NanoImpact 25 (2022) 100385

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact

Safe(r) by design guidelines for the nanotechnology industry

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ARTICLE INFO

Editor: Bernd Nowack

Keywords:
Nanoparticles
Nanoform
Safer by design
Risk assessment
Life cycle assessment
Nano-enabled products
Nanoscience

ABSTRACT

Expectations for safer and sustainable chemicals and products are growing to comply with the United Nations and European strategies for sustainability. The application of Safe(r) by Design (SbD) in nanotechnology implies an iterative process where functionality, human health and safety, environmental and economic impact and cost are assessed and balanced as early as possible in the innovation process and updated at each step. The EU H2020 NanoReg2 project was the first European project to implement SbD in six companies handling and/or manufacturing nanomaterials (NMs) and nano-enabled products (NEP).

The results from this experience have been used to develop these guidelines on the practical application of SbD. The SbD approach foresees the identification, estimation, and reduction of human and environmental risks as early as possible in the development of a NM or NEP, and it is based on three pillars: (i) safer NMs and NEP; (ii) safer use and end of life and (iii) safer industrial production. The presented guidelines include a set of information and tools that will help deciding at each step of the innovation process whether to continue, apply SbD measures or carry out further tests to reduce uncertainty. It does not intend to be a prescriptive protocol where all suggested steps have to be followed to achieve a SbD NM/NEP or process. Rather, the guidelines are designed to identify risks at an early state and information to be considered to identify those risks. Each company adapts the approach to its specific needs and circumstances as company decisions influence the way forward.

1. Introduction

Designing safe and sustainable materials and products is at the top of the European chemical strategy for sustainability (EC, 2020). In the case of nanomaterials (NMs) and advanced materials, the rapid rate at which they are generated requires an agile process to effectively assess and design out the potential risk associated with those materials. The development of materials that are safe and sustainable from the beginning of the innovation process offers tremendous advantages, for example, lower uncertainty on the risks, higher ecological and economic

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https://doi.org/10.1016/j.impact.2022.100385
Received 4 October 2021; Received in revised form 24 January 2022; Accepted 24 January 2022
Available online 31 January 2022

value, increased stakeholder confidence and increased preparedness for future regulation.

The Horizon 2020 project "NanoReg2" (http://www.NanoReg2.eu/) defined SbD "as a process that aims at identifying, estimating and reducing uncertainties and risks for humans and the environment along the entire value chain, ideally starting at an early stage of the innovation process" (Soeteman-Hernandez et al., 2019). The three pillars underpinning the NanoReg2 SbD concept are:

Pillar 1: Safer materials and products by design: This refers to identifying less hazardous NMs for humans and the environment and designing nano-enabled products (NEPs) that, under normal and unforeseeable conditions, do not release free NMs (unless that is a requirement for their performance) to the environment and where the NMs can be recycled at the end of life.

Pillar 2: Safer use of products and end of life: This consists of evaluating the risks during all uses throughout the product lifecycle in order to optimize acceptable uses. Building on the first SbD pillar, when a product has been made as safe as is possible, this second pillar will facilitate an evaluation and determine any potential restrictions on the use of a specific NEP.

Pillar 3: Safer industrial production: This pillar aims to enable better control of the industrial processes along the production chain. The aim is to design processes that eliminate/reduce release of NMs to the workplace and outdoor environment, do not use hazardous chemicals, reduce NM-waste, do not pose a safety hazard (e.g. explosion) and optimize energy consumption.

This SbD concept was the outcome of the results of the FP7 project "NANoREG" (https://cordis.europa.eu/project/id/310584) and the H2020 project "Prosafe" (https://cordis.europa.eu/project/id/646325), refined and translated into practice within NanoReg2. It has recently been adopted as the basis of the description of SbD agreed by the OECD (OECD, 2020).

During the NanoReg2 project, this definition of SbD was adopted by six companies that implemented one or more of these aforementioned pillars. Overall the companies found value in the application of SbD. However, the implementation was challenging due to the different expertise required (e.g. material scientists, chemical engineers, human and environmental toxicologists, risk assessors) and the lack of data and tools available to estimate related potential risks. Results from the six case studies have been described in Sánchez Jiménez et al., 2020, Salieri et al., 2021 and Barruetabeña et al. (2020).

The hands-on guidelines are based on the experiences and the knowledge derived from these implementation activities of SbD in the NanoReg2 industrial case studies as well as the conceptual work carried out within the project and reported in Kraegeloh et al., 2018 Soeteman-Hernandez et al., 2019, Dekkers et al., 2020, Tavernaro et al., 2021 and Salieri et al., 2021.

A summary of this guidance has also been published by the OECD in a report that includes working descriptions of SbD and develops the concept of the "Safe Innovation Approach" (SIA) which combines SbD and regulatory preparedness (OECD, 2020).

All in all, the present guidelines are intended to be a practical approach that most industry innovators can follow. It has been developed and refined in collaboration between the production managers of the nanotechnology companies and the scientific experts on human and environmental hazard, occupational exposure, risk and life cycle assessment and socio-economic assessment in the NanoReg2 consortium.

These guidelines are not thought as a prescriptive protocol but as an approach that companies can adapt and incorporate to their innovation management systems.

2. Guidelines on the application of SbD in the nanotechnology sector

The hands-on guidelines propose an iterative implementation process that follows the stages of the Cooper Stage Gate Innovation Model (Cooper, 2008). The premise of this model is that innovation proceeds along a pathway with stage gates (i.e. decision points) as to whether to proceed, stop or adjust the innovation. For the nanotechnology innovation value chain, we adapted the stages to: business case (stage 1), business concept (stage 2), laboratory scale production (stage 3), pilot production (stage 4), and market entry (stage 5). Starting from stage 1, safety principles are applied throughout the development of the NM/NEP or process. As the project progresses and more information on the NM/NEP becomes available, more complete and comprehensive studies related to risk assessment (RA), life cycle assessment (LCA) and socio-economic impact assessment (SEA) can be carried out. Applying the SbD principle at later stages is still possible but may require a modification of the existing NM/NEP and/or processes to make it safer, which can (sometimes) be more costly than if applied at ealier stages. In addition, when a prototype is already available, a preliminary human and environmental RA may be required to identify and prioritize risks and decide on appropriate SbD measures.

