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Project Partners: 1. LEITAT 2. IOM 3. CEA 4. TECNALIA 5. UKCEH 6. CNRS 7. RIVM 8. GAIKER 9. FIOH 10. ISTEC 11. THINKWORKS 12. ALLIOS 13. LATI 14. NOURYON 15. SYMLOG 16. DUKE UNIVERSITY	**SAbyNA** H2020-NMBP-15-2020 Simple, robust and cost-effective approaches to guide industry in the development of safer nanomaterials and nano-enabled products Start date of the project: 01/03/2020 Duration 48 months # WP6 D6.1 – Scope, expected workflow, and overall structure of the SAbyNA Guidance Platform

WP	6	SAbyNA Guidance Platform for risk management at early stages of NFs/NEPs development process		
Dissemination level[1]	PU		Due delivery date	30/11/20
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[1] Dissemination level: **PU** = Public, **PP** = Restricted to other programme participants (including the JU), **RE** = Restricted to a group specified by the consortium (including the JU), **CO** = Confidential, only for members of the consortium (including the JU)

[2] Nature of the deliverable: **R** = Report, **P** = Prototype, **D** = Demonstrator, **O** = Other

Lead beneficiary	LEITAT
Contributing beneficiaries	WP6 partners

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Table of Content

0. Abbreviations

CB	Control Banding
CLP	Classification, Labelling and Packaging
CNT	Carbon nanotube
CO_2	Carbon dioxide
DoW	Description of Work
ECEL	Exposure Control Efficacy Library
ECHA	European Chemical Agency
ENM	Engineered Nanomaterial
HARN	High Aspect Ratio Nanomaterial
IATA	Integrate Approaches for Testing and Assessment
ISO	International Standardization Organization
LCA	Life Cycle Assessment
NEA	Nano-Enabled Article
NEP	Nano-Enabled Product
NEM	Nano-Enabled Material
NF	Nanoform
NMBP	Nanotechnologies, Advanced Materials, Biotechnology, and Advanced Manufacturing and Processing
NP	Nanoparticle
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PBPK	Physiologically-Based Pharmacokinetic
PPE	Personal Protection Equipment
QSAR	Quantitative Structure-Activity Relationship
RA	Risk Assessment
RCR	Risk Characterization Ratio
RMM	Risk Mitigation Measure
SbD	Safer by Design
SIA	Safe Innovation Approach
SME	Small and Medium Enterprise
SOP	Standard Operation Procedure
SWAP	Safety Warnings – Alternative proposed
WP	Work Package

1. Introduction

The Description of Work (DoW) included a preliminary description of the scope of the SAbyNA Guidance Platform (Section 2). The first months of the project have been dedicated to refine the scope of the SAbyNA Guidance Platform and structuring its expected workflow (Section 3). Several working groups have been created that started to develop some of the key elements of this platform, which facilitates moving away from abstract discussions and helps understanding the implications of different potential workflows. In addition, three existing industrial case studies of Safe-by-design (SbD) implementation for nanomaterials were analysed with the preliminary SAbyNA Guidance platform workflow in mind, and lessons derived from this analysis were used to refine the Platform (Section 4).

Understanding the context in which the SAbyNA Guidance Platform will exist at the end of the project is critical. The expected scenario at the end of the SAbyNA project is presented by compiling information on the scope of other available platforms/portals for SbD and risk assessment of nanomaterials (Section 5). Finally, next steps foreseen in the development of the SAbyNA Guidance Platform are described (Section 6).

2. SAbyNA Guidance Platform as described in the DoW

The guidance will:

1. Facilitate industry in choosing the optimal pathway to identify risks and the appropriate strategies to reduce or mitigate those risks.
2. Provide customized guidance for SbD implementation in different industrial sectors in their innovation models.
3. Provide resources to support industry balancing safety with technical functionality and overall life cycle costs.
4. Be based mostly on existing approaches and resources, with optimized usability for SbD purposes provided by WP2, WP3, WP4 and WP5.
5. Allow integrating future developments from other nanosafety projects and relevant initiatives.
6. Be compatible with NFs and NEPs of various complexities.
7. Demonstrate the benefits of sector-specific enhanced functionalities, by implementing such sector-specific solutions for two industrial sectors: paints and 3D Printing.

Multiple resources will be embedded in the SAbyNA Guidance. Those resources will include existing RA tools such as those evaluated under the caLIBRAte project for their utility along the innovation chain of NFs and NEPs.

[…]

Within SAbyNA, WP6 will develop sector-specific tailored versions of the GUIDEnano tool, consolidating this European nanosafety investment, extending its current SbD functionalities and incorporating new sector-specific default parameters and a user-friendly, streamlined data input process. Hence, the usability for early stages of development will be increased. Paints and 3D printing sector-specific GUIDEnano modules will be developed as proof of concept to demonstrate the value of the approach. Additionally, the lessons learnt from those modules development will allow future efficient development of other sector-specific GUIDEnano modules.

[…]

It is foreseen that the SAbyNA's SbD guidance Platform will include different SbD strategies depending on multiple variables and will direct the user to select the best SbD strategy in each particular case. Some examples of variables that will be taken into account are:

1. The stage of the product development process where SbD is considered.
2. The type of NF and its applications, which may imply different emission and exposure routes through the life cycle, needing different risk and environmental impact assessment approaches.

3. The type and level of detail of information on the materials, products and production processes that industry provides.
4. Constraints in terms of functionality and costs.
5. The extent to which alignment with regulatory required RA information is needed.

[…]

The SAbyNA guidance will be developed into an interactive web-based platform, which will guide the user into the relevant resources, accessible through links, and with any supporting documentation needed. The guidance will build upon the work carried out in the OECD project Moving Towards a 'Safer Innovation Approach' for More Sustainable NFs and NEPs: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations.

[…]

1. Positioning of the resource maps delivered by WP2, WP3, WP4, WP5 and WP6 into the SbD structural diagram (including support in the risk assessment and risk management, technical functionality prediction/testing, cost estimation, and overall environmental sustainability). Such resources are foreseen to include:
   - Quick-scan / checklists to support industry in quickly identifying the main aspects for concern in relation to their use of NFs, and alert them on the need for a more detailed assessment, and the most suitable scope for it.
   - Generic SbD support tools (Risk Assessment, LCA, cost evaluation): e.g. GUIDEnano, Nanosafer, Stoffenmanager nano, Swiss Precautionary Matrix, simplified LCA and cost analysis (developed in WP6)
   - Databases such as eNanomapper and NIKC for NF data, GUIDEnano exposure scenarios database, and efficiency and costs of exposure control equipment and PPEs building existing databases, such as ECEL or those embedded in GUIDEnano
   - Testing and non-testing predictive methods to generate input data for the SbD support tools. In addition to the test methods, links to available standards or SOPs will be provided, as well as links to guidance on the interpretation of results and their alignment to expect input parameters in different tools, and lists of potential testing service providers, and order of magnitude costs.
2. Definition and identification of pathways and decision flows to be followed for different SbD purposes (e.g. reduction of hazard or exposure, release to the environment). Hierarchies for overarching generic SbD support tools will be established based on the checklists and the purpose of the assessment (e.g. stage of product development, industrial sector, life cycle stages use of the NEP, occupational, consumer, and/or environmental risk domains…). These will be linked to the specific supporting resources to obtain the required data/information
3. Inclusion of a series of case studies, general approaches and main lessons learnt in each of them derived from previous EU and national projects that will provide the potential user with examples on how to use the guidance.

3. Refined scope, structure and workflow of the SAbyNA Guidance Platform

3.1 Basic scope and structure of the SAbyNA Guidance Platform

The SAbyNA Guidance platform is envisaged to consist of two parts. As illustrated in Figure 1, the first part will mainly consist of checklists and multiple-choice options that will collect a series of basic information on user needs and the specific case to:

1) Allow defining the scope of what the user intends to achieve with the assessment (e.g., comparing hazard profile of two NFs or designing a SbD production process).
2) Define what will be the most adequate workflow in Part 2.

3) Identify early in the process some main aspects for concern that can be associated with safety recommendations.

