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Status, implications and challenges of European safe and sustainable by design paradigms applicable to nanomaterials and advanced materials

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Current European (EU) policies, such as the Green Deal, envisage safe and sustainable by design (SSbD) practices for the management of chemicals, which cogently entail nanomaterials (NMs) and advanced materials (AdMa). These practices, applied at the earliest stages of innovation and throughout the life-cycle of chemicals, materials and products, could prevent and/or minimise their environmental, health and safety (EHS) and sustainability impacts. This requires a shift from the established risk control paradigms towards prevention-based approaches at the design stage that accelerate the development of safer and more sustainable chemicals, materials, products and processes, while promoting a transition towards a circular economy and a more sustainable future. The EU commission has funded several Horizon 2020 projects applying the concepts of SSbD to nanotechnologies, biotechnologies and advanced materials. This article is inspired from the answers and opinions shared during a stakeholders meeting arranged throughout the workshop entitled '*Safe and Sustainable by Design Paradigms applied to NMs and AdMa*', held in Venice, Italy, in September 2022. The goal of the workshop was to identify differences and overlaps between the SSbD approaches and to provide common messages on the progress towards the implementation of concrete SSbD concepts, and to reveal challenges faced in their realistic and straightforward execution. In this article, we provide insights into the intersecting industrial domains, the technical and organisational challenges to the practical implementation of the SSbD, and future financial directions in supporting and maintaining the digital products currently under development within the H2020 projects, in order to ultimately enable their uptake by industry and regulators.

Sustainability spotlight

The EU commission has funded several Horizon 2020 projects applying the concepts of safe and sustainable by design (SSbD) to nanotechnologies, biotechnologies and advanced materials. This article is inspired from the answers and opinions shared during a stakeholders meeting arranged throughout the workshop entitled '*Safe and Sustainable by Design Paradigms applied to NMs and AdMa*', held in Venice, Italy, in September 2022. The goal of the workshop was to identify differences and overlaps between the SSbD approaches and to provide common messages on the progress towards the implementation of concrete SSbD concepts, and to reveal challenges faced in their realistic and straightforward execution. All project are contributing towards the United Nations sustainable development goals (SDG 3, 6, 9, 12, 13).

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1 Introduction

The European Union (EU) and its Member States are aiming to reach climate neutrality with a net-zero greenhouse gas emissions economy by 2050 (ref. 45) and a toxic-free environment presented by the chemical strategy for sustainability,[46] encouraging innovation for the development of safe and sustainable alternatives. Those elements are part of a bigger scheme, *i.e.*, the EU Green Deal committed to tackling climate and environmental-related challenges.[47] To meet those policy goals, novel frameworks are required such as the safe-and-sustainable-by-design (SSbD) notion. This strategy addresses the safety and sustainability of materials, products and related processes at every stage of their life cycles: from research and development to manufacturing, use, recycling and disposal.

Table 1 NMBP 12, 15 and 16 coordinators (or representatives) present during the workshop and who participated in the survey

Call	Project acronym	Project full title	Project website	Coordinator
NMBP 15 projects (2020–2024)	ASINA	Anticipating safety issues at the design stage of NAno product development	https://www.asina-project.eu/	Anna L. Costa
	SAbyNA	Simple, robust and cost-effective approaches to guide industry in the development of safer nanomaterials and nano-enabled products	https://www.sabyna.eu	Socorro Vázquez-Campos
	SABYDOMA	Safety BY design of nanoMAterials – from lab manufacture to governance and communications: progressing up the TRL ladder	https://www.sabydoma.eu/	Thomas Chamberlain (representative)
	SbD4Nano	Computing infrastructure for the definition, performance testing and implementation of safe-by-design approaches in nanotechnology supply chains	https://www.sbd4nano.eu/	Carlos Fito López
NMBP 16 projects (2021–2025)	HARMLESS	Advanced high aspect ratio and multicomponent materials: towards comprehensive intelligent testing and safe-by-design strategies	https://www.harmless-project.eu	Wouter Fransman (representative)
	SUNSHINE	Safe and sustainable by design strategies for high performance multi-component nanomaterials	https://www.h2020sunshine.eu	Danail Hristozov
	DIAGONAL	Development and scaled implementation of safe by design tools and guidelines for multicomponent nanomaterials and high aspect ratio nanoparticles	https://www.diagonalproject.eu/	Susanne Resch (representative)
NMBP 12 projects	SusNanoFab	Towards a competitive and sustainable nanofabrication industry	https://susnanofab.eu/	Margherita Cioffi
	NanoFabNet	International hub for sustainable industrial-scale nanofabrication	https://www.nanofabnet.net/	Steffi Friedrichs
RESILIENCE 01–08 (2022–2025)	IRISS	The international ecosystem for accelerating the transition to safe-and-sustainable-by-design materials, products and processes	https://www.ivl.se/english/ivl/project/iriss.html	Cris Rocca (representative)
H2020-NMBP-13-2018 RIA	RiskGONE	Science-based risk governance of nano-technology	https://riskgone.wp.nilu.no/	

The EU Horizon 2020 projects funded under the call 'Foundations for tomorrow's industry – safe by design, from science to regulation: metrics and main sectors/multi-component nanomaterials' are delivering approaches, frameworks and paradigms for the implementation of SSbD materials, products and processes in all nanotechnologies related application areas. Such projects, supporting the commission in realising the SSbD policy objectives, are targeting higher goals such as the EU's zero pollution ambition for a toxic-free environment – a key commitment of the EU Green Deal. Through industrial case studies, the cluster of SSbD projects will ultimately offer stakeholders a suite of digital products (*i.e.* assessment tools and/or e-infrastructures) to support and facilitate the selection of design options and the decision making process enabling small and medium-sized enterprises (SMEs) and industry to weight different criteria such as technological and regulatory requirements, health and environmental impacts and socio-economic factors. Those digital products address the life-cycle of manufactured nanomaterials (materials with a nano-component, NMs) or Advanced Materials (NMs displaying additional complexity *e.g.* a new or enhanced functionality and/or multiple components, AdMa[48]), from the synthesis, manufacturing *aka* their integration into products (nano-enabled products, NEPs), to the use phase and end-of-life. Those approaches will enable the industrial development and manufacturing of SSbD NMs/NEPs and processes, and reduce delays to market launch of products due to regulatory uncertainties, while extending their design processes according to the SSbD philosophy.

The first stakeholder workshop, organised by the H2020 ASINA project aimed to identify common approaches and current challenges faced towards the realisation of the SSbD concept. The workshop brought together the EU H2020 NMBP-15-2019 (ref. 49)/NMBP-16-2020 (ref. 50) projects that are currently exploring the integration of human and environmental safety research with sustainable and techno-economic (and societal) aspects of nanotechnologies (Table 1). Present in the workshop were also representatives from the DT-NMBP-12-2019 projects (SusNanoFab,[51] NanoFabNet[52]), whose focus is mostly on the establishment of a sustainable nanofabrication community as a large scale high-tech industrial manufacturing process, as well as the newly launched HORIZON-CL4-2021-RESILIENCE-01-08 project IRISS,[53] a Coordination and Support Action (CSA) which aims (i) to harmonise and translate the SSbD concept for industries, with a specific focus on SMEs, (ii) to build an EU-led international network for cooperation between the members, (iii) to engage partners beyond consortia level, during and after the duration of the project (Appendix A – participants). Also present were representatives from the EC-Joint Research Centre (JRC), the Organisation for Economic Co-operation and Development (OECD), and the U.S.-EU NanoEHS Communities of Research/Sustainable Nanotechnology Organisation (SNO). A roundtable discussion took place at the workshop to reflect on and clarify inputs collected in response to an online survey (Appendix B – questionnaire). The next sections of this article stem from the questionnaire responses, the outcomes of the workshop and the roundtable discussions with the project coordinators and members from the international organisations (Appendix C – questionnaire's results).

2 Results and discussion

2.1 Industrial targeted sectors

A number of companies are involved in EU-funded SSbD projects, bringing realistic case studies at laboratory scale, in test beds or as pilot plant facilities to transform materials, processes and products not just to safer, but also greener and economically feasible alternatives (Appendix B – questionnaire, Q1). The industry sectors most influenced by nanotechnologies are broadly identified in the "Roadmap draft for an EU wide strategy on nanofabrication"[54] published by the SusNanoFab project which is developing a Digital Platform that interoperates current projects and other EU initiatives.