Fig. 1 shows a flow chart of a typical SbD implementation process for a NM, starting from the point when the material is designed until its market entry. The boxes on the right hand side suggest a set of data to be considered for the risk and LCA. At each stage of the innovation process, risks, functionality and costs have to be considered and based on the RA and LCA results the company should decide whether to move to the next stage in the innovation process, stop the innovation, reduce the uncertainty by carrying out further tests or reduce the risk by modifying the properties/process linked to the risk concern. If a change is required and agreed, a (revised) SbD goal should be established and a SbD measure (method or procedure) agreed upon in order to achieve that goal. To decide on the most appropriate SbD measure, the impact of such measure on the NM/NEP functionality, the risks to human and the environment over the life cycle and the associated costs and benefits must be considered. For example, coating an NM to reduce dustiness or toxicity implies a new raw material, and a further step in the process, which may impact exposure to workers and/or the environment through the generation of more waste and higher energy consumption. As such, the consequences of such SbD measures might outweigh the hazard reduction. Therefore, the adequacy of any SbD measure should be evaluated prior to its implementation, through an integrated RA and LCA and put into context alongside its impact on functionality and cost.

In NanoReg 2 the term functionality was defined as "the quality of being useful, practical, and right for the purpose for which something is made. It is neither a property nor an application itself. It is rather the relationship between the properties and the practical use of a material in such a way that the use of the NM has a positive influence on a task or a potential application" (Tavernaro et al., 2021).

The risk uncertainly is likely to be high at very early stages (1 and 2) when there is no prototype yet, and the assessment is mainly based on literature data on the bulk materials or similar NMs/processes. However, the results may be used to design the needed assays for a risk and LC assessments to reduce the uncertainties in the subsequent stage (i.e. in stage 3). In the case of designing a NEP, where there might be already sufficient information on the candidate NMs, the uncertainty may be high related to the effects of interaction of the NMs with other components of the NEPs.

Across all stages, the aim is to achieve safer NMs (e.g., modifying the properties responsible for the hazard while preserving functionality), safer NEPs (e.g., by modifying the matrix, so there are no unwanted releases of the NM during use and the product is recyclable), and/or safer processes (e.g., by reducing waste and aerosol releases to the outdoor and workplace atmosphere). SbD can be applied at different technology readiness levels (TRLs) as illustrated in Fig. 1.

- TRL 1: basic principles observed.
- TRL 2: technology concept formulated.
- TRL 3: experimental proof of concept.

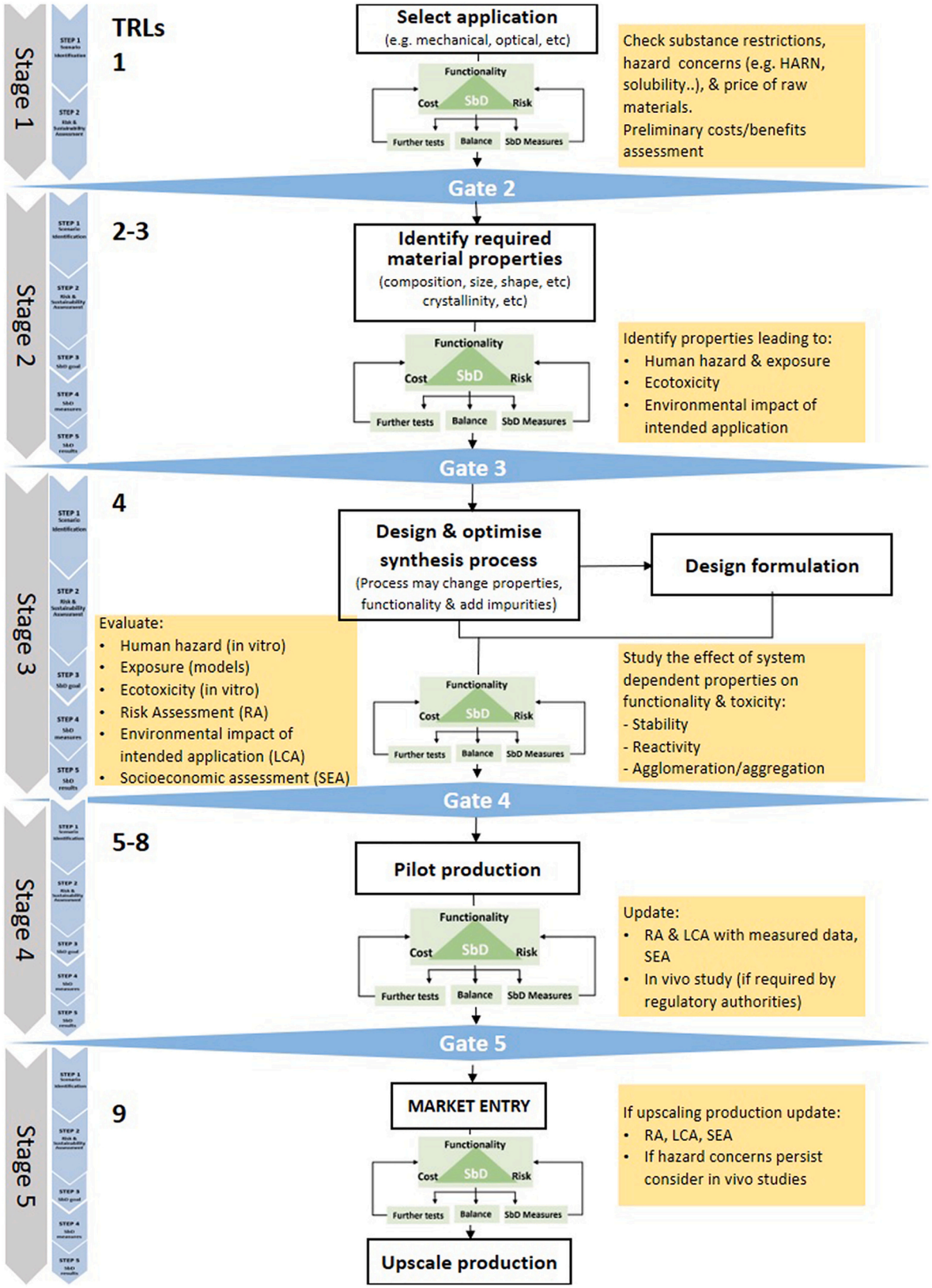

Fig. 1. Flow chart for implementation of SbD in the manufacturing of nanomaterials.
LCA: Life Cycle Assessment; TRLs: Technology Readiness Levels.

- TRL 4: technology validated in laboratory.
- TRL 5: technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies).
- TRL 6: technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies).
- TRL 7: system prototype demonstration in operational environment.
- TRL 8: system complete and qualified
- TRL9: system available for consumers

Fig. 2 shows a more detailed ilustration of the different steps that should be taken at each stage of the innomavation process to implement SbD.