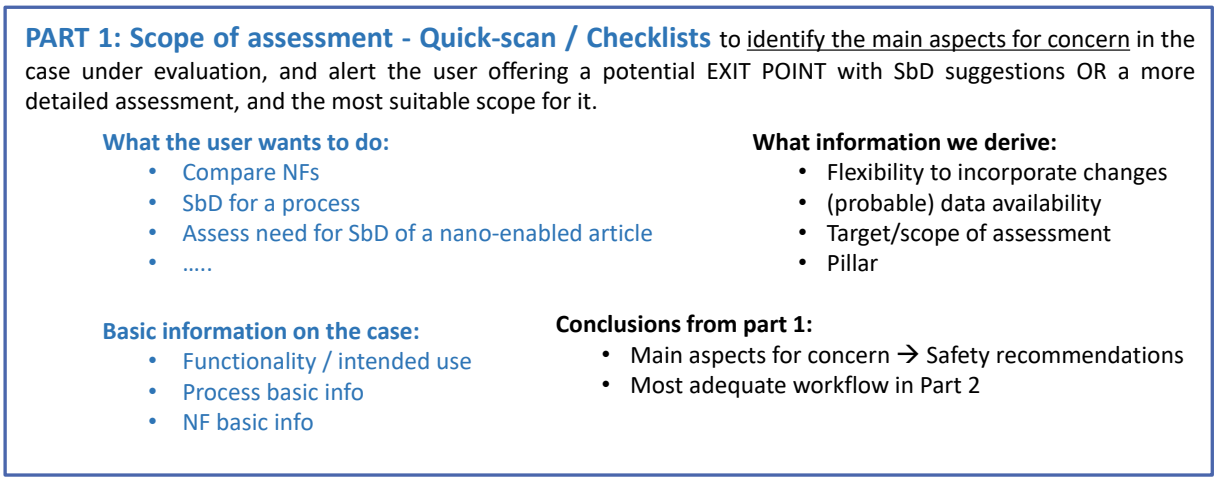

Figure 1. Overview of Part 1 of the SAbyNA Guidance Platform

It is foreseen that Part 1 will include questions to define the type of user needs and basic information on the actual case. From this information, the target and scope of the assessment will be derived (including 'the pillar', as in nomenclature used in Nanoreg 2), the likelihood of data available, and the potential flexibility to incorporate changes at different levels. During the collection of basic information on the case, if clear aspects for concern are identified, these will lead to safety recommendations for the user (see preliminary flow in Figure 2). Independently of whether such concerns are or not identified, all this collected information will allow defining the most adequate workflow in Part 2.

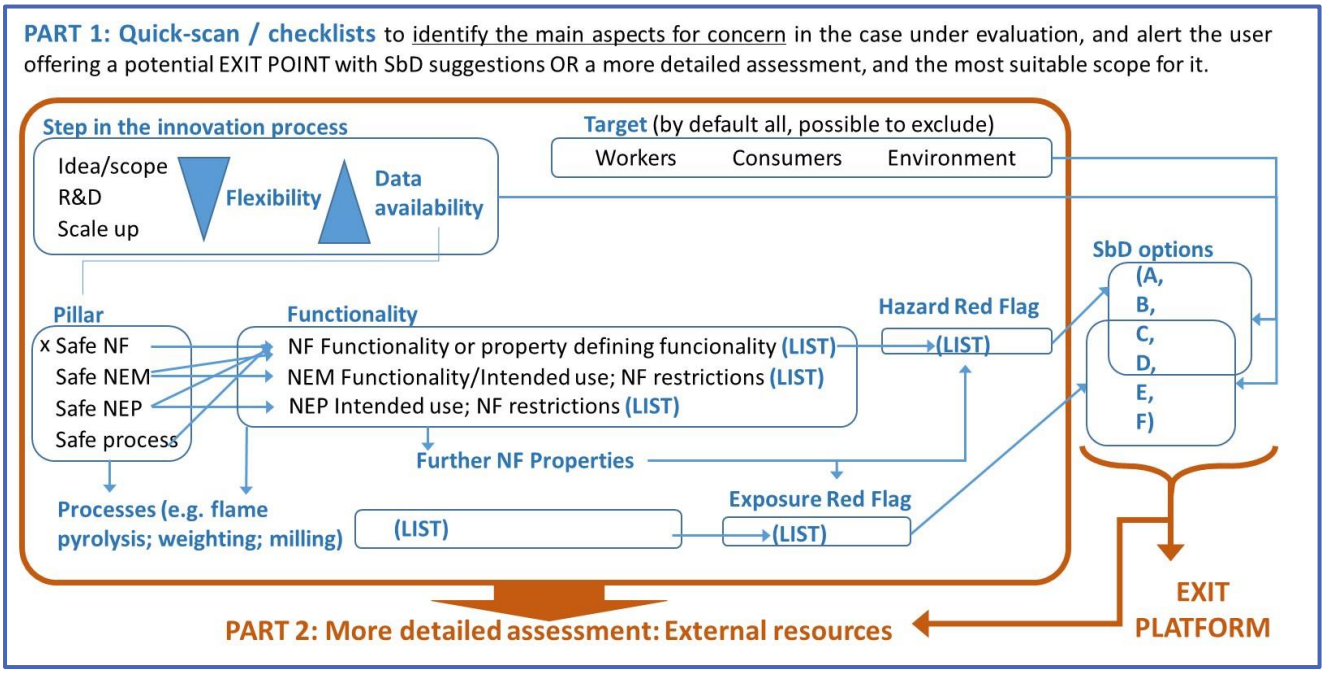

Figure 2. Overview of preliminary flow in Part 1 of the SAbyNA Guidance Platform

The second part of the SAbyNA Guidance Platform, will define suitable workflows that will fit the different predefined categories of users' needs, and take also into consideration the specifics of each case study (Figure 3). For example, in terms of data availability, type of NF or NEP, type of process, etc. Risks, technical functionality, costs, overall benefits, and sustainability are aspects that may deserve consideration within Part 2, depending on the user priorities. Part 2 will suggest a workflow which will include guidance on when/how to use different types of external resources. Part 2 will also include the library of categorized SbD strategies from which relevant resources will be presented to the user depending on the case under assessment.

With regards to risk evaluation, it is envisaged that control banding and risk assessment tools will be central in the workflows, with connections to supporting guidance documents, standards, SOPs, and testing strategies to generate input data requested by such tools, including as well connections to databases (and guidance on how to extract relevant data from them).

Building the decision logic for choosing different workflows for part 2 will be one of the main activities of WP6 in the coming period. In parallel to this process, all resources considered to become part of the SAbyNA platform will be categorized in terms of their applicability, data needs, etc, so that their relative suitability for a given case can be concluded.

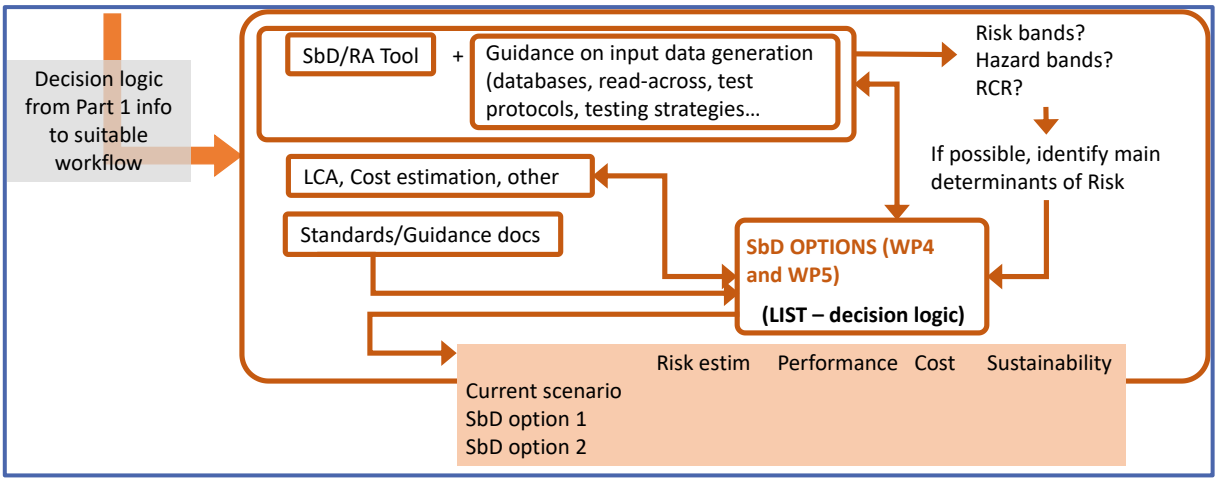

Figure 3. Overview of Part 2 of the SAbyNA Guidance Platform

3.2 Further development of some of the elements of the SAbyNA Guidance Platform

Due to the multidisciplinary nature of the project and diversity in background of the different partners, working groups were created to address specific needs during the development of the SAbyNA Guidance Platform. These working groups are:

A) Identification of safety warnings – alternatives to be proposed

Already during the first part of the SAbyNA Guidance platform, some basic information on the case will be needed, including information on the NFs or the NF-enabled products (which may be NF-enabled materials or NF-enabled articles). We initiated a compilation of clear safety warnings that can be identified based on such basic information and have related them with safety recommendations. In this way, a user would not need to complete a full assessment in order to receive early indications on potential opportunities for SbD. It would be up to the user to continue or not the assessment following this stage. Note that there are several other parameters that are key determinants of fate and hazard of nanoforms (e.g., dissolution rate and attachment

coefficient), which do not appear in this table of early safety warnings. We consider that despite these parameters are key in the risk assessment of NFs (and will as such be definitely considered in Part 2 of the SAbyNA platform), they are by themselves not intrinsic reasons of concern. Their impact on hazard will depend on the actual composition of the material and hazard endpoint (in the case of dissolution rate), and on the environmental compartment under evaluation (in the case of attachment efficiency).