The majority of the currently running SSbD projects target the health sector (*e.g.*, Nanobiosensors, smart drugs, medical implants, cosmetics, medical/functional textiles *etc.*) (Appendix C – questionnaire's results, Fig. 3). ASINA, for example, is targeting (i) antimicrobial coatings for textiles using silver NMs and various SSbD synthesis formulation alternatives and (ii) nanoencapsulation systems carrying antimicrobial or anti-aging ingredients for cosmetics (such as essential oils enclosed into polymeric capsules within a cosmetic cream). SABYDOMA's industrial case studies cover medical dental implants and NMs coatings production. SbD4Nano is targeting a number of sectors, including food additives, cosmetics, biomedicine and construction, exploring specific NMs such as functionalized TiO_2 and ZnO additives, carbon nanofibres, graphene oxide and silica. One of the sectors targeted by SAbyNA is Additive Manufacturing (AM) and one of the selected case studies within this sector for medical applications are the antibacterial 3D printed polymeric nanocomposite splints. DIAGONAL, in one of the case studies within, is focusing on metallic NMs for applications in cosmetics and biomedical industries (different types of ZnO based NMs applied in sunscreens and as bioimaging probes).

Another sector covered in the EU projects is the Digital/space/industry (*e.g.*, nano semiconductors, flexible electronics, microfluidics; thin-film silicon electronics, smart manufacturing machines, nanocomputing and the internet of things (IoT), multi-functional components for the space industry *etc.*). ASINA is exploring the digital twins technology for a spray coating manufacturing process.[1] SABYDOMA's industrial case studies in this sector examine materials such as CuO, TiO_2 and SiC/Ni composite electroplated coatings. SAbyNA targets two main sectors with their case studies: paints and additive manufacturing (3D printing). However, their tool which considers sector-specific information has the potential to capture other sectors such as the ones mentioned above. DIAGONAL is exploring SSbD nano-size reinforcement of titanium carbide NMs used in lightweight alloys for aerospace and automotive applications.

Other sectors have similar coverage, comprising of (i) climate change/energy (*e.g.*, solar; batteries; hydrogen fuel cells, air/

water purification systems), (ii) mobility (*e.g.*, automotive; engine components, composites for aircraft fuselage and wings, nano-coatings, nanoadditive, reinforcers), (iii) paints (*e.g.*, nanopigments, resistance to weathering, light, anti-scratch; self-cleaning, self-healing; additive manufacturing) and (iv) agriculture (*e.g.*, nanopesticides, biocides, nutrients; soil remediation; biodegradable coatings *etc.*). For example, ASINA is tackling climate change with photocatalytic coatings (air purification systems) utilising SSbD alternatives for the nano-TiO_2 synthesis. SUNSHINE is addressing graphene–carbon nanotube hybrids for electrodes and energy storage. SAbyNA and HARMLESS are investigating paint formulations and SUNSHINE is targeting the mobility sector by including multi-walled carbon nanotubes/silica nanocomposites used as fillers in the rubber matrix of tires. DIAGONAL is applying SSbD in the production of ceramic substrates doped with metallic oxide NMs used in the development of automotive catalytic converters and nanocomposite coatings composed by a nickel phosphorus metal matrix and commercially available graphene nanoplatelets. SUNSHINE addresses the agriculture sector of food and feed technology, by exploring AdMa incorporated into biocidal coatings for anti-pest packaging, and SbD4Nano is exploring antioxidant loaded lipid-based formulation for use in food supplements. Some questionnaire respondents replied other, for example industrial floor coatings and construction (DIAGONAL).

The health sector is the most represented, contributing to the United Nations sustainable development goals (SDGs, for example targeting SDG 3: good health and well-being). Cosmetics seem to be a focus across the health subdivision, due to the regulatory maturity and the ban on *in vivo* testing that puts pressure on the industry to develop alternative SSbD solutions for new formulations. The digital/space/industry cases contribute to SDG 9 (industry, innovation and infrastructure) and other sectors address SDG 6/13 (clean water and sanitation, climate action). The SSbD overall concept greatly contributes to SDG 12 (responsible consumption and production). The sector classification provides insights into the expected knowledge, data and sector-specific criteria upcoming in the near future. It is worth noticing that the synthesis of a SSbD NM can target multiple sectors simultaneously due to the great diversity and multiplicity of NMs and their vast range of potential applications, for example, silver NMs that are intrinsically safe (based on defined hazard properties) can be used either in cosmetics and/or textiles adding enhanced antimicrobial functionalities.

2.2 The SSbD framework

Recently, the EC-JRC published a framework for the definition of SSbD criteria and evaluation procedures for chemicals and materials.[2] Developed within the action plan of the European Chemicals Strategy for Sustainability (CSS), the framework foresees the assessment of the entire life cycle of a chemical, capturing the human and environmental safety aspects, and the environmental, social and economic sustainability dimensions in the approach. The dimensions covered in the framework are

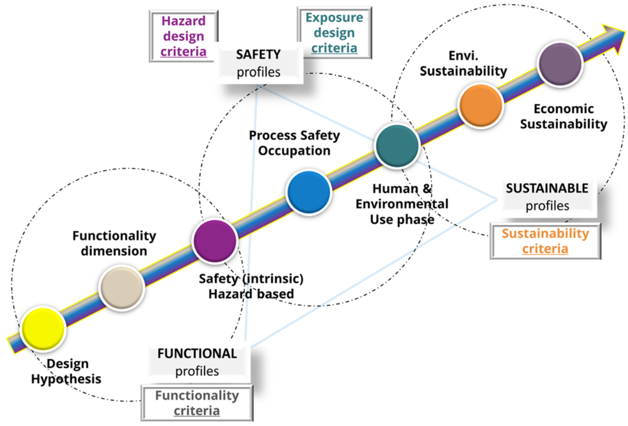

Fig. 1 Dimensions of the SSbD framework, following a hierarchical approach in which safety aspects are considered first, followed by environmental sustainability and socio-economic aspects, while assuring the material and product functionality (image adapted from the JRC framework).

shown in Fig. 1 demonstrating the re-design phase supported by a hypothesis formulation and the dimensional targets: functionality, safety aspects across the life cycle (*e.g.*, intrinsic hazard properties, human health and safety during the production and processing stages, and human and environmental health for the use phase), and environmental (such as climate change, resource use, *etc.*) and socio-economic sustainability. For each dimension criteria are envisaged to stimulate sustainable research and innovation, beyond the current regulatory requirements.

The resulting digital products of the projects can be differentiated based on the described SSbD dimensions (Appendix B – questionnaire, Q2). The majority of the H2020 SSbD projects take into account the material functionality in the re-design phase of the materials or product development (Appendix C – questionnaire's results, Fig. 4). Functionality is a key element to be considered in the alternative assessment of materials, as highlighted in recent frameworks of chemical alternative assessment.[55] For example, in ASINA the functionality is being addressed initially through a tailored design of experiments approach based on a hypothesis rationale and the SSbD NMs alternatives are synthesised with the goal of achieving enhanced antimicrobial, photocatalytic and antiaging functionality, while ensuring safety and economic feasibility. In SAbyNA a variety of SbD strategies towards safer NMs/NEPs and nanoprocesses are proposed, with an emphasis on maintaining the technical functionality of products. In SbD4Nano, the functionality dimension plays a key role to calculate a SbD index. SbD4Nano is working on the elucidation of refined hypotheses based on the structure–property parameters of NMs that impact on the material's functional performance.

The human health safety dimension (covering intrinsic hazard properties and occupational exposure/consumers use safety) across the life cycle, is addressed to the same degree in the SSbD projects as functionality (Appendix C – questionnaire's results, Fig. 4). In ASINA the potential human health risks of NM's is assessed based on their intrinsic hazard properties while for NEPs the potential human risk is evaluated starting from likely exposure scenarios[3–6] followed by the study of potential Adverse Outcome Pathways (AOPs) translated into *in vitro* studies. SUNSHINE and HARMLESS are also addressing toxicity based on AOPs following inhalation/pulmonary exposure using relevant endpoints such as inflammation, cancer, fibrosis and cardiovascular diseases. The platform developed in SAbyNA will allow the use of the GRACIOUS framework for grouping and reading-across to estimate human and environmental toxicity. The projects are addressing products' safety by identifying any potential health risks and diminish them either by reducing/eliminating hazards or exposure (release). SbD4Nano's performance index (an SSbD index which is currently under development) is calculated based on the combination of hazard, exposure and product functionality scores. The hazard dimension is analysed considering *in vitro* studies related to inhalation route. To this end, a methodology based on the use of the biological expression language (BEL) is used to capture relationships between biological entities and activities.