2.1. STEP 1: Scenario identification

This step addresses the pillars of safe NM/NEPs, safe production and safe use and end of life, the desired functionality and the stage of the innovation process. The functionality desired for the NM/NEPs drives the context of the scenario, with due consideration of the current and potential regulatory framework that could be implemented in the future. This includes general regulations, such as REACH (Reg. EC No 1907/2006) or CLP (Reg. EC No 1272/2008) in the EU, but should also include sector or use specific regulatory frameworks that are applicable for a specific use of the NM or NEP, such as Novel Foods or Medical Devices.

Comprehensive knowledge of NMs is necessary, in order to establish correlations between intrinsic physicochemical characteristics, use-oriented properties, applications, and human and environmental hazard. Specific guidance on how to balance functionality and safety of NMs from the NanoReg2 project is reported in Tavernaro et al., 2021. Whilst pillar 1 looks at the functionality of the NM in the product, any SbD measure taken to improve the safety of the NEP during use (pillar 3) should assess the impact of such measure on the product performance.

In this step, it is very useful to apply the Gracious framework developed by Stone et al. (2020) for grouping of nanoforms. The framework develops a number of hypotheses that allow grouping and read-across of nanoforms, facilitating the incorporation of safety into the design of new nanoforms.

2.2. STEP 2: Risk and Sustainability evaluation along the life cycle

When the NM/NEP has been designed following the SbD principles from stage 1 and 2, it is usually known where the risks arise from, as information has been collected during the NM/NEP development and taken into account for the design of the prototype in stage 3. However, if the SbD considerations and implementation start later when a prototype is ready, (stage 3 and beyond) the type of risks might not be that clear. To identify the risks and prioritize where to focus the measures (human or environmental hazard, exposure or both) to achieve a safer NM/NEP, a full RA along the life cycle may then be necessary.

The hazard and exposure information required for the RA increases as product development moves along the stages because less uncertainty is allowed to pass to the next stage. There are a range of RA tools specific to NMs and these have been compiled in the NanoReg2 SIA Toolbox.[1] This includes 33 tools and leads the user to the selection of the most appropriate tools depending on the user's needs, the level of available information on the product being developed and the accessible resources at a user's disposal. Each tool has its limitations in terms of the assumptions made, the outcome (qualitative or quantitative) and the level of information required. Ongoing EU—funded projects (SAbyNA, ASINA, SABYDOMA, SbD4Nano) are working on further development of computational infrastructures for the implementation of SbD.

A LCA is proposed to ensure a life cycle perspective in the evaluation of all potential hazards. This goes beyond risks and benefits related to human and ecotoxicity by including, for example, energy efficiency, contribution to climate change or ozone depletion. The results from the LCA will help industry to evaluate whether all the benefits from such a nano application outweigh the related environmental impacts. LCA can be therefore seen as complementary to RA.

In addition, a Socio-Economic Assessment (SEA) is also proposed. SEA is a well-established method of weighing up the pros and cons of an action for society as a whole, and plays a vital role in the restrictions and authorisation processes under REACH. Restrictions proposals need to contain a description of the risks as well as information on the health and environmental benefits, the associated costs and other socio-economic impacts. Companies that apply for an authorisation to use substances in the ECHA Authorisation List may include a SEA as part of their application.

The combined application of RA, LCA and SEA within an integrative framework is described in more detail in Salieri et al., 2021.

Table 1 shows the type of data that can be collected at each stage of the innovation process to assess the risks, as well as the most suitable RA tools. Our criteria are based on the time and costs of the analysis in the various NanoReg2 case studies (Sánchez Jiménez et al., 2020). However, this is not a prescriptive list and the order presented along the different stages is indicative. The information collected at each stage depends on the decisions made by the company based on the results from the previous stage and the level of uncertainty allowed. For example, if at stage 2 there is a high concern with a specific physicochemical property (e.g. low solubility leading to bioaccumulation and persistence) the company may decide to perform some in vitro tests before moving to pilot production or change the specific physicochemical property to increase the solubility (as long as the NM functionality is not significantly affected).

- *Stage 1. A business idea is developed.* Basic information related to regulatory restrictions for chemical substances (e.g. banned or severely restricted substances or substances that required authorisation under REACH) should be gathered, for example, from the scientific literature or the ECHA website (chemicals subject to Prior Informed Consent Regulation (PIC, Reg. (EU) 649/2012) and REACH related information) for similar well documented substances. Other relevant legislationthat includes regulations related to the NEP (food, food contact materials, medical products, etc) should be referred to.
- *Stage 2. A business concept is created and the principles of the NM functionality demonstrated.* Information on the physicochemical properties that identify the NM are obtained from literature (similar NM or bulk form). At this stage, it is critical to bear in mind that the physicochemical properties determine the NM functionality and the potential toxicity and environmental impact. Uncertainty in the NM hazard is likely to be high at this stage due to the lack of experimental data on the product under development. To reduce the uncertainty, in silico modelling can be performed before moving to stage 3.

In addition, NMs properties may change during the life cycle depending on interactions with the surrounding environment, and therefore the hazard assessment should anticipate the impact from those changes.

Human exposure should also be considered, especially when the NM is identified as having a high hazard potential. In cases, where the NM application offers outstanding benefits and critical exposure can be safely controlled, the process can continue to the next stage, bearing in mind it might require authorization under national or regional legislation (e.g. REACH in the EU).

A risk banding or risk prioritization tool may be used for stages 1 and 2 where there is only information on the physicochemical properties and potential exposure scenarios. Examples of such tools are proposed in the SIA ToolBox and include NanoRiskCat, and the Swiss Precuationary Matrix (see suplementary material for further information on the SIA