The current list of safety warnings – alternatives proposed (SWAP) is presented in Table 1.

Table 1. Preliminary list of Safety warnings – alternatives proposed (SWAP)

Safety warning	Alternative proposed (as long as compatible with required functionality)
HARN	Reduce fiber length or reduce rigidity or durability. Process related to reduction in exposure.
CLP or low OEL of NF/ constituents/ bulk	Substitute to less hazardous materials. Coat to reduce bioavailability. Process related to reduction in exposure.
High-dustiness	Reduce dustiness by generation of stable aggregates Avoid manipulation of powders: consider the possibility to use masterbatches or liquid dispersions.
Based on specific functionalities that either relate to reactivity of materials (e.g., redox potential) or to release of toxic ions (or any other property of concern)	Only if there are ways to preserve functionality while reducing hazard.
Very small sized NFs (<5 or 10 nm??)	Consider use of stable aggregates, temporary coatings, or larger size NFs.

B) Definition of functionalities to be considered

Nanoforms may be used to achieve different type of technical functionalities within a nano-enabled material of a NEP. Identifying which physicochemical properties of the nanoform are key for the technical performance and how they relate to the hazard/release profile is important to guide adequate safe by design strategies for each case. For example, some nanomaterials are used as antimicrobial agents based on their sustained release of ions that are toxic to microorganisms, but sometimes are also toxic to other environmental organisms or humans. Modifications to reduce their toxicity based on the modulation of such ion release, will also reduce their technical functionality, and other type of SbD strategies may be more adequate.

To collect and structure this information, a preliminary template table has been generated, containing already several examples. The fields included in this template are presented in Table 2. This template will be refined and the entries to the table will be extended in the coming months.

Table 2. Definition of technical functionalities in relation to NF properties and consequent hazard/release characteristics

Intended USE of the nano-enabled product
Nano-enabled product
Nanoform
Technical functions of NF in a process/product/article
Constituent(s) of nanoform
Role of constituent(s) of nanoform

Technical functions of constituent(s) in the nanoform
Phys. Chem. properties of constituents conferring the technical functions to the nanoform
Specific Phys. Chem. properties of constituents conferring the technical functions to the nanoform
Reason(s) why the specific Phys. Chem. properties of constituents are needed in the nano-enabled product
Phys. Chem. properties of nanoform related to hazard/exposure/release/fate that play a role under the intended use of nano-enabled product
Mechanism of hazard/exposure/release/fate of nanoform
Possible design features to mitigate hazard/exposure/release/fate of nanoform

C) List of activities

Selecting among predefined activities, each of them with associated information on potential NP release, is considered a very useful way to rapidly define the scope of the assessment. To start with, we have created lists of activities that are relevant to the industrial sectors in which SAbyNA focuses on. The ambition is to attribute different release potentials to each of these different activities and, when release strongly depends on additional key parameters, define them already at this early step.

Table 3. Additive manufacturing activities from WP7

Process	Activity	Release potential, Key release determinant factors
Filament production	Weighing	Potential for release. Key release factors include if manual or automated process, dustiness of powder, particle size
	Mixing	Potential for release. Key release factors include if manual or automated process, dustiness of powder, particle size
	Extrusion	Possible potential for release. Key release factor is agglomeration
Pre-processing	Powder filling	High potential for release. Key release factors include use of metal powders, cleaning printer heads/nozzles and heating nozzles
	Resin filling	
	Sieving	
AM	Multi Jet Fusion (MJF)	Potential for release of nanoparticles and VOCs during additive manufacture. Key release factors include filament composition and temperature
	Stereolithography (SLA)	
	Digital Light Processing (DLP)	
	Fused Deposition Modelling (FDM)	
	Selective Laser Melting (SLM)	
	Other	
Post-processing	Part cutting	Potential for release. Key release factors can include feedstock (filament) composition and nanomaterial used
	Support removal	
	Sandblasting	
	Shot peening	
	Curing	
Cleaning and maintenance	Cleaning (including the use of solvents)	High potential for exposure from solvent use
	Maintenance	Potential for higher exposure

Table 4. Paint activities from WP7

Process	Activities	Release potential, Key release determinant factors
Formulation	Synthesis (i.e synthesis of colloidal silica)	Low release potential- performed in solution and closed systems
	Weighing	Low release potential. Key release factors include manual/automated process, volume handled
	Mixing	Low release potential. Key release factors include manual/automated process, volume handled

	Blending (high energy blending and stirring)	Low release potential- performed on a slurry; closed process
	Colour control step (addition of colorant to a slurry)	Low release potential- performed in solution
	QC testing	
	Ion exchange (use of ion exchange resins for removing ions)	Low release potential- performed in solution and closed systems
	Concentration step	Low release potential- performed in solution and closed systems
	Surface treatment (i.e. treatment to increase stability)	Low release potential- performed in solution and closed systems
	Storage in silos	
	Filling/canning (drum size depending on personal use/professional use)	Low release potential- in solution
Service life	Paint brushing	Low potential release. Key release factors include if the paint is water-borne or solvent-borne
	Paint rolling	
	Spray painting	High potential release. Key release factors include matrix composition, agglomeration and type of spraying performed
	Sanding (mechanical process)	High potential release. Key release factors include the abrasive material used, contact force/pressure applied and area of contact.
	Sawing	Low potential release.
	Weathering	Potential for release. Key release factors include dissolution and photo degradation of the matrix
	Abrasion	Potential for release. Type of coating is a release factor
End of life	Sandblasting	Low release potential
	Incineration	
	Leaching	Low release potential. Key release factors include pH, ionic composition, polymer matrix composition

D) User perspective

Collecting the first set of comments from a user perspective has been performed with the help of industrial partner#12 Allios.

The number one nanosafety concerns for a business are occupational and product safety. An issue in this regard is that each country has its own set of regulations, which the SAbyNA Guidance platform will not be able to address other than in generic terms (e.g. ECHA and/or OECD guidelines). In the same context, although determinant, certain social aspects (e.g. regional differences in the acceptance of nanotechnologies) will be difficult to reflect in the SAbyNA Guidance platform.

Number 2 priority for an SME in regard to the use of the platform is trust. Trust is usually built over time (e.g. Allios' involvement in the French Serenade project since 2012), but for the SAbyNA Guidance platform this needs to be translated into mechanisms guaranteeing confidentiality and/or the ability to provide (partial) answers in return for limited user input.

A third, but not least, concern is financial feasibility. Again, depending on the specific regulatory situation of the user, the added cost of a safety assessment can be addressed by the SAbyNA Guidance platform only in general terms (if this is possible at all).

The next step for WP6 is to gather more information from a broader panel of stakeholders which is the purpose of a systematic questionnaire to be released shortly.

E) Analysis/categorization of resources

At this point, the analysis and categorization of resources that can support SbD is being led by other WPs in the project. WP2 for exposure assessment, WP3 for hazard assessment, and WP4 and WP5 for SbD strategies.

3.3. Definition and categorization of type of assessment cases, with associated SbD workflows

Different type of user needs may require different type of SbD workflows. In order to anticipate what these workflows could be, we first outlined the type of user cases that we could envisage (see Table 5). For each of them, we have developed a preliminary workflow that will support in the later development of the SAbyNA Guidance platform.

Note that this initial list of type of user cases will be later refined based on the feedback obtained during the stakeholders' interviews and the case studies to be developed within WP7.

Table 5. Type of user needs

Type of user needs	Additional detail / Variations
Design/produce a new safe nanoform with a defined functionality	- Some ideas/existing options (provided by the user) on nanoforms and select from there. - Baseline nanoform (provided by the user) and suggestions to reduce its hazard/risk* profile.
Selecting a nanoform with better hazard and/or risk profile when designing a nano-enabled product.	- From pre-defined options provided by the SAbyNA Guidance platform. - Some ideas/existing (provided by the user) on NFs and select from there. - Baseline nanoform (provided by the user) and suggestions to reduce its risk.
Improve risk profile of a nano-enabled product	- Same as above, but in addition: - SbD options centered on nano-enabled product design: matrix or physical conformation.
Increase performance of a nanoform without increasing its risks	- Baseline nanoform (provided by the user) and suggestions to increase performance without increasing its risk.
Design a new production process for nanoform or nano-enabled product.	- From existing options provided from SAbyNA Guidance platform. These need to have a relatively narrow scope: only related to the case studies in the project. - Some ideas/existing options (provided by the users) on production processes and select from there.
Improve an existing (production) process to make it safer	- Baseline process (provided by the user) and suggestions to reduce its risks.