The two first dimensions consist of the first optimization strategy that is being developed, where the knowledge of functionality is combined and balanced with safety at the earliest point of the innovation. In this manner, the efforts align with the overall objectives of the CSS[56] *e.g.* "ensure that all chemicals and materials placed on the market are in themselves safe and that they are produced and used safely and sustainably".[7] demonstrate in their work a tactic for the combination of the two dimensions while providing suggestions for the type of information needed through a literature-based case study on carbon nanotube-based transparent conductive films. DIAGONAL is relying on experimental and modelling research to understand and predict the interactions among the NM components, their transformation products, and between the NMs and cellular components, promoting a better understanding of potential adverse effects on human health.

The environmental safety dimension, also capturing sustainability, is addressed to a lesser extent in comparison to functionality and human health (Appendix C – questionnaire's results, Fig. 4). Sustainability is implicit in SABYDOMA whereby NMs screening and production are developed as an online flow through technologies coupled together, that result in real-time feedback to the designer, ultimately operating as a control system minimising manual handling and waste and encouraging recycling. ASINA solutions are applied to the environmental sustainability of the manufacturing process and particularly the synthesis stages. SbD4Nano is generating environmental hazard data to better understand the effects of surface by design approaches on the ecotoxicological behaviour of a number of materials, supporting decision making from an environmental impact perspective. SAbyNA is developing a hazard strategy which includes both human and environmental hazard assessment, as well as providing guidance on how to assess exposure based on the release and fate processes occurring along the product's life cycle. Furthermore, SAbyNA Guidance Platform will include a simplified Life Cycle Assessment (LCA) methodology to consider sustainability aspects.

Some NMBP 15/16 were originally called to address SbD paradigms. However, the projects are up to date with the current requirements of the sustainability aspects. Retrospectively, an ad hoc transformation of the project motivations can be witnessed, where sustainability elements become centered amid other dimensions. SUNSHINE framework is based on criteria and design principles addressing specific environmental impacts and greenhouse gas emissions as well as the optimisation/reduction in the usage of raw materials, energy resources and toxic substances. In addition, SUNSHINE is involving design strategies to minimise the release in the end-of-life stage (recycling, disposal, incineration), while DIAGONAL is developing environmental exposure models, based on the combination of refined material flow models (MFM), Bayesian probabilistic models (BN), and newly multimedia fate models, considering parameterization of processes affecting the behaviour and transport of NMs, in a given environmental setting (*i.e.* air, water, soil, and sediment).

Economic sustainability is captured in more than half of the projects, while less than half address social aspects (Appendix C – questionnaire's results, Fig. 4). ASINA economic aspects are covered for the synthesis and production stage under a Life Cycle Costing analysis (LCC).[8] SAbyNA's guidance platform (currently under development) is providing estimations of costs as well as overall sustainability associated with the implementation of SbD strategies *via* the integration of LCA and LCC tools. SbD4Nano performance index is calculated on the basis of a tailored designed cost-benefit and product performance analysis algorithm, which is based on cost provided by the users, as well as a new cost estimation approach considering the life cycle stage and scale of the process. SABYDOMA's philosophy of the control system and the SbD4Nano tool can also be applied to environmental, governance, economic and social issues. DIAGONAL and SUNSHINE are acquiring a holistic perspective of the SSbD principles by including Life Cycle Sustainability Assessment (LCSA) methodologies. The latter is achieved (i) integrating new experimental data into the LCA system *via* characterization factors, (ii) developing a LCSA including LCA, LCC and social-organisational (SOLCA) methodologies, with the ultimate goal of assisting in the development of novel materials which are not just safer and economically feasible, but also greener. SUNSHINE has introduced a tiered approach to sustainability assessment using screening-level qualitative self assessment tools and semi-quantitative methods from decision science in the early stages of innovation, while in the later stages the established higher-tier quantitative approaches for LCA, social LCA (S-LCA) and LCC are applied.

In literature further examples of integration of social dimensions are reported.[9] combined in a stepwise nested approach risk assessment, LCA and Socio-Economic Analysis (SEA) to support the SSbD efforts. The authors implemented the Cooper's Stage-Gate model which was also proposed by the pioneers of the SbD iterative approach in nanosafety (NanoReg2)[10–13] proposed a semi-quantitative methodology grounded on the combination of S-LCA and multi-criteria decision analysis (MCDA) methods to support the initial screening and decision making upon socio-economic impacts over the life cycle of a product at each stage gate of the innovation process. The application of their methodology is a scoring procedure (Excel based self-assessment tool) to facilitate its uptake by industries. This methodology has been converted to an R code and implemented in the digital e-infrastructure to be delivered by the SUNSHINE project. While the cost effectiveness plays a central role to every business in the industry, academia and regulators seem to have a reverse role, targeting safety first and the profit last.

2.3 Life cycle stages

The SSbD concept is mainly addressed to the interventions performed as early as possible in the innovation process. However, to fulfil all the SSbD criteria, projects are simultaneously and holistically supporting safety and sustainability throughout the life-cycle stages and not only the production or synthesis phase.[14] Each life cycle stage might require a different alteration aka intervention for the materials intrinsic/extrinsic physicochemical properties or process design parameters. For example, an alternative synthesis to silver NM, may reduce intrinsic hazard, and/or reduce the environmental impact during the synthesis stage, however, the same materials embedded into a product *i.e.*, functional textiles, may have an increased leaching rate from dermal simulation testing in sweat. While the dimensions require a weighting scheme to satisfy all requirements, an additional weighting scheme is required within each life cycle stage itself, throughout the distinct dimensions.

The SSbD projects are proposing strategies to address risks as early as possible in the innovation process, that eliminate or reduce hazard and/or exposure, considering the occupational, consumer and environmental risk domains at all life cycle stages of nanotechnology based products, and balancing product functionality and overall sustainability (Appendix B – questionnaire, Q3). The life cycle stages receive balanced care in EU projects, as it is expected (Appendix C – questionnaire's results, Fig. 5). Interestingly, the use phase (human health and environmental aspects in the final application phase) receive slightly more resources as this is the stage where data is the most absent. Despite the significant advancements the scientific community has made in the last two decades in revealing the toxicological nature of NMs, the issue of safety of consumers and sustainability during the use phase remain open. This is attributed to the various matrices a NM is incorporated into, its dynamic properties and the diverse use-oriented properties that might influence safety.[15] The use phase is becoming more challenging with the introduction of AdMa that actively respond to external stimuli, also known as "smart NMs".[16]

The SSbD actions performed at the earliest stage of the innovation process must capture consumers safety and environmental sustainability, since interventions in the later stages suffer from a decreasing degree of intervention freedom and increasing costs and efforts.[7] It is worth to notice that[17] showed that the use of common terms as 'product', 'material', and 'chemical' do not have the same meaning across disciplines and may thus create confusion and ambiguity. In combination with varying definitions of 'life cycle', applying SSbD can result in different trade-offs being found and conclusions being reached depending on the life cycle perspectives or, in other words, system approach(es) adopted. Therefore, a clear definition of the aforementioned common terms and life cycle is crucial, and inclusion of these terms into a recognised ontology would support their re-use in modelling studies in an interoperable manner.