[1] https://www.siatoolbox.com/tool

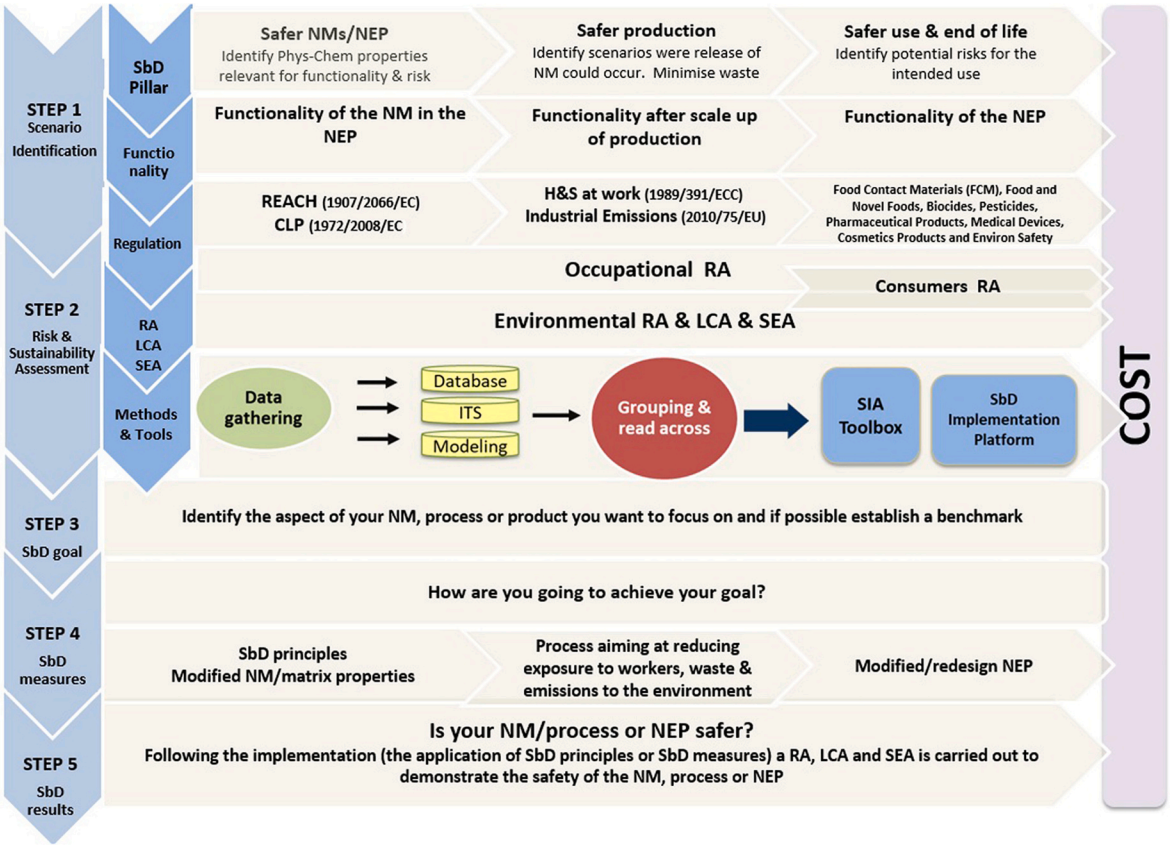

Fig. 2. Step-by-step processes for the implementation of SbD.
NEP: nano-enabled proudct; RA: Risk Assessment; LCA: Life Cycle Assessment; SEA: Socioeconomic Assessment; ITS: Intelligent Testing Strategy; SIA: Safe Innovation Approach.

tools). Another useful resource is the standard ISO/TS 12901-2 (Nanotechnologies — Occupational risk management applied to engineered nanomaterials —Use of the control banding approach (ISO, 2014)) for managing all the risks associated with occupational exposure, even if knowledge regarding their toxicity and quantitative exposure estimations is limited or lacking.

At this stage information is still too limited to perform a full LCA, but it is important to start considering potential impacts of the NM over the life cycle, even if it is in a qualitative or simplified basis, as well as regulation related to the industrial emissions to air, waste and water. For this purpose the LICARA nanoSCAN (also included in the SIA Toolbox) is useful.

- *Stage 3. Laboratory scale & production of prototype*. The synthesis method may impact the properties of the NM and therefore affect the desired performance and risk. Physicochemical properties should be measured and a screening toxicity assessment mainly based on in vitro experiments is recommended to evaluate the risk. However, it should be noted that the material properties may change during pilot production and therefore further testing will also be required.

Physical hazard data (explosivity and flammability index), biological effect (toxicity) data and conditions for safe exposure scenarios are also collected/produced at this stage. If the collected data shows concerning results and the NM property(s) responsible for such results are known, the company may consider to change those properties as long as functionality is not significantly affected, or if the uncertainty of the results is too large, they may consider further testing to reduce the uncertainty.

An alternative approach is to try to reduce the risk by reducing the likelihood of exposure and releases to the environment (e.g. changing the physical form of the formulation). However, the NM will still have to comply with toxicity regulatory requirements. In any case, within NanoReg2 the safety of the NEP was considered within the intended use (safer use, pillar 3) and pillar 1 (safer NMs and NEP). If the properties of concern are those that give the NM its functionality but the use is safe because there is no release along all the life cycle stages and therefore no exposure, then the product is considered safe.

At stage 3, as data on the production process are available, the application of Stoffenmanager-Nano[2] and/or NanoSafer[3] can help to identify Risk Management Measures (RMMs) for workers. Preliminary data on the energy consumption, emissions and waste flows will allow a preliminary (or simplified) LCA calculation to be undertaken.

The information on the environmental impact provided by such a (simplified) LCA can prove very useful when evaluating the benefits of using certain NM against human toxicity concerns.

- *Stage 4. A pilot line is developed for the industrial manufacturing of the NM/product*. Data on workers exposure concentrations for comparison with Benchmark/Occupational Exposure Limits and releases to the environment is collected. In this stage, all the information to comply with regulations should have been already gathered and the NM should present a low risk. If the risk is not acceptable SbD must be applied (STEP 3 of this guidance, 'Setting a SbD goal').

The LCA can be updated with measured data on releases and energy consumption in order to achieve a full LCA study, and the RA should also be updated with measured data on worker's exposure and more precise

[2] https://nano.stoffenmanager.com/
[3] http://www.nanosafer.org/

Table 1
Indicative list of information for the risk assessment and sustainable assessment per stage of the innovation process.