*In some scenarios the intended use of a NF may not be fully defined and SbD measures may be limited to addressing hazard. When intended use and use conditions are defined (both in occupational and consumer settings), SbD measures can also focus on limiting release and exposure.

Preliminary workflows were designed for each of these different user cases. Different partners where in charge of developing each of these preliminary workflows, considering the scope and structure of the SAbyNA platform

(as described in Section 3.1). These preliminary workflows are presented below, followed by a summary table that highlights the common elements of these different workflows.

a. Preliminary workflow to Design/produce a new safe nanoform with a defined functionality

The goal of this preliminary workflow is to reduce the uncertainty involved in the design of a new NF with a defined functionality. We foresee the following steps to reduce this uncertainty.

1. First of all, the user should be informed, regardless of their objectives, about NFs that fall in one (or more) group listed in Table 1, and possibly look, since the beginning, to alternatives. The user should know immediately what should be avoided.
2. The user should define/identify the functionality needed and select it from the list (Table 2). This selection will be linked to the physical-chemical properties that determine the requested functionality.
3. Given the physical-chemical properties needed, a set of candidate NFs and/or chemical component will be provided together with available, or suggested, SbD options to consider.
4. Finally, comparative risks, costs, and performance indicators would be provided for the different SbD options (note that at this stage performance cannot be evaluated in a final product, as this is not yet defined).

For example, let's assume that the functionality needed is "biocidal". This functionality arises from different physicochemical properties: 1) release of ion, 2) surface photo-reactivity, 3) oxidative dissolution. These properties guide the user to choose between three classes of NFs: 1) NF that dissolve in water or biological fluids and release biocidal ions, 2) photoactive NF, and 3) NF that react with the biological environment leading to biocidal outcomes.

NF that dissolve are generally compounds (oxides, sulphides) that contain metal ions with low valences (charge < 2, e.g., ZnO, CuO); the user can decide to use some of these compounds or mixture of them, or develop a new composition based on these compounds. The user will be alerted that the rate of release of ions, which determine functionality and hazard at once, should be controlled through SbD options (e.g., embedding in an inert porous matrix, doping).

Photo-reactive nano-materials are semiconductors composed of Si, Ge, or containing metal ions at high valences (i.e., charge >=4), TiO_2, WO_3, $BiVO_4$) or quantum dots (e.g., CdS, which, however, would immediately be discarded because Cd is a known toxic component).

Oxidative materials are materials that react spontaneously with oxygen and generate ions that can be released into the biological medium. These materials are composed of elemental metals (e.g., Fe, Ag). Metal oxides can also generate oxidative stress and form redox couples with standard biomolecules.

The user may also opt for a mixture of mechanisms, that is, a mixture of different classes of NF.

The final choice, however, will depend on the intended use. In any case, at the end of this workflow, the user should be informed about:

- The aspects that must be considered to achieve the goal of designing a new, safe NFs with a new functionality,

-A selection of suggested solutions (either NFs candidates or starting components) with SbD actions to consider;

-A list of classes of NF that should be avoided because they are known toxicants.

b. Preliminary workflow to select a nanoform with better hazard and/or risk profile when designing a Nano-enabled product

The goal of this preliminary workflow is to provide advice and guidance to aid product developers in selecting a nanoform (NF) with an optimal hazard and/or risk profile when designing a nano-nabled product (NEP). This work-flow is specifically designed for the situation where the form and intended use of the NEP are already defined – therefore the desired functionality of the NF is constrained by the intended use.

To provide flexibility we have devised a workflow which allows for both user and system selection of NFs, to provide a candidate set to assess for SbD considerations. Under this workflow, the user can specify that one or more NFs be included in the candidate set, and/or allow the SAbyNA Guidance Platform to add to the candidate set based on functionality and suitability criteria defined by the user.

The full workflow is shown in Figure 4. Firstly, the user provides a set of information on the manufacturing process, use and expected lifecycle of the NEP. As far as possible, this is done by selecting on a predefined list of activities. Then, depending on the inputs of the user, one of a number of pathways is followed:

(i) If the user does not wish to specify any particular NF, the system requests information on the desired functionality of the NF and the NEP in order to interrogate the library of material-function relationships to extract suitable candidate materials. Information on the functionality of the NEP is required because of the possible requirement to choose both an NF and a matrix material that are functionally compatible with each other. A list of candidate NFs is then derived, and each candidate is subjected to risk assessment based on the information provided regarding NEP production processes, desired use and life cycle. The list of candidate NFs is then ranked on the basis of risk and cost of their use and output to the user.

(ii) If the user provides one or more candidate NFs for ranking, the system firstly highlights any which have specific hazard concerns (Table 1) and offers the opportunity to (a) remove the NF from consideration; (b) replace the NF with a material selected by the system based on the process/use/lifecycle information; (c) end the analysis. The workflow then continues into the listing of candidate NFs, as in (i).

(iii) If the user specifies a single NF for improvement, the system then requests information on the specific aspects of the NF that must be retained. It then checks for specific hazard concerns, as in (ii). If the user does not terminate the process after the hazard check, the system then generates a list of possible NF refinements from a library of safety refinement approaches. These approaches are not limited to modification of the NF itself, but may include modifications to the NEP production process to minimise exposure of workers and releases to the environment, and modifications to the NEP itself, for example to minimise release of the NF during product use. The system then performs a risk assessment on each possible refinement, followed by a risk/cost ranking, as in (i), and outputs these options to the user.

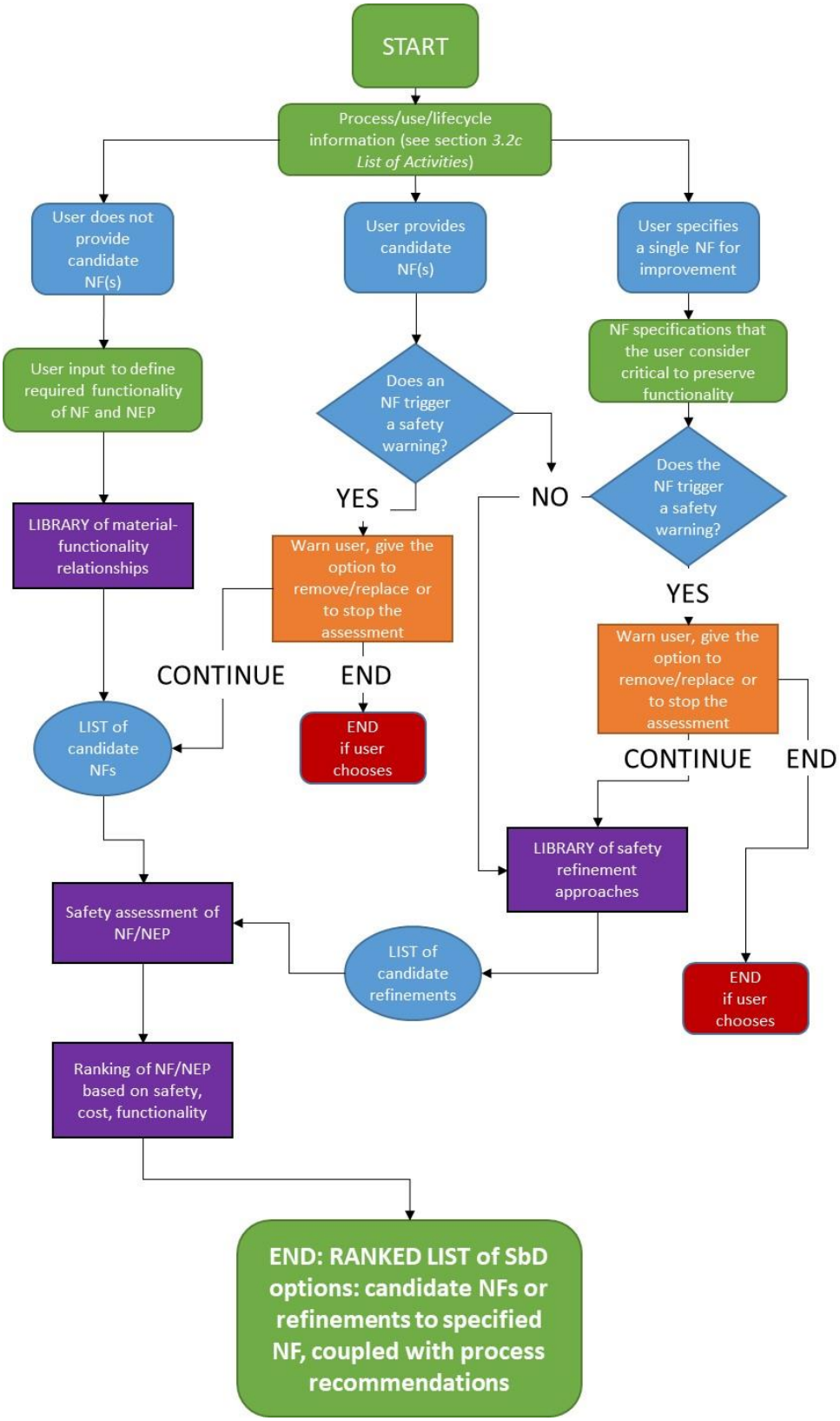

Figure 4. Preliminary workflow for the process of selecting a nanoform with better hazard and/or risk profile when designing a nano-enabled product

c. Preliminary workflow to improve risk profile of a Nano-enabled product

The aim of this preliminary workflow is to suggest to the user how to reduce the risk associated with a nano-enabled product (NEP).