2.4 FAIR data management and timeframe

A cornerstone aspect of the successful implementation of the SSbD concept is the data quality and availability *i.e.* data FAIRness. To enable the SSbD execution, all the knowledge needs to be handled according to the FAIR-principles to secure its access and use in the long-run.[18] The commission has released guidelines on FAIR data management in H2020 projects and included the data management plan as an intrinsic deliverable of any project that generates, assembles or processes research data.[19] The commission efforts resulted in cultivating project management skills among researchers that make data management mostly relatively straightforward and controllable (Appendix B – questionnaire, Q4 and Q5, Appendix C – questionnaire's results, Fig. 6, left). However, there is a notable percentage of researchers that still find it confusing. There is general consensus that data become freely available either during a project or shortly after (taking into account intellectual property rules) (Appendix C – questionnaire's results, Fig. 6, right) that shows stakeholders comprehension of the importance of data accessibility during the innovation process. The data needed are often not shared in a timely or effective manner. Restrictions on data sharing often are an issue within research consortia, and clear rules are needed for academia to share the data at the right time to be useful to the industry and regulators, while still allowing the data owners to exploit the publication potential and other intellectual property rights.[20] For the moment, a great amount of information produced by H2020 projects is stored online in private servers, locked to external users, making the data re-usability unfeasible while hindering progress and data integration, especially for modelling purposes.[21]

Having handy data enables development of computational models (*e.g.*, machine learning tools) able to simulate and predict SSbD criteria, significantly reducing the R&D time and costs, as well as making the user-friendliness of tools, requested by industry, more feasible. The SSbD projects exist in the centre of data reusability requisite and the management of the new information generated either from experimental testing or through *in silico*/modelling approaches. In either case, data has to be managed in a FAIR manner, to allow the framework's reproducibility and validation. For example, SAbyNA is using existing data that supports the guidance documents under development, and potentially generate candidate test guidelines generating sector-specific versions of models and tools, including *de novo* generated datasets in selected case studies. The SbD4Nano infrastructure consists of two parts; the user basic information access on data of hazard, exposure, p-chem and regulatory requirements; and a second part in which the user describes case studies and gets scores based on existing models. Moreover, SbD4Nano has developed a large dataset containing EHS information generated under the project using the eNanoMapper ontology, supporting the data FAIRification process. HARMLESS is building on large databases from previous and ongoing projects, with hazard and exposure data for a wide variety of NMs complemented by newly generated data and creates computational tools for different scales and stages of product development to feed the decision support system (DSS) under development. SUNSHINE is developing a new open and FAIR inventory of EHS and sustainability data from several finished and ongoing EU research projects. In DIAGONAL, available and newly produced hazard and exposure data are integrated in novel multi-scale modelling tools, such as exposure modelling, physiologically-based kinetic modelling, and structure–activity prediction networks. The data shepherd of ASINA has initiated the design and implementation of a data FAIRification process with multiple stakeholders who are unaccustomed with the notion of FAIR process, that is currently under development.[22,23] The process of data gathering and ensuring data quality allows the computational decision tool (ASINA Expert System, ASINA-ES) to utilise most of the data, existing or generated within the project.

In order to avoid creating knowledge obstacles for future studies, all the knowledge, tools and guidelines must be shared and exploited according to open innovation and data FAIR principles, ensuring that the SSbD results can synergise with existing databases and data generated by ongoing projects and companies, including businesses, authorities, universities and research institutes that improve knowledge. In this manner, a better understanding of potential adverse effects on human health and biota is promoted, while covering other aspects of sustainability and economic feasibility. There are ongoing efforts and incentives to facilitate mutual data sharing, and the necessary infrastructure is evolving to enable adaptation to the needs of different communities. For example, in response to this crucial need, the EU funded the establishment of a data management research e-infrastructure (NanoCommons[57]) and two research projects (NanoInformaTIX[58] and NanoSolveIT[59]) to improve the data quality and to develop regulatory-relevant informatics tools for predictive SbD, grouping and risk assessment of NMs.[24] To promote and ensure data sharing, the coordination of FAIR e-infrastructures (knowledge bases, databases), including raw data and metadata, should be done at an overarching level.[20] It is outside of the scope of this manuscript to provide details regarding the FAIR initiatives and the efforts in place in the EU. The reader can refer to the following ref. 60–62 to get an understanding of the current initiatives regarding FAIR data.

2.5 Business models

The majority of the projects aim at developing a form of digital tools (*e.g.* e-infrastructure, data repository, database, guidance platform, expert system, modelling tools) Table 1 (Appendix C – questionnaire's results Fig. 7). For example,

-SAbyNA is developing a web-based platform that includes existing safety and sustainability assessment tools tailored for SSbD purposes integrating the product performance considerations and costs when proposing re-design of products or processes towards safer solutions to be implemented. SAbyNA guidance platform allows future projects and researchers to add into the already initiated structure.

-SABYDOMA is providing a technical demonstrator consisting of a flow through an online screener coupled to a NM production line. The two main outputs are the lead technical demonstrator and the underlying control system concept for the application of SSbD frameworks.

-ASINA-ES e-infrastructure will allow nano-manufacturers to implement the SSbD approach. The system stores available information and, through a MCDA tool, is capable of managing future case studies from the users.

-SbD4Nano approach is based on an e-infrastructure as a DSS tool for the automatic generation of the SbD performance index. This e-infrastructure includes a data input module, use existing data from e-nanomapper, or use information predicted by models implemented in the tool, considering the cost and functionality dimension,

-HARMLESS is also developing a DSS tool to apply the SbD and safe innovation principles in materials and product development making use of existing models, tools, databases, machine learning and deep learning techniques.

-SUNSHINE is expanding an e-infrastructure to enable risk-benefit analysis of the SSbD-modified materials and products at each stage of the Stage Gate innovation process. This includes a digital platform for information exchange along the supply chain (and with regulators), access to FAIR databases, as well as EHS and sustainability assessment tools, and a module to assess the safety-functionality-sustainability balance of new materials/products at each stage of innovation to support 'go to development' and 'go to market' decisions.

-DIAGONAL is developing a DSS for the implementation of a multicriteria optimization process focusing on individual cases.

-In addition, the NMBP 12 project's outcomes are solely digital providing databases and access to multiple networks, cooperation activities, promotion of best practices, training services and supporting activities. The NanoFabNet project, in particular, provides a registered network – the NanoFabNet Hub[63] – that aims to combine the two communities of sustainability and high-tech experts, in order to foster collaborations and multidisciplinary innovations.

In all projects, tools are being developed that will need to be supported financially after the end of the projects. As data volumes and open data access demands increase, these repositories are coming under increasing financial pressures that can undermine their long-term sustainability. It is thus important to seek to reveal common revenue sources for the long-term sustainability of those digital tools (Appendix B – questionnaire, Q6), in the context, for instance, of the OECD report on the business models for sustainable research data repositories.[25]

Most projects integrate a mixture of revenue sources, with two projects relying solely on access charges (*i.e.* charges for contract services to other parties or for research contracts) or on host institution funding (*i.e.* direct or indirect support from a host institution) (Appendix C – questionnaire's results, Fig. 6). Since the project's target audience is research and the industry, it is logical that access charges and contract services are the common approaches. The report[25] includes a set of recommendations designed to provide a framework for developing sustainable business models and to assist policy makers and funders in supporting repositories with a balance of policy regulation and incentives. The best solution is a diversification of the revenue sources, a practice recognized and adopted. Promising tools such as the SSbD, encapsule a concept that is more advanced and complex than the solutions required by immediate potential users. Thus, the common approach is to provide a version of the tool in a more straightforward and simplistic manner (while receiving valuable feedback from users), while exploring the tool's development with continuous research through host funding. The host institution is a fundamental source of revenue for such tools to be sustained and, more importantly, to refine their approach while increasing their applicability domain with more information through the research activities. There are a number of fields of research that depend almost entirely upon the availability of global data sources provided through research data repositories, and the SSbD concept is one of those. It is thus essential to ensure that these repositories are adequately and sustainably funded.

2.5.1 OECD. OECD activities of the project Moving towards Safe(r) & Sustainable Innovation Approach (SSIA) for More Sustainable Nanomaterials and Nano-enabled Products[64] aims (a) to support innovation and to ensure that nanomaterials and advanced materials are developed in a safe and sustainable way supported by a circular approach. (b) To support a dynamic process for identifying and prioritizing the elements to be considered for safety and sustainability. This requires continuous dialogue and/or collaboration between regulators and innovators, and other relevant stakeholders.

The project comprises four activities: (i) working descriptions for Sustainability and Safe and Sustainable by Design, a first step to integrate sustainability into SIA (ii) development of an inventory of frameworks, methods, aspects/parameters, and tools/toolboxes for SSbD and regulatory preparedness, (iii) bridging SIA closer to practical applicability through the development of trusted environments and dealing with barriers and constraints, and (iv) development of a platform for sharing knowledge, learning from industry and regulator's experiences. In addition, a SSbD tool classification scheme is required to allow a distinction among the tools since many of them are targeting the same solutions while covering a combination of hazard, exposure, and/or sustainability dimensions. OECD goals with the classification tool are:

To identify the applicable domain for each tool.

• To easily compare the different dimensions addressed by the tools.

• To highlight each tools' strengths and weaknesses.

• To identify the gaps of each tool based on the OECD working description of SSbD.

• To show methodological advances on the implementation of SSbD.

The criteria for the description of the tools are also partially inspired by the JRC framework, taking into account the design component, the risk assessment, dimensions and sustainability and economic indicators. Such activities are fundamental in clarifying the utility of decision-making tools for the risk governance of nanotechnology might assist the overarching ambition of creating a fair system of risk governance.[26]

2.6 Missing knowledge

While the focus of scientific prioritisation has been the standardised measurement protocols for regulatory purposes, other emerging issues appear in the SSbD frameworks which pose more urgent issues to the SSbD development. The most sought of missing knowledge for prioritisation appears to be the life cycle analysis factors for the environmental sustainability (Appendix B – questionnaire, Q7, Appendix C – questionnaire's results, Fig. 8). Safety and sustainability are intertwined and the two aspects have to be considered equally among the basic and primary principles of design.[27] LCA is an established methodology for the assessment of potential environmental impacts across the life cycle stages of a product (ISO 14040:2006, 2006). However, this tasks poses significant challenges in the nanofield due to knowledge gaps related to the release amount into the environmental compartments, the exposure, due to the complex transformative nature of NMs,[16] due to the lack of foreground empirical or inventory data across the life cycle, and due to the lack of characterization factors for nano-environmental impacts.[28] To address those challenges, systematic and long term studies are required.[29] reviews green chemistry principles and their application in the development of bio-based nanobiotechnology and nanosynthesis, with an emphasis on the metrics of sustainability for the synthesis process.[28] recently proposed a stepwise framework based on the prospective LCA to integrate environmental sustainability aspects with toxicity aspects allowing the identification of environmental sustainability and toxicity hotspots early in the innovation process for SSbD application in the design phase. Other approaches have been suggested such as the expansion of the Ashby material selection charts to include metrics that characterise environmental impacts and economic performance.[30]

Other missing knowledge fields required are (i) realistic demo cases implementing the SSbD framework, (ii) quantitative criteria for the SSbD implementation and an (iii) agreed data management and curation framework. The quantitative criteria challenge for the SSbD implementation challenge is discussed in Section 2.9. The agreed data management and curation framework challenge has already been discussed in Section 2.4.

Few studies exist with proposed resolutions to achieve a SSbD profile. For example,[31] reviewed four criteria (product safety, low environmental impact, material & energy efficiency and process safety) derived from the twelve green chemistry principles for the SSbD of cosmetic sunscreens containing TiO_2 NMs as an alternative to the chemical UV absorbers (*p*-aminobenzoic acid and benzophenones).[14] provides a set of questions that help innovators to assess nano-specific human health safety aspects (similar approach can be applied for environmental risks) of their product or material along the various stages of the innovation process.[32] presented guidelines including a set of information and tools that will help decide at each step of the innovation process whether to continue, apply SbD measures or carry out further tests to reduce uncertainty. Those articles do not exactly provide demo cases, but rather information and instances on how to approach the SSbD.

Realistic demo cases are needed to crave the pathway towards the SSbD realisation.[33] proposed a sustainability framework combined with the SbD concept to promote the selection and use of safer and more sustainable NEPs in different conservation contexts. The application is done through a theoretical case but the example provides realistic methodological steps through the iterated decision making process.[10] illustrated the complexity of SbD measures in realistic case-studies of six different companies, each of different SbD goals. All the toxicity, exposure and RA, LCA as well as SEA were undertaken by external experts.[28] proposed a framework based on a prospective LCA for early safety and sustainability assessment. Environmental sustainability aspects, such as global warming potential and cumulative energy demand, and toxicity aspects, such as human toxicity potential and freshwater ecotoxicity potential, were assessed on a case study using P25–TiO_2 or a modified version (Cu_2O-coated/P25–TiO_2) as photocatalysts to produce hydrogen from water using sunlight.[34] developed a SbD procedure to reduce potential environmental risks while optimising functionality and costs of wound dressings containing Ag NPs based on *ad hoc* criteria and permits to identify the best one among five pre-market alternatives.

The JRC proposed SSbD framework is currently undergoing a testing phase within realistic case studies covering several types of chemicals, materials and applications to further refine the framework and advance the criteria definition.

Interestingly, while the safety dimension is an intrinsic aspect traversing all dimensions, the long term nanotoxicity received little attention (Appendix C – questionnaire's results, Fig. 8). The issue with long-term effects and the accumulation over time in organs and tissues has recently been stressed[35] with an emphasis on how those tests should have sufficient predictive power.[36] The *ibid* authors also stress that novel *in vitro* tests to predict long term effects of NMs are missing. In addition, long term studies are required for the definition of human toxicity factors for LCA impact assessment.[37] states that the adaptation of life cycle impact assessment (LCIA) toxicity characterization methodology is not yet achieved for NMs/AdMa and *in vitro* data. The *ibid* authors stress that cross-discipline discussions are a fundamental step towards a successful integration of both new data sources and new substance types into LCIA.

Realistic *in vitro* exposure has received no attention and this challenge deserves its own manuscript.[38] Few studies exist in the literature, where *in vitro* nano-dosimetry was defined after a strategic approach.[39] gives estimates of lung deposition after occupational exposure to NMs (CNTs, TiO_2, Ag) to recommend *in vitro* testing concentrations for the U.S. EPAs ToxCast™ program. The authors gathered concentrations in air in manufacturing and R&D settings, to be used as inputs in a Multiple-Path Particle Dosimetry (MPPD) model. In ASINA, the dosimetry is defined based on a robust *in vitro* exposure methodology which consists of field exposure campaign monitoring data, Multiple-Path Particle Dosimetry modelling, *in vitro* deposition efficiency and dissolution assessments.

Finally, while the science is transforming towards digital formats, the challenge of regulatory acceptance of *in silico* modelling has also received less attention (Appendix C – questionnaire's results, Fig. 8). This is due to the fact that a high amount of quality data is needed first for such approaches to be accepted. Prioritisation is given to an agreed data management scheme which will greatly accelerate the acceptance and increase the trust of such tools. It is worth to notice at this point, that the traditional risk assessment of chemical, is transforming into digital frameworks consisting of the new approach methodologies (NAMs) without animal testing[40] to meet regulatory requirements.[41] Summarise the ability of NAMs for the assessment of human health effects of industrial chemicals and pesticides within the United States, Canada, and European Union regulatory frameworks.

2.7 Certification

Another open issue is the (semi)-official validation of a concept and how could or should that be achieved (Appendix B – questionnaire, Q8). One way forward commonly accepted is a certificate of compliance to regulatory requirements (Appendix C – questionnaire's results, Fig. 9). Who will provide such a certificate is still left open for discussion. Most projects chose detailed documentation such as a roadmap based on followed guidelines outlining the methodology and a few projects chose a qualitative self-declaration form. As[16] stressed in their manuscript, an anticipatory activity could be initiated to analyse different regulatory options to promote the SSbD notion. An evaluation of the impact of each alternative, from the most stringent option of legally binding requirements to softer approaches such as guidance documents or recommendations for industry, should also be performed. Those softer approaches, while not so relevant for regulators, are important for companies, which could use the "labels" as quality certification toward the customers and consumers.[15] There are already labelling schemes focused on the environmental sustainability at product level such as the Eu Ecolabel.[65] ISO provides type I/II and III product label declarations ranging from overall environmental preference of a product (*i.e.* a good or service) based upon life cycle considerations, to detailed quantitative information.

The Nanotechnology Industries Association (NIA) already organised a series of workshops with regulators, where industry shared their activities towards safer products and how they meet regulatory requirements.[16] The International Network

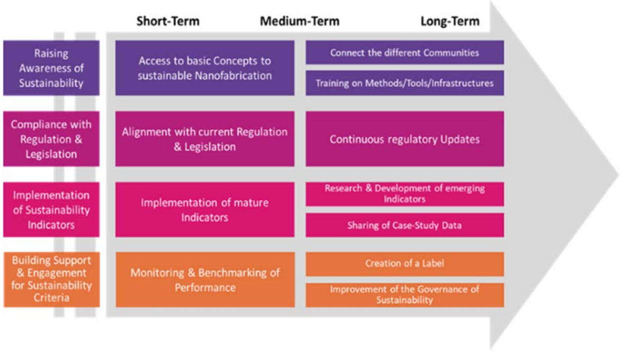

Fig. 2 Diagram summarising the actions and recommendations of the NanoFabNet strategy and implementation roadmap for sustainability in nanofabrication (source: ref. 60).

Initiative on Safe and Sustainable Nanotechnologies (INISS-Nano)[66] is investigating existing labelling schemes and are suggesting practices (together with the CEN/TC 352 Nanotechnologies Study Group) with the view of cross regional label, B2C-labelling and B2B-labelling.

The currently running NMBP-13 Horizon 2020 projects Gov4Nano, NanoRigo and RiskGone are working towards a future-proof operational Nano Risk Governance Model (NRGM) that addresses the needs of the transdisciplinary field and innovative character of nanotechnology. The novel governance model might address issues of providing the necessary expertise, or a certificate, facilitating the SbD application in SMEs.[14] However, the concept of SbD is now shifted to SSbD which might require novel funding of projects focused on the validation of such frameworks. Aiming to provide a set of recommendations that guide both the formation of a joint, interdisciplinary expert community for sustainable nanofabrication, and the adoption of sustainability into nanofabrication processes and products, the 'NanoFabNet Strategy & Implementation Roadmap for Sustainability in Nanofabrication'[67] suggest the development of a label for sustainable high-tech innovation as one of the four recommended supporting actions.

'EU 2030 Strategic Plan for Nanofabrication – a NanoFabNet Roadmap', which A standardised label should explicitly recognise products for which safety and sustainability have been transparently addressed during their development (Fig. 2).

2.8 Challenging aspects

In addition to scientific challenges addressed in Section 2.6, there are higher level challenges towards the realistic implementation and dissemination of the SSbD (Appendix B – questionnaire, Q9). The most challenging aspect in the SSbD concept realisation is the translation of the scientific findings into a decision making framework, a challenge agreed in all projects as a high priority (Appendix C – questionnaire's results, Fig. 10). The impact quantification of the SSbD outcomes on the other hand, is of medium/high priority. Indeed, to place a number on how much safer, or how sustainable a product or a process is, will be a key component for the promotion of the strengths and the realistic impacts of such an approach. Communication of the knowledge with all related stakeholders, although conceived as a high or medium priority issue, is also considered as the least challenging part in the SSbD experience. While communication with stakeholders is not a "challenge" itself, it is a necessary ingredient for a scientific achievement translation to different parties. The 3rd meeting of the EU high-level roundtable on the chemicals strategy for sustainability[68] mentions that "cooperation is essential as SSbD requires a collective effort and collaborative learning, and an exchange of best practices. This necessitates a clear (cultural) paradigm shift among all stakeholders".

The paradigm shift that is required is evident. The SSbD concept requires means to implement knowledge in a structured way into industrial innovation processes and to exchange this information between the involved stakeholders.[42] Communication could be the answer to the translation into a decision making process challenge. Once the information is collected and organised, it must be communicated. The SSbD involves expertise from safety and sustainability areas (*e.g.* safety, environmental, circular, governance, economic and social). Under such a transdisciplinary integral, creating a common language across all the relevant parties is challenging. Agreed terminology fosters mutual understanding between scientists, industry and regulators within the same field, and it is necessary for defining the applicability domain of legislation.[20] There is also a need for a common understanding of terms like smart nanomaterials for regulatory purposes, and a common understanding of the term advanced materials should also be developed. Progress in the assessment of safety and sustainability of these materials must not be blocked by the lack of a harmonised terminology.[20]

Recently, the OECD published a working description for advanced materials.[43] This working description can form the basis for further research activities such as those related to standardisation and harmonisation, both within the OECD as well as by research organisations and industry.

Lastly data finding, access, collection and usage is at the centre of divergent opinions among researchers and perhaps some confusion results from how data should actually be managed or where to be found (see Section 1.4). The management of the data communication between involved actors is central to having an effective innovation project. There is sensitive data that is restricted to the company (or to a person in the company), but other data needs to be communicated to customers (*e.g.*, labelling information, use instructions, hazard classification) or to suppliers (*e.g.*, exact specifications of the NMs). Therefore, it has to be possible to "assign" certain information to a certain target group to make it selectively visible.[42]

None of these challenges could, or should be tackled by just one expert community or stakeholder group alone; the 'EU 2030 Strategic Plan for Nanofabrication – a NanoFabNet Roadmap'[69] therefore defines prerequisites and requirements for the establishment and long-term growth of sustainable high-tech, anticipates their necessary implementation in three predefined time-ranges (*i.e.*, (i) short-term (2022–2025), (ii)

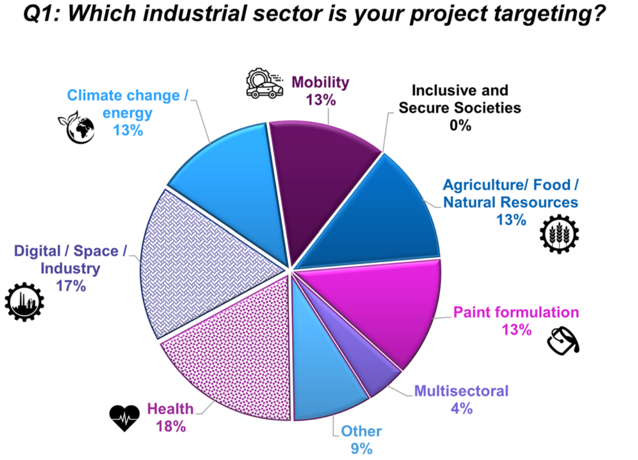

Fig. 3 Responses from workshop participants to question 1: which industrial sector is your project targeting?

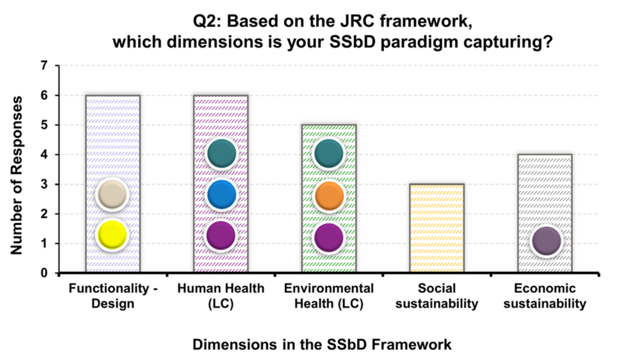

Fig. 4 Responses from workshop participants to question 2: based on the JRC framework, which dimensions are you addressing in your project?

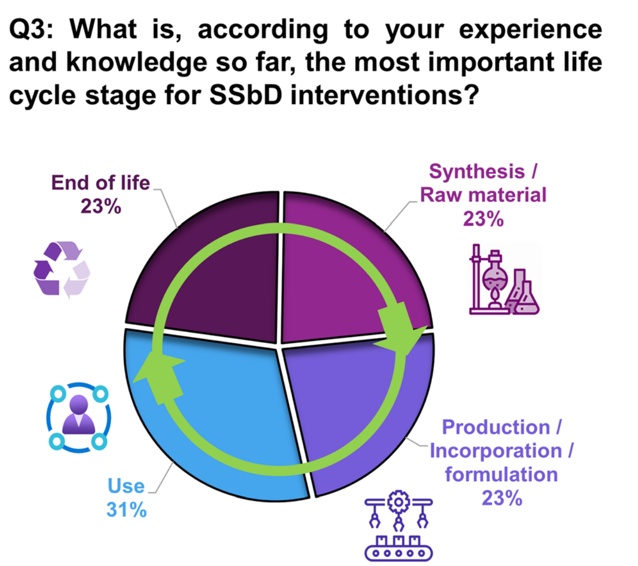

Fig. 5 Responses from workshop participants to question 3: what is, according to your experience and knowledge so far, the most important life cycle stage for SSbD interventions?

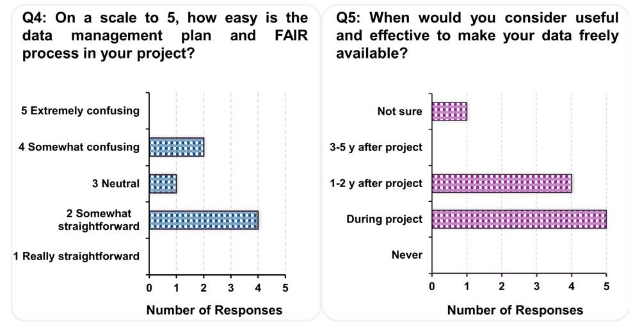

Fig. 6 Responses from workshop participants to question 4: on a scale to 5 (5 being extremely confusing), how easy is the data management plan and FAIR process in your project? and question 5: when would you consider useful and effective to make your data available?

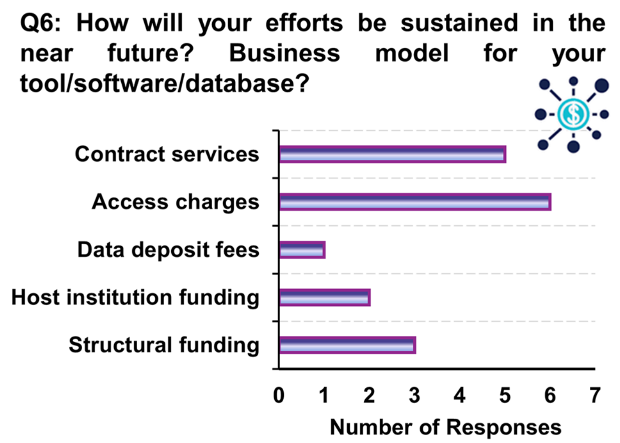

Fig. 7 Responses from workshop participants to question 6: how will your efforts be sustained in the near future? business model (ongoing revenue sources) for your tool/software/database?

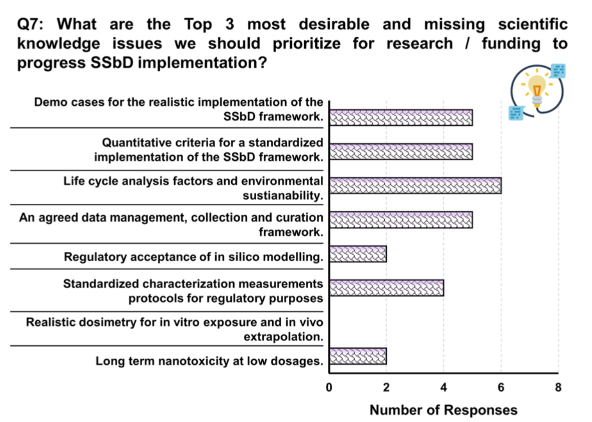

Fig. 8 Responses from workshop participants to question 7: what are the top 3 most desirable and missing scientific knowledge issues we should prioritise for research/funding to progress SSbD implementation?

medium-term (2025–2030) and (iii) long-term (2030 onwards)), and identifies the organisation that is best suited to take the respective responsibility.

2.9 Future goals

Identifying common criteria to address the SSbD multicriteria decision problem is one of the most significant goals where collective robust efforts must be placed on (Appendix B – questionnaire, Q10, Appendix C – questionnaire's results, Fig. 11). All current SSbD projects are working to cover functionality, human and environmental safety and sustainability aspects while including social and economic indicators, all under one unified umbrella of S(S)bD solutions. The solutions to be proposed should comply simultaneously to all the dimensions criteria (to be unravelled) with performance constraints. The development of clear, agreed and quantitative criteria is a logical step forward. A challenge that appears in the criteria development is the threshold definition for deciding when a product is deemed safe and sustainable.[20] For each dimension, the projects are asked to identify and analyse the most relevant parameters, (key performance) indicators, criteria, factors, features, inputs and outputs, to capture the knowledge in a digitised manner and translate that into a practical quantified guidance for a decision making process. For example, the integration of the dimensions is a challenging task because it requires to expose the relationship between pchem properties and safety (*i.e.*, toxicological outcomes) while including LCA and LCC impact values (determining sustainability). Thus, a list of key ingredients to be considered for each specific criteria must be developed, accompanied by acceptable levels, merged into one final SSbD score/indicator. At the end of a project, quantifiable results must be provided to demonstrate how the alternative design solutions improved safety and sustainability, compared to existing materials in similar applications.

One challenge in addressing the SSbD criteria throughout research, design, manufacture and marketing phases is the diversity of nanotechnology and its related heterogeneous products, but also the diversity within a single NM and its functionalization potentials. In addition, the diversity expands to the process technology that uses NMs in the production phase. Thus, the criteria developed must be derived from sector specific case by case approaches initially and then merged into a bigger picture.[16] Finding all the relationships between the data along the life cycle stages of a product, is a challenge indeed. However, the true challenge lies within the common criteria across different industrial sectors. For the moment, it appears that a case-by-case analysis is required for each instance (see Q7, demo cases). Such approaches in the near future should be generalised with the aid of artificial intelligence and the internet of things in the nano-manufacturing process, *i.e.*, digital twins.

The 3rd meeting of the EU high level roundtable on the chemicals strategy for sustainability[70] mentions that design criteria for chemicals, materials, products and processes will move from qualitative to quantitative assessments, with more data becoming available between the ideation phase and the pre-market stage. The true disappointing goal to see failing is data. How can this concept be replicated solely on data? Metadata capturing is not frequently promoted in regular academic

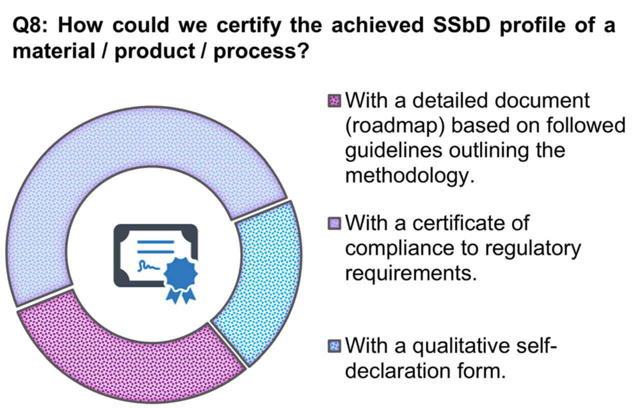

Fig. 9 Fig. 8 Responses from workshop participants to question 8: how could we certify the achieved SSbD profile of a material/products/process?

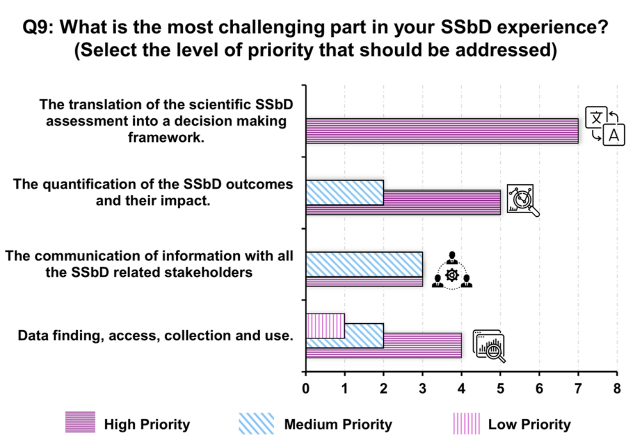

Fig. 10 Responses from workshop participants to question 9: what is the most challenging part in your SSbD experience? (please select the level of priority that should be addressed).

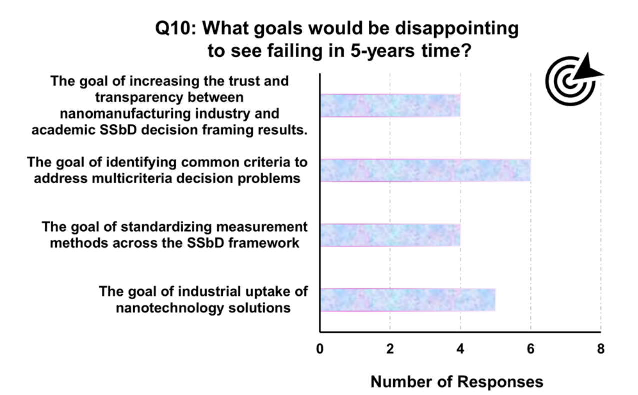

Fig. 11 Responses from workshop participants to question 10: what goals would be disappointing to see failing in 5 years time?

practice, despite its importance. This is due to a lack of data management training and a prevalent perception of something that happens after data has been thoroughly evaluated and published. This FAIR challenge requires the active involvement and constant participation, engagement and collaboration of participants with different expertise. The transparency of the methodologies will allow a shared responsibility for increased societal trust and ethical outcomes by promoting early dialogues between stakeholders sharing similar interests. The more FAIR data becomes available through democratic participation in a data economy era, the more the applicability of such a framework increases ensuring effective policy making and societal acceptance.

SSbD frameworks/paradigms tools are now in their infancy with tremendous efforts being put towards the realisation of the concept by research hubs such as the JRC (the Framework). Recently, a collaboration between Dutch and German governmental (research) organisations developed a system called Early4AdMa.[44] Which can be used to identify safety, sustainability and regulatory issues of advanced materials. The system can be used as an anticipatory risk governance tool, however, it could also guide industry in their innovation process by identifying potential issues of concern, and, thereby, stimulate the SSbD of advanced materials. There is a clear need for the development of such tools, including those developed in the projects discussed here. Critical for the use and acceptance of such tools is that they are validated through case studies and fit in with other available tools, frameworks and regulations. As such, international collaborative action with all relevant stakeholders (*e.g.* regulators, industry and researchers) is critical. While all the projects are working in concert to achieve such a multitask challenge, this will require tailored workshops in the near future that should address such criteria across the dimensions. How the projects concluded on those criteria, and which guidelines and protocols they considered, or which artificial intelligent/grouping/read across tools were relied on, or which inputs are the ones affecting each dimensions (per case study), or which data were used, will be of paramount importance to merge the knowledge into a decision making framework and to reveal if common features appeared across all projects.

To accelerate the merging of the projects' outcomes the recently launched IRISS project will support the transition to safe and sustainably designed materials, products and processes developing a working framework for establishment of an expanded SSbD community, creating a common mechanism to engage, mobilise and bring together diverse stakeholders. In addition, the projects are called to contribute to the establishing of a nano risk governance council (NMBP-13-projects: Gov4Nano; NanoRigo; RiskGone) and a sustainable nanofabrication community (NMBP-12-projects: NanoFabNet; SusNanoFab). A centre was recently proposed[24] envisioning a sustainable governance and service management scheme, bringing together providers of nanosafety services to deliver collaborative services, harmonise service provision and create novel service schemes. The idea is an open hub of service providers able to offer collaborative and extended expertise and science-based advice on the evolving spectrum of advanced materials, notably through SbD/SSbD.

3 Conclusions

Recent EU stakeholder workshops,[71,72] networking events (Sustainable Nanofabrication Networking Event, Portugal (Braga) 2022), conferences (Nano-week and NanoCommons Final Conference, Evolution of Nanosafety and materials sustainability as we transition into Horizon Europe, in Limassol (Cyprus), 2022) and nanosafety expert training (Nanosafety Training School: Towards Safe and Sustainable by Design Advanced (Nano)Materials, Italy (Venice), 2022) made evident that a well-defined and straightforward approach to account for sustainability aspects within the safety elements is missing, while criteria are still under development. However, the horizon is visible and clear. In the next few years, a shift of the field focus from the conceptualisation of theoretical frameworks (as established from current EU collaborative efforts), towards the realistic implementation will appear and pragmatic instances addressing challenges in the EU strategy for sustainable materials will be revealed, combining state-of-the-art knowledge and methodologies with novel approaches. Ultimately, the projects will collectively equip stakeholders with indispensable tools to be integrated in a wider SSbD implementation roadmap, which will eventually provide resolutions of nanosafety debates between academia, regulators and industry.

4 Appendix A –participants

5 Appendix B – questionnaire

Type	Potential answers	Examples
Q1	Which industrial sector is your project targeting?	
Multiple choice	Health	Nano-biosensors, smart drug delivery, medical implants, wearable systems, cosmetics, functional/medical textiles
	Digital and industry	Nano semiconductors, flexible electronics, microfluidics; thin-film silicon electronics, smart manufacturing machines and advanced sensing units, nanocomputing, multi-functional components for space industries including electronics, *etc.*
	Climate change/ energy/environment	Solar PV; catalysis, batteries & supercapacitors; hydrogen fuel cells, nanocrystalline magnetic materials for power electronics and nano-porous hydrogen storage materials, industrial chemical production processes, air/ water purification systems, nano-filtration
	Mobility	Engine components and batteries, embedded electronics and micro-sensors, carbon fibre moulds, chassis or hull components, composites for

(*Contd.*)

Type	Potential answers	Examples
		aircraft fuselage and wings, turbine parts, nano-coatings, nano-filtration, nano-additive/reinforcers *etc.*
	Secure society	Wearable and flexible electronics, portable biosensors for food safety and traceability of molecular biology; sensors for air quality control; lab-on-chip devices, cyber security and disaster resilience approaches, nano-enabled imaging systems *etc.*
	Agriculture	Nano-enabled pesticides/herbicides/biocides/veterinary medicines;/nutrients; nano-scale sensors for plants/soil/microbes/aquaculture/animals targeting both diseases and infestations; soil remediation; seed coatings, biodegradable coatings *etc.*
	Paint formulation	Nanoscale pigments, rheology modifiers, anti-clumping agents, resistance to weathering/light; anti-scratch properties; hydrophilic/hydrophobic/self-cleaning/self-healing properties; printing inks; additive manufacturing *etc.*
	Multisectoral	Military/defence/dual use *etc.*
	Other	—
Q2	Based on the JRC framework, which dimensions is your SSbD paradigm capturing?	
Multiple choice	Functionality	Design/molecular redesign, desired property optimisation
	Human health	Hazard assessment of the chemical/material (intrinsic properties); human health and safety aspects in the chemical/material production and processing phase; human health aspects in the final application phase
	Environmental safety	Ecotoxicology, environmental sustainability assessment. In the production and processing phase; end of life
	Social	Social sustainability assessment
	Economic	Economic sustainability assessment

(*Contd.*)

Q3	What is, according to your experience, the most important life cycle stage for SSbD interventions?	Q4	On a scale to 5 (5 being extremely confusing), how easy is the data management plan and FAIR process in your project?
Multiple choice	Synthesis/raw material	Singular choice	1 Really straightforward
	Production/Incorporation/		2 Somewhat straightforward
	Use		3 Neutral
	End of life		4 Somewhat confusing
			5 Extremely confusing
Q5	When would you consider useful/effective to make your data freely available?	Q6	How will your efforts be sustained in the near future? What is the business model for your tool/software/database?
Singular choice	Never	Multiple choice	Structural funding (*i.e.* central funding or contract from a research or infrastructure funder.)
	During project		Host institution funding (*i.e.* direct or indirect support from a host institution)
	1–2 years after project		Data deposit fees (*i.e.* in the form of annual contracts with depositing institutions or per-deposit fees)
	3–5 years after project		Access charges (*i.e.* charging for access to standard data or to value-added services and facilities)
	Not sure		Contract services (*i.e.* charges for contract services to other parties or for research contracts)
			Other (give details)
Q7	What are the top 3 missing scientific knowledge issues we should prioritise to progress SSbD?	Q8	How could we certify the achieved SSbD profile of a material/product/process? (pick one)
Pick at maximum three	Long term nanotoxicity at low dosages	Singular choice	With a detailed document (roadmap) based on the following guidelines outlining the methodology
	Realistic dosimetry for *in vitro* exposure and *in vivo* extrapolation		With a certificate of compliance to regulatory requirements
	Standardised measurements protocols for regulatory purposes		With a qualitative self-declaration form
	Regulatory acceptance of *in silico* modelling		Other
	An agreed data management, collection and curation framework	Q9	What is the most challenging part in your SSbD experience? (please)
	Life cycle analysis factors and environmental sustainability	Select the level of priority	Data finding, access, collection and use
	Quantitative criteria for a standardised implementation of the SSbD framework		The communication of information with all the SSbD related stakeholders
	Demo cases for realistic implementation of the SSbD		The quantification of the SSbD outcomes and their impact
	Other		The translation of the scientific SSbD assessment into a decision making framework
			Other
Q10	What goals would be disappointing to see failing in 5 years time?		

(*Contd.*)

Dual choice	The goal of industrial uptake of nanotechnology solutions The goal of standardising measurement methods across the SSbD framework The goal of identifying common criteria to address multicriteria decision problems The goal of increasing the trust and transparency between nanomanufacturing industry and academic SSbD decision framing results Other

6 Appendix C – questionnaire's results

Author contributions

Conceptualization: IF, AC, funding acquisition:: IF, AC, SVC, CFL, DH, JATR, SR, MC, SF, CR, EVJ, IL, SJA, methodology: IF, AC, supervision: AC, visualization: IF, MC, CR, writing – original draft: IF, writing – review & editing: AC, SVC, CFL, DH, JATR, SR, MC, SF, CR, EVJ, IL, SJA, LF.

Conflicts of interest

There are no conflicts to declare.

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