	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
	TRL 1	TRL 2–3	TRL 4	TRL 5–8	TRL 9
	Business idea	Business concept	Lab scale prototype	Pilot production	Market entry
Human hazard	• NM & product legal restrictions - REACH - CLP	• Identify Phys-Chem properties: - Composition - Solubility - Size - Surface Area - Shape - Crystallinity - Surface reactivity • Toxicity reported in scientific literature for selected NM or bulk form	• Measured phys-chem properties, impurities, dissolution rate. In vitro tests: - inflammation, - oxidative stress, - cytotoxicity, - genotoxicity & mutagenicity - ocular, skin irritation & sensitisation, dermal toxicity in case of dermal expousre route. • Biopersistency in body • Explosiveness • Flammability	• Air-liquid interfaces for lung toxicity • More complex in vitro experiments. • Consider In vivo experiments: (depending on the in vitro results: inhalation, genotoxicity, mutagenicity) • Reprotoxicity	• Health surveillance on workers
Human Exposure	• Intended use • Population exposed (children, health related groups). • Exposure route	• Intended formulation (powder, suspension, etc)	• Release/Exposure Scenarios (safe conditions of use using modelled or read-across approaches) • Process safety (risk of explosion, fire) • Form of release: agglomerates, embedded matrix etc. • Safe packing & transportation	• Measured workers exposure concentration for comparison with OELs • Modelled consumer exposure	• Periodic occupational exposure assessments • Quality Assessment of product to avoid unwanted releases to the environment
Ecotoxicity	• NM & product legislative restrictions - REACH - CLP • Ecotoxicological (potential accumulation/ persistency) information (e.g. basic information on potential ecotoxicity, read across data…) in scietific literature	• Additional Ecotoxicological information (more specific information on potential acute & chronic ecotoxicity, potential bioaccumulation)	• Growth inhibition in aquatic plants • In vitro tests using relevant cell lines: - cytotoxicity assays for metabolic activity, - membrane integrity, - lysosomal function • Biopersistency • Biodurability	• In vivo essential acute ecotoxicity tests: - Algae growth inhibition test - Daphnia acute immobilisation test - Fish acute toxicity test • Depending on the production volume: - Toxicity on fish development & growth - Bioaccumulation test	• Additional testing (i.e. acute and long term) in relation with upscaling the production: - Daphnia long term toxicity - Fish long term toxicity - Bioaccumulation (fish) • If not generated previously it could be necessary to obtain information about effects on development with fish embryo toxicity tests, or fish growth tests, etc.
Environmental release & fate	• NM & product legal restrictions	• Intended used • Potential waste • Release compartments • Environmental fate & pathways • Solubility in relevant media • Hydrophobicity • Dispersibility in relevant media	• Potential release rate to the environmental compartments (air, sediments, soils) • Release from product • Dissolution rate (i.e. marine water, freshwater etc)	• Measured release rates • Release form • Potential behaviour in the environment	• Periodic release assessments • Measured concentrations in the environment
LCA information	• Not action required	• LCI: values on estimated production chain are collected (material & energy input; waste & emission • Toxicological data from litterature e.g. ED50/ LC50 (on human & on thropic level of fish, crustaceans, algae) • LCIA: data on degradation process in environmental media EC	• LCI: values on lab scale production chain (material & energy input; waste &emission) • (eco)-Effect: EC50 values on at least two trophic levels (interim) • (eco) -Exposure = 1 (precautionary approach) • (human)-Effect: EC50 values from in vitro test or in vivo test (from RA based activity/ literature/ read across data). Interim Effect Factor is calculated	• LCI: update with values from pilot scale production • (eco)-Effect: EC50 values on three trophic level • (human)-EF: interim values on in vivo test (e.g. mouse) and in vitro (from literature/ read across data • Fate Factor water/air outdoor: USEtox4Nano • Fate Factor air: calculated according to USEtox and Walser et al. (2015) • (eco)-Exposure represent the bioavailable (free species) fraction of species 4 • (human) Exposure: indoor setting (USEtox)	• Update LCA with current production volume

(*continued on next page*)

Table 1 (*continued*)

	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
	TRL 1	TRL 2–3	TRL 4	TRL 5–8	TRL 9
	Business idea	Business concept	Lab scale prototype	Pilot production	Market entry
			• (human) Exposure: indoor/outdoor calculated in accordance with USEtox and Walser et al. (2015). • Fate Factor water = calculated according to simplified FF matrix (Salieri et al., 2015) • Fate Factor air indoor/ outdoor: calculated according to USEtox and Walser et al. (2015).		
SIAToolbox Suggested tools	LICARA nanoSCAN; NanoRiskCat; CB Nanotool; ANSES; SPM	LICARA nanoSCAN; NanoRiskCat; SPM; CB Nanotool; DREAM; ANSES; NanoFASE; SimpleBox4Nano; REACH HIA; CENARIOS® Risks management and monitoring system	LICARA nanoSCAN (updated data); NanoSafer; Stoffenmanager Nano; Lab scale LCA; SUNDS; GUIDEnano tool; ART; dART; MARINA RA Strategy; Nano solutions; ESIG-GES-EGRET; NanoFASE; SimpleBox4Nano; REACH HIA; CENARIOS®; Nano CRED	NanoSafer; SUNDS; Full scale LCA; GUIDEnano tool; ART; RiskofDerm; ECETOC TRA; FNN-BBN; ConsExpo Nano Tool; MARINA RA Strategy; SprayExpo model; BAMA indoor air model; NanoFASE; Nano solutions; AISE react; REACH HIA; Nano CRED	Australian guidance on regulation impact statement (RIS) cost-benefit analysis; Societal incubator; ECHA SEA for the analysis of Restrictions or Authorizations under REACH; Golden Egg Check; Lean Business Canvas, safety and society check.

TRL: Technology Readiness Levels; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals EU regulation; CLP Classification, Labelling and Packaging EU regulation: LCA: Life Cycle Assessment;SIA: Safe Innoavation Appraoch; OEL: Occupational Exposure LImites; EF: effect factor; HEF: human toxicological effect factors; EC50: Half maximal effective concentration;ED50:Half maximal effective dose;LD50: Lethal Dose 50%.

information about hazard.

At this stage a tool that provides a quantitative RA along the life cycle is more appropriate (such as e.g. GUIDEnano[4] tool or SUNDS[5]). The assessment should be carried out with measured data for the pilot production.

- *Stage 5. The product is in the market* and sufficient information has been collected to demonstrate the NM/product is safe and complies with current and likely future regulatory requirements.

The focus should be on monitoring workers' exposure and environmental releases. In case of planning an upscale of the production, the (full) LCA should be updated with the expected scaled up values prior to the increase in production.

Prior to industrial scale production, a SEA allows the understanding of the impact of the NM in society (human health and environmental benefits and costs) in comparison with its alternatives.

2.3. STEP 3: Setting up a SbD goal

This step refers to the purpose and the ambition of the company to achive SbD. The setting of the ambition is most often driven by the requirements within regulatory frameworks and policies which have been put in place by competent EU authorities (e.g. ECHA, EEA, EFSA) or national authorities (e.g. RIVM, ANSES, BAuA) (Shandilya et al., 2020). Based on the potential risks identified in step 2, the company should establish criteria that would mean a 'no-go' to the next stage of the innovation process. When the SbD implementation has not started at stage 1 and there is already a prototype, the focus will be on prioritizing the aspects which need to be changed or modified to increase the safety of the NM/product or process.

In terms of hazard to humans, the potential risk posed has to be justified by the societal benefits. For example, a hazardous NM used in batteries for electric vehicles can result in a reduction in greenhouse gases. Therefore, considering a possible negligible exposure to humans and the environment, if the battery is properly produced, used and recycled and workplace emissions are controlled, the use of such a NM could be justified.

2.4. STEP 4: SbD measures. How are you going to achieve your goal?

This step refers to the principles and methods followed to achieve the defined goal set in step 3.

2.4.1. Measures for Safer NMs

The methods will have to be tailored to the desired application as the required functionality has to be preserved. A rule of thumb is to minimize the use of well-known toxic elements like Cadmium or Chromium and instead use lower toxicity elements. Other methods involve changing the properties that have been linked with the biological and environmental effect. The design of the material should take careful consideration on the shape, size, and reactivity: surface charge andsurface chemistry. For this, there are computational approaches such as Quantitative Structure-Activity Relationships (QSAR) and more specifically Quantitative Nanostructure Activity Relationship (QNAR) models for the prediction of the biological and toxicological effects of NMs based on their properties. Significant advances have been developed in this area to reduce the need for experimental input and accelerate the toxicity assessment (Afantitis et al., 2018, 2020).

Some basic principles are:

- *Changing the oxidation state* to reduce surface reactivity or masking the reactivity by coating the NM as long as this does not affect the desired functionality. As a principle, catalyst residues and other impurities that can contribute to toxicity should be eliminated (e.g. Polycyclic Aromatic Hydrocarbons on carbon based NMs).
- *Decreasing the length of HARNs.* There is evidence of length-dependent toxicity since these long materials prevent complete

[4] http://www.guidenano.eu/
[5] https://sunds.gd/

ingestion by macrophages contributing to a build-up of the dose (Poland et al., 2008; Donaldson et al., 2010; Shi et al., 2011; Bianchi et al., 2020). The key length appeared to be between 15 and 20 μm, beyond which macrophages cannot stretch and enclose the fibre, eliciting frustrated phagocytosis (Donaldson et al., 2010). When performing toxicity testing, high energy sonication could lead to shortening of the fibres as observed in the NanoReg2 Group Antolin case study (Barruetabeña et al.), which could mislead the result: CNFs produced by the floating catalyst technique are highly entangled and aggregated due to this entanglement. High energy sonication or wet milling leads to fibre shortening, decreasing the size of the aggregates.

- *To reduce their biopersistence* high surface energy that leads to aggregation and higher solubility and dissolution rate is desired (Casals et al., 2012).
- *Agglomeration of the NM to reduce dustiness.* Nanomakers NanoReg2 case study successfully reduced the dustiness of silicon from 1163 mg/kg to 150 mg/kg by agglomerating the nanoparticles with a reversible process. Carbon coating of silicon also results in a decrease of their dustiness.
- Surface modification to prevent release of NPs from the matrix. Rosset et al., 2021 reported lower release of TiO_2 NPs from a oganic matrix based paint with photocatalytic activity, when the NPs were coated with biocompatible ligands or grafted onto cellulose nanocrystals. The coated NPs decreased the degradation of the binder and prevented the release of NPs.

These approaches can negatively impact functionality and therefore require careful consideration.

2.4.2. Measures for Safer processes and handling methods

A SbD process should consider not only the prevention of accidents and the optimization of process conditions but also the possible emissions of NMs to the workplace as well as to the environment (either as air emissions or solid or liquid waste). Consideration should be given to the entire production process line (synthesis, collection, purification, drying, packing, etc) and end of life (e.g. recycling). The concept is not new and has been previously refered to as "Prevention through design (PtD)" or intrinsic safety (Cowley et al., 2000; NIOSH, 2011).

The control of airborne emissions of NMs becomes more important than those from materials outside the nano-range due to the higher human and physical hazard. Some NMs may initiate catalytic reactions, which could lead to explosions that would not otherwise be anticipated based on their chemical composition (Pritchard, 2004). Carbonaceous and metallic NMs can have explosion classifications ranging from St0 to St3 (being St0 no explosion and St3 the highest level of explosion) (Vignes et al., 2019; Turkevich et al., 2015; Bouillard et al., 2010; Wu et al., 2010). Therefore, efforts should be put into the design of processes to prevent NM releases into the work environment in order to reduce the occurrence of accidental explosions or fires.

As previously discussed, in Europe there are several directives in place for managing health and safety at work (Dir. 89/391/EEC), industrial emissions (Dir. 2010/75/EU) and machinery safety (Dir.2006/42/EC). These directives establish a priority of risk management measures where the top is to eliminate the hazard, second to substitute the hazard, third to use technical measures/engineering controls, fourth the use of adminsitrative controls and as a last resort to protect the worker with personal protective equipment. However, the elimination of the risk at the source is usually challenging and not always possible and usually engineering controls to reduce exposure are applied instead of designs that eliminate the hazard.

The SbD measures will have to be tailored to the type of process or activity. As a general principle handling of NM in powdered form should be avoided. It is preferable to produce them and store them suspended in a liquid or bound to a solid matrix. When this is not achievable, enclosed systems with controlled ventilation should be used for handling.

Local exhaust ventilation systems to reduce exposure once there has already been an emission into the workplace are not strictly SbD as they do not prevent the emission, they act on the transmission from the source to the receptor. As such they are not discussed in this manuscript but information on these techniques can be found in, for example, NIOSH (2012, 2013).

Some SbD methods reported in previous studies include:

- *Wet synthesis of NMs*: For example, synthesis of graphene by mechanical exfoliation of graphite in water with water recirculation to reduce waste (NanoReg2 Avanzare case study, Sánchez Jiménez et al., 2020).
- *Avoid handling dry dusty powders.* Encapsulating powders in pellets, by embedding in suitable matrix, coating them to reduce dustiness (e.g. NanoReg2 Nanomakers case study, Sánchez Jiménez et al., 2020; Shandilya et al., 2019).
- *Granulation into micron-size agglomerates*, that can be re-dispersed into their original size, by using spray drying (Faure et al., 2010; Lindeløv and Wahlberg, 2011), spray freeze drying (Wassim et al., 2006; Raghupathy and Binner, 2012) or pelletizing/self-agglomeration (; Perrin and Oudart, 2017).
- *Optimize operating conditions* such as reaction temperature, pressure, solvents in order to reduce waste and fugitive releases. Optimization of the furnace reaction temperature in the production of carbon nanotubes (CNTs) by chemical vapour deposition resulted in a reduction of the release of CNTs in the furnace exhaust (Tsai et al., 2009).
- *Dip coating* or rolling are preferred to spraying.
- *Use high volume low pressure or airless spraying systems instead of conventional spraying* as they produce less overspray.
- *Use wet suppression techniques for machining processes* (Bello et al., 2009).

Some of these methods may have a negative impact from the point of view of the LCA, as they may increase the energy consumption, waste generation or may involve the use of additional raw materials (for example in the case of an additional coating). Therefore, before taking a decision on the SbD measures it is important to evaluate the human and environmental impacts by means of LCA.

The design of closed systems like automation and enclosures can be very efficient to isolate the NM and prevent exposures, especially when the NM is in a powdered aerosolisable form. However, the efficiency of the measures can differ from that attained with non-nano materials and therefore performance should be tested. The ECEL library (https://diamonds.tno.nl/#ecel) offers a searchable library of occupational and environmental Risk Management Measures including the effectiveness of exposure controls for nanospecific activities. Below there is a summary of techniques that have been reported in the literature (NIOSH, 2013).

- *Use automated systems to transport NMs and for collection* to minimize fugitive emissions and manual contact. Automated processes can considerably reduce emissions to the workplace, especially for vapour or aerosol phase synthesis techniques. However, this technique does not completely eliminate the problem as the NM have to be collected in a High Efficiency Particulate Air (HEPA) filter, HP14, before venting to a safe place outside the building.
- *Use ventilated enclosures for capturing emissions when handling NMs* (weighing, mixing or performing mechanical processes such as sanding, cutting, and sawing) or *when using small reactors or small devices* (e.g. lyophilizer, centrifuge, rotary evaporator, ball milling units etc). Enclosures include fume hoods, biological safety cabinets, and glove box/isolators. A low exhaust flowrate should be sufficient to maintain negative pressure in the enclosure and contain emissions. Enclosures for powder handling in pharmaceutical applications typically operate at an average face velocity between 65 and 85

ft per minute (NRC, 2011). The enclosures should be equipped with HEPA filters as stated above.

- *Large custom-fabricated enclosures or booths* (often constructed from a polycarbonate, transparent thermoplastic material) or vinyl curtains.

Table 2 highlights the main aspects to consider during the process design.

2.4.3. Measures for Safer products

Companies are responsible for the environmental and human impacts of their products. Under EU legislation products have to be safe under normal and reasonable abnormal conditions of use along their entire life cycle (Dir. 2001/95/EC).

The main SbD goals include preventing NM's release during use, improving the recyclability and safe degradation at the end of life. When NMs are embedded in a matrix, the release will depend on the forces affecting the NM-matrix bond: Van der Waals, ionic, coordination and/or covalent bonding (Hsu et al., 2015). Several mechanisms have been described for NM release from NEP: passive diffusion, dissolution, and desorption of the added NMs into liquid media (Duncan and Pillai, 2015); and matrix degradation including photo-degradation, thermal decomposition, mechanical treatment, and hydrolysis (Duncan, 2015).

Dissolution of the NM under ionic form can be prevented, for example, by coating the NM, whilst preserving its functionality. ZnO kept their functionality when coated with a nanothin layer of amorphous silica (Sotiriou et al., 2014). Or when the functionality is based on the release of ions, developed a method where such release is minimal as in Gardini et al., 2018 or in the NanoReg2 nanoComposix case study, where a silver antibacterial coating was developed (Sánchez Jiménez et al., 2020). The release of NM should be fully characterized (particle and ionic species) and when the product replaces another technology, their benefits should be considered in the framework of an LCA.

2.5. STEP 5: Cost and benefits of SbD

The cost is a critical aspect that needs to be assessed during the whole process, because it will impact directly on the potential industrialization and in the market penetration, these being the final aims of the industrial development. In order to implement the SbD it is necessary to consider three primary and critical costs on top of the costs associated with non-SbD NMs (Table 3):

1. *Costs related to the SbD of the NM/product.* SbD requires the expertise of a suitably qualified human and eco toxicologist in the design phase that may not be directly available within each company. Once the physicochemical characteristics required for the use-oriented properties (e.g. optical, mechanical performance, etc) have been defined, the correlation of those properties and the biological effects should be assessed considering the potential changes of the properties along the life-cycle of the NM.
2. *Cost of the SbD RA as compared to a regulatory RA.* In EU, for those NMs where a chemical safety assessment is required by REACH the cost will be similar. The main difference is that on SbD the testing is carried out earlier in the innovation process.
3. *Cost of the SbD production process in comparison with the non-SbD scenario*. The design of the production process has to take into account safety aspects specific to the presence of NMs. Automation may be given special consideration to prevent releases given the high explosivity index of some NMs and the hazard potential for workers. Initially this can have an increased initial cost but bring about reductions in the long-term. For example, automation can be more cost effective than relying on exhaust ventilation, which requires high energy consumption.

Table 2
Summary of considerations to take into account during the process design.

STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
TRL 1	TRL 2–3	TRL 4	TRL 5–8	TRL 9
Business idea	Business concept	Lab scale prototype prod.	Pilot production	Market entry
Consider the fire & explosion potential when designing the NM.	Optimize operating conditions to reduce waste & emissions as well as fire & explosion potential.	Plan SbD measures for all process steps base on results from RA: - collection & handling - accidental spillage - cleaning & maintenance LCA including impact of SbD measures.	Optimize operating conditions for upscaling Check planned SbD measures work effectively at larger scales.	Monitor implemented measures.

Table 3
Aspects to consider when estimating the costs and benefits of SbD.

	Aspects related to the cost		Aspects related to the benefits
	Conventional Innovation	SbD Innovation	
Design NM	Define required functionality & select synthesis methodology	Define required functionality & select synthesis methodology linked with the toxicity & environmental impacts. (An external expert may be required)	New market opportunities Longer market presence Possible reduction in insurance costs. Better ability to address customers safety concerns of using SbD NMs in their products
Production	Materials, equipment, energy, personnel, maintenance, waste treatment. Process safety as required by current legislation	As in Conventional Innovation & might require: - Extra production steps. - Automation.	Lower cost due to reduced waste. Lower cost due to reduced energy consumption Better compliance with Health and Safety regulations due to lower exposures.
RA	In EU depends on tonnage of NM produced (ECHA) & regulatory body for the NEP	Screening RA is independent of tonnage.	Certain testing might not be required as the NM is safer compared to the non SbD NM.

However, these additional costs are balanced with the benefits that arise by applying the SbD measures. Some of these benefits include:

- Minimisation of waste leading to savings on waste management and loss of NMs.
- Wider acceptability and use of the NM in wider applications as the NM is safer.
- Fewer changes are required if regulation becomes stricter.
- Less losses of material because of more efficient processes.
- Fewer recalls once the product is on the market because safety aspects have already been considered in the design.

The H2020 projects SAbyNA, ASINA and SbD4nano are working on the implementation of a systematic cost benefit analysis within the SbD strategy.

2.6. STEP 6: Data integration

The last step before making a decision on the SbD measure is to evaluate the impact of such measure on the risk to humans and the sustainability of the nano-enabled product. At early stages, a qualitative RA together with a simplified LCA have been proposed. A full LCA can be performed at later stage when higher quantities of data are available (i.e. pilot plant). Notable, SEA can only be performed at later stages when robust data have been generated (i.e. quantitative RA and LCA, as well as economic data). An integrated approach combining RA, LCA and SEA is reported in more detail in Salieri et al., 2021. Overall, such an approach aims to guide industry to perform both the safety and the sustainability evaluation alongside such development processes.

3. Discussion

The potential emerging risks from new technology have to be dealt with at an early stage for successful risk management and a profitable R&D investment. This is especially true for the multitude of NMs/NEPs continuously being delivered into the market.

Appropriate decision-making frameworks and suitable testing have to be done in accordance with the present uncertainties. To deal with the risk posed by NMs and to implement the most appropriate SbD measures to reduce those risks, a life cycle perspective has to be taken into account. Research innovations cannot be directly applied to materials or pilot lines without a previous assessment of the overall human and environmental impact and associated costs.

We propose here a guideline for the implementation of SbD that includes a functionality, human and environmental risk assessment and a cost-benefit analysis. The implementation of SbD has to be flexible. The process is not linear but iterative and if the desired reduction of risk is not achieved after applying the most appropriate SbD measure the cycle must start again. The challenge is to account for all the possible risks of the NM and NEP along their lifecycle, and design out the risk whilst preserving the functionality. This should be common practice on the design of industrial processes and machinery as it is required under the EU machinery directive (2006/42/EC) and the design of products directive (2001/95/EC). However, the approaches should account for the specific risks posed by NMs.

Designing out the hazard of chemicals whilst preserving their functionality is more novel and requires knowledge of the relationship between the physicochemical properties, the use-oriented properties and the hazard (Kraegeloh et al., 2018). The NanoReg2 SbD concept advocates that safety should be considered as an integral part of the design process (together with functionality and costs), rather than at a later and well advanced design stage.

Each scenario presents particular challenges since NMs can vary in multiple physico-chemical characteristics that can affect hazard and there are a wide range of industrial methods than can have different environmental impacts. SbD therefore faces multitude of challenges, from practical implementation to unrealistic risk reduction expectations. These challenges have to be dealt with the current knowledge at the time. In this regard there are several projects working on intelligent hazard testing strategies (PATROLS, NanoSolveIT, HARMLESS), grouping strategies and read-across to reduce the exposure and hazard testing of every nanoform (GRACIOUS), advanced tools (NanoInformaTIX, SAbyNA, ASINA, SABYDOMA, SbD4Nano, Diagonal) and data sharing platforms (NanoCommons, e-nanomapper) under the FAIR principles (Findable, Accesible, Interoperable, Reusable), that will further prove the SbD concept including nanostructured materials, and will help to streamline the implementation.

In these guidelines we have dealt with some aspects of environmental sustainability (in relation to LCA and SEA). However, the new recommendations from UN on sustainable and circular economy (UN, 2019) and the EU strategy on sustainable chemicals (EU, 2020) demands economic and social sustainability to be included in the assessment. In this regard, the OECD Working Party on MMNs which already published a report on the SIA is currently working in another report to bring sustainability into SIA.

A remaining issue is how safe a NM, NEP or process has to be so it can be labelled 'SbD'. Some companies argued that their investment in SbD could leave them at a disadvantage without a clear measurement and labelling system being adopted. Such a system should include metrics not only to measure the risk of the NM, NEP and process to human health and the environment but also sustainability aspects like societal and economic and other environmental impacts not considered in the LCA in a multi-criteria decision analysis model as, for example, that proposed by Subramanian et al., 2014.

This guidance does not intend to be a prescriptive protocol where all suggested steps have to be followed to achieve a SbD NM/NEP or process. Rather, the manuscript is intended to identify steps and information to be considered, with each company adapting the approach to its specific circumstances as well as their innovation needs, as company decisions influence the way forward.

4. Conclusion

There is still not standardized definition of SbD. The NanoReg2 concept aimed at identifying, estimating, and reducing uncertainties and risks for humans and the environment along the entire value chain, ideally starting at the earliest stage of the innovation process.

This guidance provides a step by step approach to implement SbD and includes risk, functionality and cost considerations. However, it can only be taken as initial guidelines that have to be tailored to each company specific situation.

The approach and the tools described need to be streamlined in order to be applied cost efficiently in industry.

Author contributions

Araceli Sánchez Jiménez; conceptualisation, methodology, investigation, writing – original draft and review & editing to incorporate co-authors contribution, work package supervision.

Raquel Puelles, Marta Perez-Fernandez and Julio Gomez-Cordon: methodology, investigation, writing original manuscript. Writing – review & editing. Supervision of SbD implementation in Avanzare.

Leire Barruetabeña writing – review & editing of the parts on LCA and the information needed to carry out the LCA.

Nicklas Raun Jacobsen, conceptualisation, methodology, investigation, writing – review & editing of the parts related to human hazard and toxicity assays.

Blanca Suarez-Merino, Roland Hischier and Christian Micheletti, conceptualisation of SbD. Review & editing.

Nicolas Manier, conceptualisation, methodology, investigation, writing – review & editing of the parts related to ecotoxicity.

Beatrice Salieri conceptualisation, methodology, investigation, writing – review & editing of the parts related to the integration of the RA, LCA and SEA data.

Rositsa Tsekovska' Yordan Handzhiyski, and Margarita D. Apostolova: conceptualisation, methodology, investigation, writing – review & editing of the parts related to human hazard and toxicity assays.

Jacques Bouillard, conceptualisation, methodology, investigation, writing – review & editing of the manuscript. Funding acquisition.

Yohan Oudart, conceptualisation, methodology, investigation, writing – review & editing of the parts related to the SEA. Responsible of the SbD implementation in Nanomakers.

Karen S. Galea, conceptualisation, methodology, investigation, writing – review & editing of full manuscript.

Sean Kelly, conceptualisation, methodology, investigation, writing – review & editing.

Neeraj Shandilya and Henk Goede, review & editing of full manuscript. Writers of the supplementary material.

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Isabel Rodríguez Llopis, conceptualisation, methodology, investigation, writing – review & editing of the full manuscript.

Disclaimer

The contents, including any opinions and/or conclusions expressed of this manuscript, are those of the authors alone and do not necessarily reflect the opinions or policy of the organisations to which they are employed.

Declaration of Competing Interest

All companies that participated in the study commercialised NMs. GAIKER and INERIS have worked as consultants for Grupo Antolin and Nanomakers, respectively. GAIKER and Safenano (IOM) have worked as consultants for Avanzare.

Acknowledgements

This work was performed within the EU project NanoReg2, funded by the Horizon 2020 Framework Programme of the European Union under Grant Agreement Number 646221. We gratefully acknowledge the contributions of all the industrial partners and the entire NanoReg2 consortium for their continuous support and advice on the case studies. NRJ and KAJ also received funding from FFIKA, Focused Research Effort on Chemicals in the Working Environment, from the Danish Government.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.impact.2022.100385.

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