1. The first step should be an assessment of the risks currently involved with the nano-enabled product with the following questions to be answered by the SAbyNA Guidance platform:

   i. Formulation of the nano-enabled product (to be answered by the user) - common NFs/NEPs/matrix materials in a drop down list or similar? This could include the user inputting the NF in the NEP, information on how the NF is contained in the NEP and where exposure could be an issue (Workers? Consumers? Environment?)
   ii. Identification of risks associated with the nano-enabled product.
   iii. What are the main risks to human health/environments of exposure (CLP?). List of possible effects?
   iv. What are the potential exposure levels? How would exposure be measured? Dependent on product, for example leaching for paints
   v. Are there any regulatory requirements associated with the NEP?
   vi. Quick analysis of risk (similar to precautionary matrix) - is there a potential risk? Overall risk score/rating?

2- The next step should be the identification of the functionality/use of the nano-enabled product. The user should be able to select from a list (similar to Table 2 options?)

3- SbD options should be identified by the SAbyNA Guidance platform and options provided to the user. Possible options could include:
   i. Possibility of addition/modifying matrix – list of matrix materials that could reduce risk profile.
   ii. Possible physical conformation options.
   iii. Other potential SbD options for reducing risk.
   iv. Decision logic tree for identifying best option to reduce the risk profile.

4- The SbD options could be compared to the current case by the SAbyNA Guidance platform. This could include:
   i. Comparison of SbD options compared to current nano-enabled product- risk band/score?
   ii. Does the SbD option have the required functionalities of the NEP?
   iii. What are the costs (LCA) of these SbD options (Task 6.2) and how will they reduce risk- perhaps a ranking system with the SbD option that reduces the risk the most at the top?
   iv. Other relevant aspects for comparison such as sustainability of options etc.

d. Preliminary workflow to increase performance of a nanoform without increasing its risks

1. The first step will be to **know which is/are the Technical Function of the NF within a material or a NEP**. The TF of the NF are the ones providing the actual technical performance of the NF within a material or NEP. At this stage we propose to use and add/adapt the Technical Function categories (TF) as defined by ECHA R-12 to be suitable for application to NMs/NFs (note that ECHA R-12 document is not meant for NMs/NFs). In this document “the TF are designed to describe the role that the substance fulfils when it is used (what it actually does as such in a process or what it actually does in a mixture or article)”.

2. The second step would be to **know the actual performance** or to **know how measure the performance of a NF within a material or NEP.**
3. The third step would be to **know which physicochemical properties of the NF are providing the technical functions and the desired performance of the NF within a material or NEP**. Moreover, we will need to **define relationships between physicochemical properties of the NF and functionalities.** This will give a first understanding of which NMs/NFs might have the potential to enable a specific functionality (and therefore certain performance) in a certain material and/or NEPs. For those NF made by more than one component (multicomponent NF, core-shell NF, etc), we will need to **know each component of the NF** and define **relationships between components and physicochemical properties and consequent functionality and performances within the material/NEP.** This will give a more in depth understanding of which physicochemical properties of a specific component of a NF have been used to enable a specific functionality in specific materials and NEPs.
4. The fourth step would be to **modify the physicochemical characteristic of a NF (or of one of its component) that will modify the desired performance of the NF within a material or NEP, for a specific application.**
5. The fifth step would be to **measure again performance of the modified NF within a material or NEP** (possibly with the same methods/tests used at the starting point of the workflow) to compare the performance of the "starting NF/NEP" with the one of the NF/NEP after modification. In this way it will be possible to **check/demonstrate the increase of the NF performance** within a material or NEP.
6. In many cases the same physicochemical properties that are making appealing a NF for a certain application are also those one responsible for a specific adverse effect (toward the human population, environmental and all the species living in the environment). Therefore, we need to monitor how changes in the NFs physicochemical properties can affect both the NF technical performance and the risks. Therefore, we will need to know and compare the risk profile of the "starting NF/NEP" with the one of the NF/NEP with improved performance. This will be done by using the Preliminary workflow to improve risk profile of a Nano-enabled product. In this way we will demonstrate the improvement of NF performance without increasing the risk.

e. **Preliminary workflow to design a new process for the production of a nanoform or a nano-enabled product.**

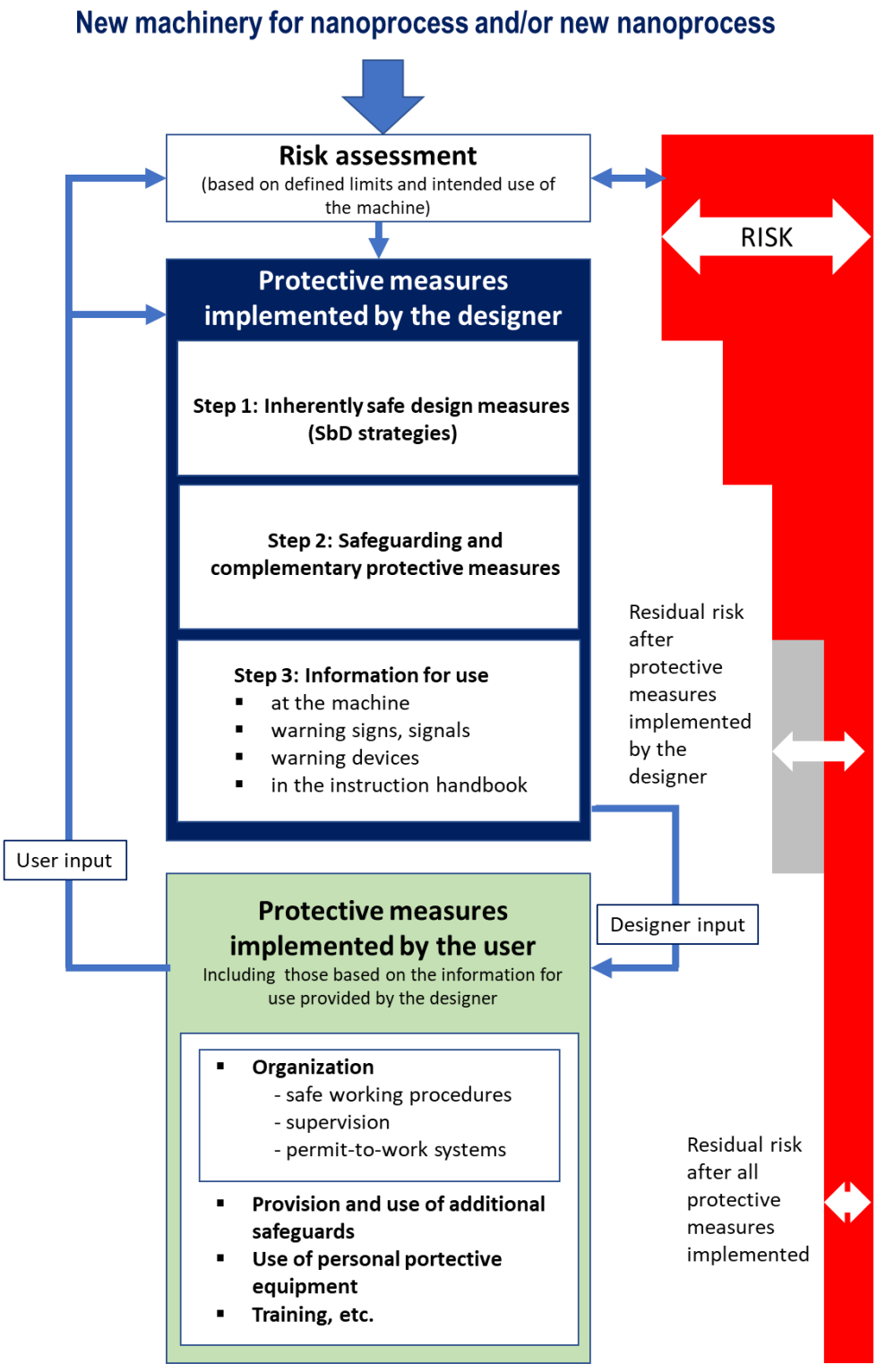

Figure 5. General steps for designing safe processes according to ISO 12100.

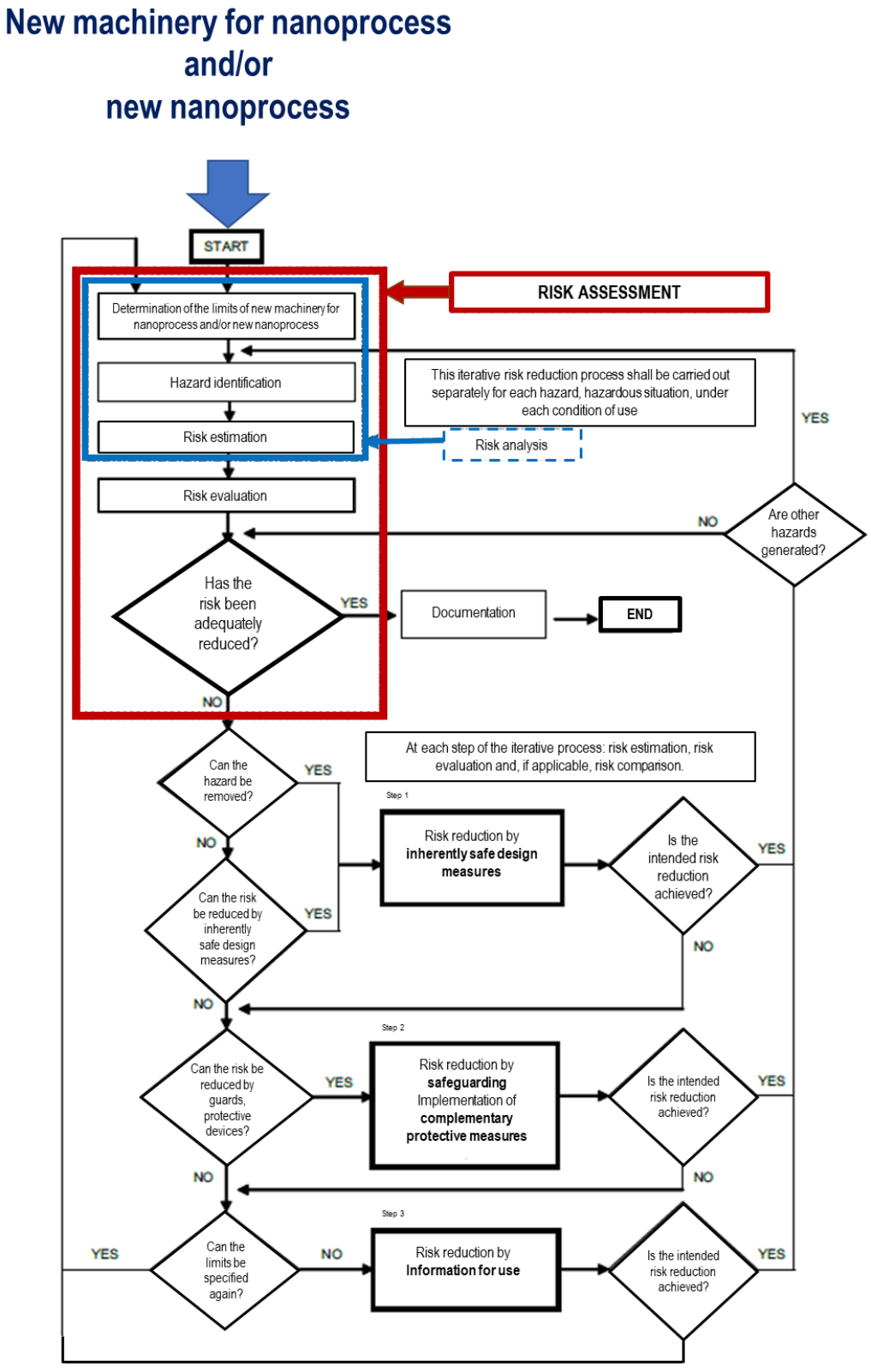

Figure 6. Three-step iterative process for designing safe processes according to ISO 12100.

The workflow for this type of user case would be inspired on the flow of ISO 12100 on safety of machinery, although recognizing that machinery are only some of the elements of a process, and therefore applying the same principles and logic to the processes as a whole (i.e., also on

steps that do not involve use of machinery) and including any industrial process (production, storage, etc).

The SAbyNA Guidance Platform will help the user to follow the principles of ISO 12100 safe design procedure, which are displayed in Figures 5 and 6. The scope of ISO 12100 is much broader than that of SAbyNA: ISO 12100 includes several type of risks that are beyond the scope of SAbyNA, such us mechanical risks, noise, etc. The SAbyNA platform will only support the implementation of the principles of the ISO12100, when it relates to emission of nanomaterials, fire and explosion. The key value of the SAbyNA platform will be providing solutions to cover the different currently existing gaps in the risk assessment procedure for such type of risks, as well as providing tailored SbD options and risk reduction measures.

One key aspect of the ISO12100 that has been typically overlooked in previous initiatives on SbD for nanotechnologies is the fact that risks associated to accidental and non-intended use conditions are considered beyond the typically evaluated 'normal operating conditions'.

At the moment, the specific workflow of this type of user case and how it will relate with elements of the workflows for the remaining type of user cases is still under discussion.

f. Preliminary workflow to improve an existing (production/ manufacturing) process to make it safer

1- Definition of process characteristics

2- CB tool to identify hotspots in the process

3- RA methods to identify which of the potential hotspots are relevant risk scenarios.
   i. How to assign OELs to nanoforms under consideration – link to database of existing OELs, guidance on how to identify potential analogues, etc
   ii. Guidance on how to plan exposure assessment campaigns – link to relevant standards.

   [we envisage that in some cases an actual risk assessment may not be needed, and that CB tools may be sufficient]

4- Identification of SbD options applicable to the process. How to?
   i. Link to ISO standards that already compile multiple SbD options?
   ii. Link to a nano-specific compilation of SbD options that we create for SAbyNA?
   iii. Decision logic based on process characteristics leading to different SbD options?
   iv. Introduce also risk levels into the decision logic to select SbD options?

5- Evaluation of efficiency of SbD options, by:
   i. Approaches to evaluate/compare hazards (CLP?, OELs? or more basic descriptors from assays selected/developed in WP3? other approaches for hazard scoring?) of potential NFs for substitution?
   ii. Approaches to evaluate efficiency of exposure control measures:
      1. Experimentally case by case?
      2. Predetermined efficiency values per type of exposure control measures?

6- Evaluation of any other consideration relevant for selection of SbD options: functionality, costs, sustainability, etc

[Actually 5 and 6 should be in parallel. All theoretical assessments should be done prior to initiating experimental work for refining any of these aspects]

g. Overview of the workflows for the different type of user cases.

Table 6 provides a schematic summary of the workflows that have been described in sections a) to f). Common elements are depicted using the same colors.

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Table 6. Schematic overview of the preliminary workflows devised for different type of user cases.

New NF with defined functionality	Selecting a NF when designing a NEP			Improve risk profile of NEP	Increase performance without increasing risks	New process for production of NF or NEP	Improve existing process to make it safer
	No NF upfront	NFs from user	NF for improvement				
1. Hazard flags? – alternatives 2.Identify functionality from Table 2* and select NFs from list 3. SbD options to consider for each selected NF 4. RA and ranking based on risk, costs, and performance (only NF production)	1.Activity list 2.Identify functionality NF and NEP and select NFs from list -compatibility- 3.RA and ranking based on risk, costs, and performance	1.Activity list 2. Hazard flags? – alternatives 3.RA and ranking based on risk, costs, and performance	1.Activity list 2.User defined specifications needed for function -compatibility- 3. Hazard flags? – alternatives 4.SbD options to consider 5.RA and ranking based on risks, costs, and performance	1. RA for NEP (or user input if RA already available) 2. Identify functionality for NF and NEP 3. SbD 4. Ranking of SbD options, risk band, functionalities, costs, sustainablility	1.Identify functionality in NEM/NEP, and opportunities to modify physchem properties. 4.SbD (NF, NF-matrix, NEP design….) 5.Compare risk profiles, costs, and performance	Following ISO12100 and aligning with SAbyNA platform elements: 1.Hazard identification in the processes (Activity list) 2. SbD options (including risk reduction measures) as provided by ISO12100 3. RA, costs, and performance Iterative process	1.Activity list + process characteristics → select CB tool → identify hotspots 2. RA for hotspots 3. SbD options. 4. Ranking of SbD Comparing hazards Efficiency of exp controls. + functionality, costs, sustainability

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3.4. Integration of costs and LCA concepts into the SAbyNA Guidance Platform (T6.2- IOM and Gaiker)

This subtask will provide resources to evaluate potential impacts and cost implications from a global point of view. The strategy selected aims for a balance between low data demand, low expertise required and acceptable level of uncertainty, in order to provide a basis to support decision making even at early stages of development.

3.4.1. Life Cycle Assessment

Subtask 6.2 intends to develop a simplified LCA tool in order to support streamlining LCA for nanoforms and nanoenabled products. A flexible tool is proposed, compatible with the level of uncertainty existing at the early stages of development, aiming to facilitate approximative results on impacts over the life cycle. It will be possible to adapt the use of the tool depending on:

- Life cycle stages that want to be assessed*
- Application of the nanoform, which will be linked to different processes and release data (based on data available up to date)*
- Data available for the processes to be evaluated, being possible to use own data or default estimations

*Note that some of this information (and other in the following bullet points) is also collected for risk assessment purposes and can therefore be reused for LCA.

In this context, the tool will incorporate different elements:

- Inventory data for the user:

  This simplified approach will still require inventory data for the calculations, both nanospecific (Eg. Nanoform release over the life cycle) and generic (for example, CO_2 emissions associated to the use of different energy sources, transportation means, etc.).

  The Nanospecific data in the tool will incorporate information from different resources (publications, models, etc.) related to nanoform release over the life cycle (depending on the application of the nanoform) and approximations to the environmental impacts of existing processes for production of nanoform. Regarding the generic inventory data, the tool will incorporate public emission factors available (e.g., per unit of energy consumed, or per kg of raw material used).

  The tool will also integrate open fields for the user to fulfil (Eg. Process specific data, such as energy and material consumption) but there the availability of default data and/or proxies will enable to approximate different life cycle stages, even those out of the scope of the user.

- Algorithms for the calculation of different Life Cycle Assessment Impact Indicators
  Life cycle impact assessment (LCIA), the third step in LCA, aims to improve the understanding of the relative importance of the individual emissions in life-cycle inventories. This is done using a weighted summation of the releases of substances of a product system with help of a Characterization Factor. The Characterization Factor of substance x emitted to compartment i the degree of contribution of that substance to a specific impact category.

Within LCA multiple impact categories can be assessed (Global Warming Potential, Eutrophication, Acidification, Ozone Depletion Potential…). Following the simplified approach proposed for the tool, a limited number of impact indicators are proposed for the tool to be developed. As a starting point, the following ones are proposed although open for discussion with WP3 experts:

- Global Warming Potential: expressed as CO2 equivalents, this impact category indicator is a summatory of the potential influence on Global Warming of the substances emitted during the life cycle assessed.

- Cumulative Energy Demand: expressed as MJ, this impact category indicator reflects the total energy consumed by a system, from the extraction of the resources to the final use.

- Toxicity (focusing on damage by inhalation, for outdoor emissions): The well recognized Life Cycle Impact Assessment method USEtox (Huijbregts et al. 2005)[4] expresses the result of the Category Impact "Human Toxicity" as disease cases (at midpoint indicator level) or disability-adjusted life years, DALY (at endpoint level). More details about the calculation of this indicators are detailed below.

- Ecotoxicity (focusing on damage to freshwater ecosystems)

  The well recognized Life Cycle Impact Assessment method USEtox (Huijbregts et al. 2005) expresses the result of the Category Impact "Ecotoxicity" as PAF/kg (Potentially Affected Fraction) which is the fraction of species exposed above the no-effect concentration (NOEC). The PAF is a measure that allows a comparison in toxic stress between substances and areas. More details about the calculation of this indicators are detailed below.

- Characterization Factors

  The Life Cycle Impact Evaluation phase within LCA requires using multiplying factors, specific for each substance, which reflect their relative contribution to each environmental impact assessed.

  - Global Warming Potential: The potentially emitted nanomaterials are not expected to have a direct impact on Global Warming, and therefore, no need for adapting the Characterization Factors is foreseen in order to evaluate nanoforms or nanoenabled products.

  - Cumulative Energy Demand: Also, in this case, there is no need for adapting the Characterization Factors in order to evaluate nanoforms or nanoenabled products.

  - Toxicity (focusing on damage by inhalation, for outdoor emissions): Currently there are no validated Characterization Factors to model the potential impact on Human Health of nanoforms, although some factors are available in literature.

    The Life Cycle Impact Evaluation method USEtox calculates CF is as: CF=FF*XF*EF*SF

    The Fate Factor (FF) represent the persistence of the substance in the environment, XF accounts for the human exposure to the substance, and the toxicity of the substance is revealed by the effect factor (EF).

[4] Huijbregts MAJ, Rombouts LJA, Ragas AMJ, van de Meent D (2005): Human-toxicological effect and damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment. Integrated Environmental Assessment and Management 1: 181-244

In USEtox two exposure routes are currently considered: inhalation and ingestion. For the simplified assessment aimed in the tool to be developed, it is proposed to focus on the toxicity effects via inhalation, as starting point.

The human toxicological Effect Factor is calculated under the assumption of linearity in concentration–response up to the point of at which the life time disease probability is 0.5.

For carcinogenic and non-carcinogenic effects, the effective dose affecting 50% of exposed individuals (ED50) for a defined health endpoint for humans related to inhalation or oral (ingestion) exposure (kg/person/lifetime) is calculated from the daily dose for animal a (e.g. rat) and exposure duration (e.g. subchronic) per kg body weight that causes a disease probability of 50% for a specific exposure route (mg/kg/d), an extrapolation factor for interspecies differences, an extrapolation factor for differences in time of exposure, i.e. a factor of 2 for subchronic to chronic exposure and a factor of 5 for subacute to chronic exposure (Huijbregts et al. 2005), an average body weight of humans, an average lifetime of humans, and the number of days per year. The extrapolation factor for interspecies differences is by default 1 if the ED50 is given as concentration in the air. Metabolic activity and inhalation rate are assumed to have the same ratio for all species.

In the case of effects other than cancer, for most of the organic substances insufficient data are available to recalculate an ED50 with dose–response models. In those cases the ED50 is estimated from no-observed effect level (NOEL) by a NOEL-to-ED50 conversion factor of 9. In case only a LOEL was available, a LOEL-to-ED50 conversion factor of 2.25 has been applied.

As for non-cancer effects for inhalation, the critical effect concentration is defined as the concentration in the air, the interspecies extrapolation factor for inhalation is in principle 1, assuming that inhalation rates between species scale proportionally to metabolic rates.
For carcinogenic effects, the ED50 can also be estimated from the carcinogenic low-dose slope factor (q*) by a 1/q*-to-ED50 conversion factor of 0.8, based on animal data, where q* is the carcinogenic, low-dose, slope factor for animal a (e.g. rat) and exposure duration (e.g. chronic) for a specific exposure route (kg.day/mg or m3/mg).

Considering the high complexity of the development of Characterization Factors for nanoforms, and intensive data need, within subtask 6.2 different strategies will be evaluated to develop simplified factors that may fit within the current evaluation methods.

- Ecotoxicity (focusing on damage to freshwater ecosystems): Currently there are no validated Characterization Factors to model the potential impact Ecotoxicity of nanoforms, although some factors are available in literature.

  The Life Cycle Impact Evaluation method USEtox calculates CF is as: CF = EF·FF·XF

  Where XF is the Exposure Factor, FF is the Fate Factor and EF is the Effect Factor.

  The Effect Factor for aquatic ecotoxicity of a substance value reflects the fraction of species exposed to a concentration above their EC50:

$$EF = \frac{0.5}{HC50_{EC50}}$$

$HC50_{EC50}$ represents the concentration at which 50% of species is exposed above their chronic EC50 and 0.5 is the working point (PAF=0.5) on the PAF curve. At least three EC50 values from three different phyla are required to reflect the variability of the physiology and to ensure a minimum diversity of biological responses (Henderson et al., 2011). USEtoxTM suggests to calculate the HC50EC50 as the geometric mean of the available single species EC50for organisms representative of three trophic levels: algae, crustaceans and fish.The tool

will include the Characterization Factors necessary for calculating the results for the different impact categories mentioned above. In this context, in order to account with Characterization Factors to reflect the contribution of different nanoforms on Human Health and Ecosystems, this task intends to compile published Characterization Factors for nanoforms, as well as to propose simplified approaches and proxies that can be used when no sufficient data is available for a conventional derivation of Characterization Factors.

In this context, a review of the strategies already adapted to calculate nanospecific Characterization factors (Eg. Salieri et al 2015, Salieri et al 2014, Deng 2016, Pu 2017) potential simplifications in combination with outcomes from WP2 and WP3 are being evaluated.

3.4.2. Cost Assessment

Sub-task 6.2 will also consider the costs of different of SbD measures. For example, if a whole process modification is required then costs will need to be assessed for materials, labour, investment, energy costs and material efficiency. If the SbD measure involves the addition of an exposure control element, then investment and running costs need to be considered.

It is aimed to establish a framework to measure the cost and benefits of implementing SbD. The objective is to provide a method to determine the cost of the SbD measure adopted and the benefits associated to such measure. This analysis requires the cost of non-implementing any SbD measure.

A preliminary literature review has been undertaken to date for assessing costs and benefits with the approach used by regulatory authorities i.e. ECHA to be looked at further. Work has also commenced on methods to derive costs and benefits with the first focus being on costs and benefits for health derived from the reduction in exposure.

Costs and benefits will be monetised where possible. Monetisation involves summarising the impacts of the concern in the form of a single metric (utility or value (such as in Euros) as the measurement unit. The impacts are weighted against each other and then converted to a common measurement scale. This process can involve the derivation of the monetary values for each health outcome followed by summarise these values across all health outcomes to allow and overall, monetary measure to be derived.[5]

DALYs (Disability Adjusted Life Years) will be used for estimating the burden of ill health. A DALY is considered to be one year loss of healthy life. This is calculated as the sum of Years of Life List (YLL) due to premature mortality and the Years Lost to Disability (YLD) for people with cases of ill health.

- Costs of SbD measures

An initial list of potential costs to be considered for SbD measures are summarised in the following table. The costs will depend on the type of specific measure.

Table 7. Key cost determinants for Cost-Benefit Analysis

Costs	Measure	Detail
Direct costs	Manufacturing cost before implementing suggested SbD measures (baseline scenario – unit of product)	What are the manufacturing costs before using the platform. This can include: - Material costs - Energy costs - Current engineering measures - Current PPE - Current maintenance costs etc.
	Costs of implementing suggested SbD measures (process and NF/product modification)	This can include: - Initial installation costs of new equipment ('one shot' cost) - Maintenance costs (reoccurring cost)

[5] IEHIAS. Monetisation methods. http://www.integrated-assessment.eu/eu/guidebook/monetisation_methods.html

		- Training costs (reoccurring cost) - Depreciation costs of the new equipment (over a time span of 5- 20 years depending on the equipment)
	Human health costs (employees)	Costs due to ill health of employees (i.e. from exposure, poor mental health etc.).
	Environmental costs	This will include (non-exhaustive list): -Waste disposal costs - Changes in emissions - Higher energy consumption - Environmental impact
	Administrative costs	
Indirect costs	Availability and choice of products (i.e. will there be a reduction/increase in employees, shortage of products, higher costs of products?)	

- Benefits of SbD measures

An initial list of potential benefits to be considered for SbD measures are summarised in the following table. The benefits will depend on the type of specific measure.

Table 8. Benefit determinants

Group	Information
Human health	Decrease in ill health cases
Employees	Reduction in turnover
Environmental	Reduced emissions
Company	Positive image, increased sales? Reduction in cost from new measures Increased productivity

4. Analysis of suitability of preliminary structure based on selected existing case studies

Case studies are highly useful when discussions are otherwise kept at an abstract level. After several iterations on the design of the SAbyNA Guidance Platform, we selected three case studies (summarized in Annex 1) from other H2020 projects for evaluation of suitability of the general concept developed so far for the SAbyNA Guidance Platform. Partners were distributed in teams for each of the case studies, intentionally avoiding partners that were part of the previous projects (Nanoreg II, caLIBRAte and Protect) that handled those case studies.

The main conclusions and discussion points that derived from this analysis are summarized below.

In relation to Part 1:

- Framing the purpose of the assessment

  -We foresee two options:

  Option 1) define the questions to the user that would help framing the purpose of the assessment. E.g.:

- What is the need of the user?
  - Reduce release of the NF? Increase process efficiency? Reduce waste emissions?
  - Compare pre-defined alternatives, or make a given NF/product/process safer?
  - Evaluate whether occupational exposure is below an OEL/recommended reference value?
- Has the user already identified a risk or are they looking to identify a risk?
- What capabilities/factors could the user change and/or compromise on?

Option 2) predefine different type of assessment purposes and make the user select among these. E.g.,

- Setting up a new production process from scratch;
- Select among alternative NFs for a given application;
- Introducing SbD measures on an existing process to minimize concern related to workers exposure;
- Introduce SbD measures to minimize risk of fire and explosion;
- Introduce SbD measures to minimize waste generation and releases to the environment.

- We may want to ask the user whether regulatory constraints are relevant. We could offer the option to the user (a producer of articles) on whether selection of a NF already registered or approved for a type of use, is or not a precondition. That could be linked to a database with such information or guidance on where to retrieve it from. Otherwise, for a NF producer, we could ask on ambitions at the regulatory level: e.g., CLP classifications that would be prohibitive for their NF, etc.

- On level of information required to collect:

  -NFs: to allow categorization and alignment to the identification of hazard red flags: composition, shape category, physical state.

  -About products. What type of information will be needed?

  -For processes:

    -Minimal information required to identify likelihood of emissions and most likely routes of exposure (e.g., handling powders, high energy processes, frequency and amount of NF…)

    -What level of detail? At the level of processes or activities?

    -There is a huge number of existing processes. How to generate a usable list of processes? In the broad sense, the term “nanoprocess” would include new nanomanufacturing processes to synthesize, generate or control NMs or fabrication steps in the nanoscale (ISO/TS 80004-8), but also many other traditional production processes that can be modified for nanotechnology.

    -Do we ask on risk mitigation measures already in place? or we include such recommendations by default?

- On how SbD options (or possibly preferred phrasing “safety recommendations” at the level of Part 1) should be categorized, like: NF redesign, Process redesign, Local controls, Engineered controls, PPE, organisational measures...

- On cost/LCA considerations during Part 1. We conclude that they should be considered when developing the decision rules on 'red flags' → 'safety recommendations'. But probably it will be unnecessary to add specific questions to the user (at this phase).

In relation to Part 2:

- Criteria for proceeding to Part 2. In principle, this would be up to the user: if with the safety recommendations (potentially) provided the goals of the assessment are not covered, then part 2 would be needed.

- Selection of appropriate hazard/exposure/CB/risk assessment tools

  Purpose of assessment (=user needs), target population, and exposure routes as key for selection of tools (or other resources). At a second level, user friendliness, type of data available, accessibility, etc, WP2 and WP3 have identified a series of criteria for selection of resources to support exposure and hazard assessment. Existing resources are now under analysis against all these criteria. These will be taken into consideration in the final selection of tools within WP6.

  The selection will probably require a decision tree, to that hierarchies among different criteria are established.

  One major limitation of existing RA/CB tools already identified during the case studies, is that generally they do not have sufficient level of resolution to discriminate between hazard of different NFs if their level of variation is not major (as in some cases during SbD).

  It is also unclear how to rank different type of hazard concerns. Hazard banding approaches may help, if they are systematic enough, and the way they rank different type of hazard concerns is scientifically justified.

  Several existing tools are purely exposure assessment models, that will require a way to assign hazard reference values (OEL-like) to each material. WP3 will need to define approaches to assign default values to different type of nanoforms.

- Need for hazard testing strategies. Either as a way to fill in input requirements of assessment tools, or as a way to directly compare hazard of nanoforms, we will need to define what type of testing would be most appropriate for different cases.

- Selection of SbD options to be provided. How to identify the main drivers of risk for a case to target them in the SbD suggestions? In T5.1, resources are currently being categorized, but it is not yet clear how they will be linked to each particular case.

  We probably need to ask what aspects the user wants to consider making the final selection of SbD options provided (functionality, LCA, costs, production efficiency…). And then, would we need to prioritize / score these different considerations?

  Our main goal is minimizing risks, costs, and LCA impacts, while maximizing functionality, so it is about optimizing the combination of all these considerations.

- Workflows. We need to create specific workflows for different type of scenarios (see Section 3.3). We may need to allow for an iterative process, in which e.g., the design of the nanoprocess will be conditioned by the design of the nanoproduct to be manufactured, and once the nanoprocess has been designed, the initial design of the nanoproduct may require revision. So, we foresee an iterative product/process circular process until reaching the best overall SbD option.

- