this information is provided by the data producers in a harmonised form that is still flexible enough to include new developments and data types.

HOW TO CLOSE THE GAPS?

Optimal use of existing data and predictive safety/sustainability models from all available sources should reduce in vivo experiments. Life cycle assessment tools are necessary to be applied at the design phase of the materials (ex-ante) and validated at prototype and field level. These tools should provide information on human and environmental safety, on sustainability considering the complete value chain and lifecycle, and on circularity, as well as on social impact and their relationship to techno-economic performance, functionality, and durability. This will be achieved by:

- ### Digital chemical/material passport

  Integrate the SSbD criteria into the digital material passport following the requirements from the EU SSbD Framework and recommendations from different industry organisations (e.g., CEFIC) and projects (e.g., IRISS). Semantic integration of SSbD data into the materials digital ecosystem should include alignment of and further developing semantic tooling and resources used in materials and medical/biological research. This includes extending, mapping, and complementing existing ontologies.

- ### New standards for documentation of data

  Work towards new standards for documentation of data generated for or used in regulatory settings (e.g., OECD harmonised templates) to align with the material's digital ecosystem and the FAIR data management principles. Make data management and interoperability a central part of new and updated testing guidelines and guidance documents.

- ### Artificial Intelligence

  Apply new, innovative integrated workflows using data-driven/AI and physics-based approaches. These can profit from synergies from methods originally developed for characterisation, functional optimisation, safety, and sustainability assessment.

- ### Promote implementation of FAIR principles

  Communication, awareness spreading, guidance, and support for implementation of FAIR principles. For this purpose, a FAIR implementation network (IN) has been established for advanced (nano)materials, the AdvancedNano IN[69]. This provides a starting point for effective data-driven safe and sustainable development and application of advanced (nano)materials.

- ### Use service providers

  Another way to potentially close this gap is to have better service provision that industry can access. In the medical and biotechnology sectors, there is a thriving service economy of companies that provide data and data services. In the materials world, it is more challenging to encourage industry to use service providers.

REGULATORY PREPAREDNESS

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

Regulatory Preparedness (RP) refers to the capacity of regulators, including policymakers, to anticipate the regulatory challenges posed by emerging technologies such as advanced materials, particularly human and environmental safety challenges. This requires that regulators become aware of and understand innovations sufficiently early to take appropriate action, and that appropriate regulatory tools are modified or developed as needed. RP helps to ensure that advanced materials and products undergo suitable (and if appropriate, adapted) safety and sustainability assessment before entering the market. RP requires dialogue and knowledge-sharing among regulators and between regulators and innovators, industry, and other stakeholders. This communication and interaction help regulators to anticipate the need for new or modified regulatory tools and reduce the uncertainties for innovators and industry associated with the future development of the safety and sustainability legislation and regulations applicable to emerging technologies[70]. RP is part of the Safe and Sustainable Innovation Approach (SSIA) which is the combination of RP with SSbD. Both SSbD and RP concepts are supported by a process to share and exchange knowledge, information, and views in a Trusted Environment (TE). SSIA thus relies on dialogue between innovators and regulators[71]. A TE is a physical or virtual space in which industry, innovators, governmental institutions, and other stakeholders can share and exchange knowledge, information, and views on innovative technologies (e.g., innovative nanomaterials, nano-enabled products, and advanced materials). A TE invites trust by ensuring confidentiality and protecting intellectual property. This dialogue ideally starts at an early stage of the innovation process.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

There is a need for a systematic approach to help regulators deal with the safety (and sustainability) of innovations such as innovative advanced materials. This systematic approach for safety and sustainability governance should include:

- **An anticipatory approach**

  Regulators and policymakers need ways to anticipate the regulatory challenges posed by innovations such as innovative advanced materials. The tools and approaches for identifying upcoming issues as early as possible include horizon scans and foresight.

- **Trusted environments**

  An environment of trust is needed (e.g., regulatory sandbox) to facilitate dialogue between regulators, innovators (industry) and other stakeholders for confidential inquiries and information sharing early in the innovation process. Regulators need to become aware of innovative products under development to ensure that the legislation and methods for safety (and sustainability) assessment are available and adequate.

- ### A platform for exchanging knowledge, information and expertise

Processes and infrastructure are needed to facilitate the exchange of knowledge, information, and expertise in a trusted environment.

- ### A monitoring & evaluation system

A monitoring & evaluation system is necessary to ensure timely actions are taken. This should ensure that regulators become aware of and understand innovations sufficiently early to take appropriate action, and that appropriate regulatory tools are modified or developed as needed.

HOW TO CLOSE THE GAPS?

- ### An anticipatory approach

The development of an anticipatory risk (and sustainability) approach to proactively prevent the occurrence of potential unexpected risks of innovative advanced materials. This anticipatory risk and sustainability approach should include:

- The further development and operationalization of the Early4AdMa[72] system to systematically identify emerging issues of innovative advanced materials within the OECD WPMN Advanced Materials Steering Group and beyond.
- In addition, an inventory is needed on ongoing activities related to innovative advanced materials to connect them with each other (e.g., national governments, OECD, ISO, etc.).

- ### Founded on trust & dialogue

The building blocks for trusted environments are currently being developed in the OECD WPMN Safe and Sustainable Innovation Approach Steering Group: Confidentiality agreements and terms of references are essential for confidential inquiries and information sharing early in the innovation process between regulators, innovators (industry) and other stakeholders. Promoting a two-way dialogue between innovators and regulators is essential to facilitate that the safety concerns of regulators are addressed in initial stages of innovation. This can reduce the R&D and regulatory compliance costs of industry and can shorten the time and increase the chances of these novel innovative advanced materials-based technologies to reach the market.

- ### A platform for exchanging knowledge, information & expertise

As current information is fragmented, an open access platform for exchanging knowledge, information, and expertise needs to be developed, preferably in collaboration with the activities already available within the OECD WPMN Safe and Sustainable Innovation Approach Steering Group[73].

Four layers of knowledge exchange must be considered:

1. between regulators (trans regulatory).

2. between innovators and regulators facilitated by TEs linking innovation to regulation

3. between science and policy/regulatory, and

4. between the stakeholders in the value chain (from R&D/innovation to end-of-life).

In addition, this knowledge exchange platform should have an overarching digital platform for exchanging knowledge, information, and expertise (e.g., the SUNSHINE e-infrastructure[74]).

- ## A monitoring & evaluation system

  A monitoring & evaluation system needs to be developed to systematically measure the progress of SSbD operationalization and implementation and to ensure timely actions. This monitoring & evaluation system should be linked to parallel activities on innovative advanced materials (e.g., by national governments, OECD, ISO, CEN).

HARMONISATION / STANDARDISATION

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

Standards and OECD Test Guidelines (TGs) play a crucial role in safety testing for chemicals and materials. They aid in the implementation of chemical legislation, ensure comparability of test results and data, and assist industries in regulatory compliance. However, established TGs for conventional chemicals may not always be applicable to nanomaterials (NMs) and/or other (advanced) materials due to the unique (physical) characteristics of these materials. Efforts towards standardisation began with the FP7 project NanoImpactNet, which collected harmonised standard operating procedures. Subsequent FP7 projects like NANoREG and ProSafe focused on generating regulatory data, developing standard procedures, and supporting risk assessment for nanomaterials.

The importance of Safe by Design (SbD) principles emerged that emphasise the need for safety thinking in the early design phases, and further highlight the need for internationally accepted guidelines to ensure nanosafety through harmonisation and standardisation. ProSafe played a key role in promoting SbD within the EU. The resulting White Paper emphasised the crucial role of applying SbD principles throughout the nanomaterial life cycle for cost-effective risk management.

Following these initiatives and catalysed by the Malta Initiative, NMBP projects such as RiskGONE, Gov4Nano, NanoHarmony, and NANOMET contributed to OECD TG development for nanomaterials. These projects developed the necessary science for TG developments, and also produced Guidance Documents and Detailed Reviews necessary for their use, including identification of areas that still need to be developed.

Projects like NanoHarmony expanded the support for TG developments with tools like the OECD TG Process Mentor, Training Material, and online workshops for stakeholder exchange. While the need for standardisation in testing methods for other innovative advanced materials is not clearly defined, emerging projects such as MACRAMÉ, nanoPASS, POTENTIAL, iCare, and ACCORDs focus on developing and standardising test methods for 2D-materials and advanced materials in complex matrices, addressing the evolving landscape of material technologies. For these types of materials, the Graphene Flagship initiated first method developments to enable their characterisation.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

- ## Testing of nanomaterials

In the last 10 years, various standards and TGs/GDs were adapted or newly developed to allow testing of nanomaterials. Nevertheless, some endpoints are still not sufficiently covered by standardised and harmonised test methods applicable for nanomaterials and other innovative advanced materials. An overview of gaps and further actions towards harmonisation of testing of nanomaterials for EU regulatory requirements on chemical safety is presented by Bleeker et al.[75] and the Malta Initiative published a "Priority List".

- ## Method applicability for innovative advanced materials

As the development of new innovative advanced materials with yet unknown composition, properties and functionalities is a continuous process, the applicability of test methods needs to be assessed continuously as well. To date, there is a clear need for test method standardisation for graphene and related two-dimensional (GR2D) materials (e.g., solving issues on detection in a carbon-rich environment, preparation of suspensions, hazard triggered by morphology). As a minimum, demonstration is needed on which of the current test methods are fit for purpose in this context and which ones need to be adapted to also accommodate advanced materials and materials based on graphene. In addition, OECD WPMN also pointed out issues with testing methods applicable for encapsulations.

- ## Consider new (regulatory) requirements and new method development needs

Apart from covering new materials, new (regulatory) requirements and new method developments need to be considered for the development of TGs/GDs (OECD) and standards (ISO, CEN). Strategies are needed to improve validation of alternative testing approaches (e.g., new approach methodologies, in-vitro assays, and modelling) to support the transition towards animal-free testing and enable testing for SSbD in early design stages, where no or tiny amounts of material is available.

- ## Method developments towards exposure and sustainability

Whereas test methods towards hazard of chemicals and materials are far advanced and well covered in standards, method developments towards exposure and especially sustainability are lacking behind. To enable better risk assessment the measurement and the prediction of potential exposures need to be advanced by standardisation of release tests, exposure measurement strategies and exposure modelling. To advance the assessment of sustainability, clearly defined endpoints are required as well as methods to determine them.

- ## Coordinated effort by European Union

To bring test methods to international acceptance, e.g., as OECD TGs, they need validation or at least international consensus finding. These steps follow the scientific development of test methods. Developing and validating TGs and standards to keep pace with innovation is a challenge that is often underestimated in both time and resources needed. Scientists, industry, and regulators need to cooperate to enable timely development of TGs and standards. Therefore, a coordinated European Union effort is needed as promoted in the Malta Initiative Position Paper[76], the European Test Methods strategy.

- ## Facilitate timely OECD TG developments

The NanoHarmony White Paper[77] makes further recommendations to facilitate timely OECD TG developments. In general, a more effective transition of scientifically developed SOPs into standards and OECD TGs is needed, requiring several ways of support. To better engage the scientific community, we need training of students and scientists on the importance of harmonised test methods and how to contribute to their development. The scientific community needs to improve the FAIRness of their research data to facilitate the validation of test methods. Long-term, dedicated additional funding is required, especially towards the higher technical readiness levels (TRL) to also ensure the validation of test methods and make them applicable for regulatory testing. Industry needs to participate in the TG development and needs to be actively involved. This enables the development of adequate test methods that are fit-for-purpose and highly required to keep pace with innovation. A clear list on the top priorities that also are relevant to innovative advanced materials has been published by the Malta Initiative[78]

HOW TO CLOSE THE GAPS?

Strategic documents like the NanoHarmony White Paper and the Malta Initiative Position Paper provide directions in closing the gaps. In line with these documents the following actions are suggested:

- ## Development of test guidelines and other standards

Funding should be made available for project calls for proposals and calls for tender specific for the development of OECD TGs and other standards. It is not feasible to cover the entire process of the scientific development and standardisation (including validation) towards internationally accepted test methods within the period of one research project. Therefore, project calls and calls for tender specific on validation and standardisation of test methods are needed in addition to calls for method development. Sufficient funding is a prerequisite for researchers to prioritise and speed up the work on standardisation.

- ## Establishing an exchange platform for development of OECD TGs and other standards

NanoHarmony has shown that regular sharing of information (e.g., in (online) workshops and webinars or using other formats) is an important accelerator for the development of TGs and their acceptance. Such activities allow easy involvement of experts, including those that are not linked to standardisation bodies. This international platform for collaboration and exchange between stakeholders should be continued and supported by long-term funding to provide:

- Formats for exchange with stakeholders on the development of specific OECD TGs and other standards for expert input and increasing international acceptance.

- Support for international collaboration between researchers, regulators and industry in standardisation and harmonisation.

- Support for developers of OECD TGs and other standards by sharing information and offering training on the development process.

- Initiation of discussions on relevant endpoints, methodological gaps, and related methods ready for validation, harmonisation, and standardisation.

The platform feeds into the specific projects as well as into the group that takes decisions on TG development for advanced and nano materials.

• Establishing a steering group

A steering group can be created that takes decisions on OECD TG development and update prioritisation. This group should steer the amendment and development of TGs in Europe to support regulation and broader policy goals by:

- Reviewing the status and applicability of TGs for nanomaterials and other advanced materials,

- Surveying ongoing TG developments and amendments,

- Setting priorities for upcoming TG amendments and

- Initiating project calls to support the amendment and development of TGs.

This group should cover the views of policymakers, regulators, industry, and scientists and have the power to initiate and fund projects and calls for tender to support the work on TG developments.

ORGANISATION OF GOVERNANCE-STAKEHOLDER ENGAGEMENT

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

Governance refers to the "actions, processes, traditions and institutions by which authority is exercised and decisions are taken and implemented" (International Risk Governance Council). This implies that the organisation of governance is a multidimensional task, crosslinking activities along the innovation and product life cycle, wide-scale stakeholder engagement and an accompanying societal discourse via appropriate organisational forms. Pre-emptive methodologies (SSbD) as part of the R&I process expand the temporal reach of innovative advanced materials' product life cycle, entailing broader stakeholder engagement in the assessment of potential hazard, safe production, safety in application, environmental and socio-economic sustainability. Past initiatives (i.e., the NMBP-13 projects NANORIGO, RiskGONE, and Gov4Nano) aimed at developing an efficient and effective risk governance process for nanomaterials, and innovative advanced (nano)materials-enabled products. Top achievements, encouraging active stakeholder engagement and better decision making, included infrastructure for collaboration and communication, access to high quality data and tools and multidisciplinary knowledge, and guidance through the risk governance process by an implemented risk governance portal.

Potential organisational forms (e.g., council, round table, house) that can enable sustainable stakeholder involvement and mandates for the NMBP-13 framework curation were assessed, but an implementation was abandoned. Establishing such an overarching organisational form may be seen as open issue. The EU Recommendation 2022/2510 (8 December 2022)[79] established a European assessment framework for 'safe and sustainable by design' chemicals and materials. Yet, it does not transfer dedicated responsibility to the actors in the SSbD and assessment activities during an innovative advanced material-lifecycle and within its value chain. Moreover, while stakeholder engagement of the wider society (consumer organisations, NGOs, etc.) and evaluation of socioeconomic sustainability aspects (step 5 in the JRC proposed SSbD-framework) are positioned as a "complementary option" in the EU recommendation, the implementation of a facilitating contact point that can govern appropriate consultation has still to be done.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

Research and innovation (R&I) on nanomaterials – and more generically on advanced materials – must be guided by the principles and be adherent to the goals of the EU Green Deal. Most effectively, these include the elements of the twin digital and green transition while providing a human-centred ecosystem that incorporates the views of all its stakeholders. While the H2020-funded risk governance NMBP-13 projects intended to establish a round table to tackle the scientific discourse on the sometimes even disparate societal and economic demands, in reality industry takes the initiative in driving the R&I process. In general, it is industry that initiates R&I in order to provide products for the European market with the premise of enhanced functional performance while being safe for humans and the environment as well as being better sustainable than comparators already on the market.

Resilience and sustainable R&I is characterised by a long-term vision; for instance, products based on nanomaterials, advanced materials, and chemicals with highly disparate profiles in the different sustainability dimensions (i.e., health, environment, social, economic) will on the long run result in trade-offs to be paid for by society. This has been well recognized in the EC JRC technical report which laid the groundwork for proposing a framework for the definition of criteria and evaluation procedure for chemicals and materials. Evaluation and balancing of the afore-mentioned trade-offs are an integral part in the 5-step approach of the safety and sustainability assessment (Step 5 – Social and economic sustainability assessment) there. However, this proposed Step 5 has not been adopted into the current recommendation by the European Commission. Omitting the wider society's stakeholder interests, perception, perspective and arising concerns constitutes a gap in risk governance, particularly with increasing difficulty to meander between precautionary principle and responsible innovation by politics and regulation. This would require a mechanism for regular consultation with the stakeholders that are most relevant for the respective product development. This consultation endeavour includes the proficiency in use of the respective tools for their involvement as well as the evaluation and interpretation of the outcome of the stakeholder engagement. Such a mechanism should be operational within industrial workflows and result in a straight-forward and meaningful consultation process. Measures on how to aggregate data on materials' properties across the above-mentioned sustainability dimensions have not been installed yet. The need for consideration of the socioeconomic sustainability aspects was acknowledged in the current EU SSbD recommendation. The less mature methodological and tool landscape, however, made it not feasible to position Step 5 as a requirement in the current framework. This blank space does not fit in the ambition of inclusiveness, i.e., how the legitimate interests of citizens and stakeholders are reflected in decision making and open policy. Admittedly, the EU-SSbD recommendation calls for testing and feedback and targets to include "economic and social sustainability aspects as an additional facet."

Fast increasing capabilities and societal adoption of artificial intelligence (AI) and concomitant shifting power to AI supported methodologies may set non-transparent boundaries, e.g., by contextualization with data and information selected on the strength of public consensus instead of the strength of evidence. Reliable knowledge generation by stakeholders exposed to black box mechanisms that are actively (evaluator) or passively (responder) involved in SSbD may become increasingly compelling. Thus, methods are needed to evaluate the quality of data, information, and knowledge and to increase the level of transparency.

HOW TO CLOSE THE GAPS?

The EU recommendation for a future SSbD framework sets a testing period for member states and stakeholders. A revision process will be launched based on the feedback collected. Here we propose some actions that may help to enlarge stakeholder discourse and open an opportunity for feedback at the latest by the end of the said testing period.

- ### SSbD, Governance and Industrial Workflows

SSbD is proposed to be instrumental to raise further the standards for a better societal decision-making process. Stakeholders frequently struggle between the conflicting priorities of responsible innovation vs. precautionary principle (safe-by-design), as well as short-term benefit vs. long-term societal costs (sustainable-by-design). Inevitably, the fulfilment of the SSbD concept (including the societal aspects of a human-centred ecosystem in agreement with economic viability) would better align R&I actors to good governance principles. This can be a straight-forward achievement by implementing SSbD in industry. Rolling-out the understanding of Environmental-Social Governance to industrial R&I workflow actors must be an integral component of future activities in the NSC.

- ### Quality of Data, Information and Knowledge

Gauging risks and benefits, making transparent the type and extent of uncertainty, weighing the quality of knowledge and data, and the strength of evidence remain a challenge and must be addressed. Otherwise, biased perception of stakeholders may foster unbalanced decision making and actions, which may establish normative power. KaRL (Knowledge, Information and Data Readiness Level)[80] is a ready-to-use innovative approach originated in NMBP-13. KaRL enables stakeholders to visit all those subjects, to participate in a reflective discourse and to come forward with a holistic assessment of the knowledge readiness regarding an arising issue of concern. This aggregates into an actionable document and strength of knowledge classification. As such it mirrors the level of regulatory readiness within a go-to-market strategy of industry, concurring with regulatory preparedness activities of regulatory agencies. NSC hub functionality should be used for awareness campaigning in communication and training events.

- ### Explainable Artificial Intelligence

The advent of increasing capabilities of artificial intelligence (AI) and the concomitant shifting power to AI may set non-transparent boundaries by preceding directed contextualization of black box methodologies[81]. These may create a loss of trust, hinder stakeholder engagement and prevent societal inclusiveness. As a result, a balanced decision making may become increasingly compelling. The concept of explainable AI (XAI)[82] may help to mitigate this problem, fostering step 5 of the proposed JRC SSbD framework. Thus, proper elements of XAI must be proposed, tested, and considered in SSbD activities as part of a response to the EU's call for feedback. This may be a potential task for NSC working group "SSbD, Innovation and Regulation."

TRANSLATION AND VALORISATION OF SSBD

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

There are several aspects in seeing safety and sustainability as one of the main driving forces for innovation and fully integrating it into the industrial materials development process. On the one hand, it needs a change in basic assumptions towards innovation as a multi-objective optimisation process with full support as well as training of all stakeholders. On the other hand, it is creating itself a new market. Professional services will be demanded to provide the data needed to support every stage of the material development cycle from prompt decision making to regulatory approvals and market introduction. Such services may be offered e.g., by contract research organisations. Additionally, up-skilling of academic and industry researchers, risk assessors, and decision makers is essential. This leads to business opportunities for professional training offerings.

The decision to be made in each business case is „how much of today's resources ought to be invested for the benefits of tomorrow?"[83]. Hence, the impact of SSbD depends heavily on its implementation in real-life. The publication of the SSbD Framework and the EC-recommendation have given a strong signal to all stakeholders and especially industry. It shows how material development is expected to happen to keep innovation potential and, at the same time, reach the policy goals of the EU Green Deal. This policy push was therefore also the kick-off for broader translation and valorising of SSbD.

First experiences of implementing the SSbD approach or parts of it are presented in case studies performed by industry as well as different EU projects[84]. Execution of these was made possible in large parts by exploiting knowledge gained and made available in the past 15 years by the NSC community[85]. This community provides scientific evidence about nanomaterials' safety that is applicable for different sectors/materials/etc. Hence, this important knowledge base is ready to be further translated and valorised towards innovative advanced materials (including nanomaterials, advanced materials, etc.). International alignment and collaboration were an important factor of success and led to synergies and mutual benefits to be continued in different initiatives (e.g., IRISS-ecosystem, INISS-Nano, US-EU-CoRs[86] , NanoFabNet Hub[87] , BioNanoNet association[88], NIA[89] , etc.).
This was complemented by well-defined access points (e.g., the NanoGovernance Portal[90]) as well as supportive guidance and tooling (e.g., the PARC toolbox[91] in combination with the methods and tools developed in nano- and advanced-materials-related SbD and SSbD projects).

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

For the translation and valorisation of SSbD, it will be important to close the gaps in terms of knowledge about and application expertise of SSbD. Hence, the following list comprises the needs to be addressed to succeed:

• Access to infrastructure/ knowledge/skills

A pending issue is the access to e.g., safety testing and sustainability assessment along the complete value chain and including the full material life cycle. Additionally, the further development is needed of predictive methods (e.g., prospective, anticipatory, and ex-ante LCA), that are applicable at the early stage of materials development. Thus, gaining knowledge as well as skills is needed.

• Reliable "science/research – industry" interface

A successful translation of SSbD requires the connection between assessment methods developers, on the one hand, and technology/ product developers, on the other. Reliability plays a crucial role here. A quality evaluation process and review board for the data/knowledge needs therefore be established.

• Cross-border market access

In support of industrial uptake, the size of the market that can be entered, is important. Therefore, a cross-border support of SSbD-compliant products would be needed.

• Guidelines for the use of methods

Assessment methods used for generating evidence of safety/sustainability shall be selected according to specific needs (i.e., arranged according to the defined criteria). Needs could range from more experimental, non-standardised methods (e.g., NAMs, including data-driven computational approaches like grouping and read-across) to nano specific OECD testing guidelines that may need to be extended or adapted to advanced and innovative advanced materials in the future. Reflection is needed on the PARC toolbox and the specific demand of transfer towards different sectors.

• Visibility of the contribution to ensure/increase sustainability

Industry has a clear need to make their contribution to safety and sustainability visible. This requires a respective program supporting the knowledge transfer to different key players/ multipliers.

HOW TO CLOSE THE GAPS?

Many of the actions to fill the gaps have already been described in the sections above. Here the specific aspects to support translation and valorisation are listed with their time horizons.

- ## Access to infrastructure/knowledge/skills

Improving access to SSbD services is highly linked to the twin green & digital transition[92]. The digital infrastructure including data and software services need to be set up. This common materials data and software ecosystem needs to take requirements from all stakeholder groups into account. For industry, these include clear access rules as well as ways to protect IP. This can be achieved by a distributed and federated setup that is based on open as well as (industry-) internal components. Confidential and sensitive data will be protected by guaranteeing that it does not leave the premises of the data owner. Yet these data can still be combined with public data by providing interoperability based on the FAIR (for data and software) principles and implementing data-visiting concepts[93].

- ## Consultancy services and up-skilling services (short-term) / Educational training and formation of job profiles (mid/long -term)

Such services will support implementation of SSbD, especially in SMEs. This may potentially be supported by SSbD Translators (following the model of knowledge management translators) and SSbD Ambassadors (trainer of trainers and leader of SSbD campaigns). A strong increase in the demand for inhouse SSbD experts as well as SSbD consultancy can be expected. To address this, specific SSbD curricula need to be implemented at universities as part of existing or completely new MS and PhD programmes, supplemented by professional trainings for up-skilling of the existing workforce.

- ## Criteria for SSbD-compliance

Clearly defined and stable criteria for SSbD compliance are needed.

Visualise actions taken to ensure/increase sustainability to different stakeholder groups (short-term) / **Recognition certificates** for SSbD-implementation (mid-/long-term)

To ensure and increase sustainability, industry must be able to profit from adopting SSbD approaches. This could include showcasing use and function of smart/advanced/nano materials developed according to the SSbD principles. In the longer term, this could be supported by setting up clear and validated declarations / product labels for SSbD materials and products to inform consumers. Acknowledgement of the SSbD concepts in future regulations may also lead to streamlining the registration process(es) for SSbD products. This could lead to the competitiveness of SSbD business models over traditionally developed but cheaper materials, which may reduce the need for political pressure on SSbD compliance.

COMMUNICATION, AWARENESS AND TRAINING

STATE OF THE ART – WHAT DO WE ALREADY HAVE OR KNOW?

During the past decade, several initiatives have invested into educational efforts and training, gearing towards a better understanding of nano-related aspects and how those impact human and environmental health. Both at European and at national levels, these initiatives spanned a broad range of activities and target groups. This included continuous professional development of researchers (e.g., EC4SafeNano, NanoCommons, NSC Education Day & Training Day at nanoSAFE Digital Conference 2020), and education of experts in terms of PhD programmes (e.g., NanoTOES, PANDORA, EndoNano). Also, nano-education at pre-graduate or secondary school level (e.g., Nan-O-Style, NanoDiode), was started, next to outreach projects (e.g., SeeingNano, Nano2All) and publicly accessible platforms (e.g., DaNa 2.0, NanoInformation.at) that provide solid information for the public. Notably, the industry needs in nanotechnology education were scoped during the Cooperation Support Action NanoEIS.

A community effort was established within the Venice Nano Training Schools where experts from the nanosafety field endeavoured to train early-stage researchers in nano-related aspects. Lately these trainings increasingly included the sustainability field and expanded towards innovative advanced materials-related aspects. For instance, risk governance & sustainability appeared first-time as topics in the agenda of the 10th Nano Training School in 2021 (online), with experts from the NMBP-13 project NanoRIGO conducting a role play depicting socio-economic aspects in risk perception, while colleagues from various NMBP-15 projects introduced their SbD concepts on nanomaterials. All these materials are available online within the respective sections of the NanoCommons User Guidance Handbook.

The 11th Venice Nano Training School again covered socio-economic aspects besides solid training sessions on data and tools (FAIRness, quality, metadata completeness), with the overall direction towards innovative advanced materials. In 2023, the 12th Venice Training School was fully focussing on the elements of SSbD, resulting in risk assessment being complemented by introductory sessions on life cycle assessment (LCA). The school was organised by an array of projects displaying the broad spectrum and interdisciplinarity of SSbD ranging from plastics and nanomaterials to advanced materials.

UNRESOLVED ASPECTS, EMERGING ISSUES – WHAT IS NEEDED TO BE SUCCESSFUL?

- **Skills development and communication**

A central element of SSbD on whatever materials is its diversity of stakeholders (see the section on "Organisation of governance - stakeholder engagement"). The diverse needs of various stakeholder groups still face a disconnect. This is due both to not yet fully developed skills in different sectors, as well as to a lack of communication.

- **Awareness about the pros and cons of innovative advanced materials**

Awareness about the pros and cons of innovative advanced materials (including nano- and advanced materials) is also still a pending item, despite all efforts to bring science closer to society. On a professional level, the knowledge has not been well transferred yet. Training/education in curricula is not featuring innovative advanced materials and teaching is often still disciplinary differentiated. Recent efforts to shape the academic ecosystem towards a more holistic educational approach (e.g., IRISS-project) are signalling a change in mindset of professors and educators. Hence, these efforts and the experiences gained in the NSC community shall be a suiting asset for the initiatives and partnerships on innovative advanced materials. Yet, stakeholders are often unaware of reliable sources of information based on scientific evidence.

HOW TO CLOSE THE GAPS?

During the 8th International Conference on environmental, health and safety issues related to nanomaterials[94] in Grenoble, France, a panel discussion was organised with representatives from different stakeholders. Industry representation was derived from different value chains, and from different[95]. Representatives from academia, and from regulation complemented the panel. Based on the currently widely discussed SSbD Framework, the panel evaluated the way forward in respect of the specific challenges for industry to implement safe-and-sustainable R&I.

- **Education, Training and Communication**

Education in the form of continuous professional development was repeatedly advocated for. It is seen as the essential emerging element for SSbD implementation in industry in agreement with the targets in functional performance. It needs to be complemented by product sector-specific and customer-adapted training on the tools relevant for evaluating the materials' properties in the different dimensions. Here the technical and assessment-derived data are very often disparate in quality to the results deriving from stakeholder consultation events, as described above. The NanoSafety Cluster Working Group on Education, Training, and Communication is taking initiative in translating the achievements of two decades nanosafety research. This research is often based on investigating complex mixtures of nanoparticles in diverse as well as complex media that impact their physicochemical appearance. Their acting on again overly complex biological systems adds even further complexity. As discussed above and elsewhere (e.g.[96,97], all of this puts challenges onto data quality and metadata completeness.

- ## Installation of a communication structure

The NSC has proven to be a success story in terms of content creation, knowledge exchange, community building, etc. Hence, a future communication structure best uses/facilitates existing structures (e.g., NSC). If needed this could be expanded in terms of organisational structure, to accommodate implementation (see also "Implementation plan" below). A crucial item and hence a unique selling point of the NSC is its diversity of stakeholders that is formed in its ecosystem. Thus, the NSC could enable a kick-start towards an integrative approach of any future SSbD-initiative. Furthermore, the execution of the implementation plan could be put into the hands of already experienced community builders.

- ## Implementation plan

In the mid/long-term the scenario and ecosystem, as well as its needs will be volatile. Some elements – safety, sustainability – will remain as important assets. However, to cope with such changes, the development of a specific implementation plan will be needed and should include an organisational form that supports the community. The plan shall include estimations about the needed resources, as well as financial commitments (e.g., from public organisations). On the other hand, the implementation plan needs to relate to education (e.g., curricula of academia and/or schools), policy (e.g., connections with governments, etc.) and all other stakeholders, to allow for interaction and communication in a synergistic and efficient manner.

- ## Campaigning

Paired with the systematic implementation of safety and sustainability aspects into the scientific and R&I ecosystem, the (end) users of all the developments need to be addressed. This can be planned and implemented via running public campaigns to raise awareness. This could make use of social media, and other communication channels that are built on and transfer knowledge from reliable sources. Hence, the reliability checks of communicated content will be a crucial aspect of the campaigning and will need specific attention. Regaining confidence and trust into scientific information needs specific attention.

GENERAL RESEARCH NEEDS

More general recommendations that need to be considered to successfully develop and market innovative advanced materials include the following:

- ## Biological Interactions

  Understanding the interactions between advanced materials and biological systems is crucial. This involves studying how nanomaterials interact with cells, tissues, and organs at the molecular and cellular levels.

- ## Toxicological Profiles

  Understanding the toxicological effects of different advanced materials is crucial. Many advanced materials may exhibit unique toxicological properties compared to their bulk counterparts, and more research is needed to identify and characterise these effects.

- ## Dose-Response Relationships

  Establishing dose-response relationships is challenging for advanced materials, as their effects may be nonlinear and may depend on several (sometimes varying) factors such as size, shape, surface properties, and functionalization.

- ## Environmental Fate and Transport

  Investigating the environmental fate and transport of advanced materials is important for assessing their impact on ecosystems. This includes understanding how nanomaterials move through air, water, and soil, and their potential accumulation in different environmental compartments.

- ## Long-Term Effects

  Limited information is available regarding the long-term effects of exposure to advanced materials. Long-term studies are needed to assess chronic exposure effects on human health and the environment.

- ## Exposure Assessment

  Accurate assessment of human and environmental exposure to advanced materials is essential. This includes understanding the pathways through which exposure can occur, the potential for bioaccumulation, and the fate of materials in different environmental compartments.

- ## Interdisciplinary Collaboration

  Safe-by-design approaches require collaboration between researchers from various disciplines, including nanotechnology, toxicology, environmental science, and risk assessment. Bridging these interdisciplinary gaps is crucial for comprehensive safety assessments.

- ## Life Cycle Assessment

  Conducting comprehensive life cycle assessments (LCAs) for advanced materials is essential for identifying potential environmental and health impacts throughout their life cycle, from production to disposal.

- **Regulatory Frameworks**

  Establishing clear and effective regulatory frameworks for advanced materials is an ongoing challenge. This includes developing guidance for the safe use of advanced materials in different industries and ensuring compliance with existing regulations.

- **Standardised Testing Protocols**

  The development of standardised testing protocols is essential for evaluating the safety of advanced materials consistently. Standardised methods will facilitate comparisons between different studies and improve the reliability of safety assessments.

CLOSING REMARKS

It is important to note that the field of nano-technology and advanced materials safety and sustainability is dynamic, and ongoing research may contribute to addressing these knowledge gaps. Researchers and regulatory agencies continue to work together to enhance our understanding of the safety and sustainability implications of advanced materials and to develop effective strategies for SSbD.

In today‘s fast-paced world, the possibility to work with innovators from the design phase is more crucial than ever. This approach not only fosters creativity and out-of-the-box thinking. It also ensures that products are developed with the latest technologies and user-centric design principles. However, this kind of collaboration demands regulatory preparedness and foresight. It is vital to anticipate and address potential regulatory challenges early on in the design process to avoid costly delays and setbacks down the line. By staying ahead of the curve, companies can navigate complex regulatory landscapes with greater ease and confidence. Moreover, this proactive approach opens up a possibility for promoting the development of innovative advanced materials that are safe and sustainable. By integrating environmental considerations and safety standards from the outset, designers and innovators can pave the way for the creation of cutting-edge, eco-friendly materials that meet the needs of today without compromising the future.

Ultimately, it is clear that the potential for promoting the development of innovative advanced materials that are safe and sustainable exists if we follow the good advice in this roadmap. By embracing collaboration, regulatory foresight, and a commitment to sustainability, businesses can drive positive change and contribute to a more innovative and responsible future.

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In this document, frequent reference is made to EU funded projects related to safety of nanomaterials. This are all listed including reference to the websites at the Nanosafety Cluster website.

See https://www.nanosafetycluster.eu/nsc-overview/nsc-structure/ongoing-projects/ and

https://www.nanosafetycluster.eu/nsc-overview/nsc-structure/ended-nsc-projects/

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- H2020 - DIAGONAL – Development and scaled Implementation of sAfe by design tools and Guidelines for multicOmponent aNd hArn nanomateriaLs (GA no. 953152)
- H2020 - DeDNAed – Cluster decorated recognition elements on DNA origami for enhanced raman spectroscopic detection methods (GA no. 964248)
- H2020 - HARMLESS – Advanced High Aspect Ratio and Multicomponent Materials: towards comprehensive intelligent testing and Safe by Design Strategies (GA no. 953183)
- H2020 - NanoHarmony - Towards harmonised test methods for nanomaterials (GA no. 885931)
- H2020 - NanoPAT – Process Analytical Technologies for Industrial Nanoparticle Production (GA no. 862583)
- H2020 - SABYDOMA - Safety BY Design Of nanoMaterials - From Lab Manufacture to Governance and Communication: Progressing Up the TRL Ladder (GA no. 862296)
- H2020 - SbD4Nano – Computing infrastructure for the definition, performance testing and implementation of safe-by-design approaches in nanotechnology supply chains (GA no. 862195)
- H2020 - SUNSHINE - Safe and sUstainable by desigN Strategies for HIgh performance multicomponent NanomatErials (GA no. 952924)

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- HEU - ACCORDs – Green deal inspired correlative imaging-based characterization for safety profiling of 2D materials (GA no. 101092796)
- HEU - IRISS – The InteRnatIonal ecosystem for accelerating the transition to Safe-and-Sustainable-by-design materials, products and processes (GA no. 101058245)
- HEU - MACRAMÉ - Advanced Characterisation Methodologies to assess and predict the Health and Environmental Risks of Advanced Materials (GA no. 101092686)
- HEU - PINK - Provision of Integrated Computational Approaches for Addressing New Markets Goals for the Introduction of Safe-and-Sustainable-by-Design Chemicals and Materials (GA no. 101137809)
- HEU - POTENTIAL - Platform Optimisation To Enable NanomaTerIAL safety assessment for rapid commercialisation (GA no. 101092901)
- HEU - SUNRISE - Safe and sUstainable by desigN: integRated approaches for Impact aSsessment of advanced matErials (GA no. 101137324)

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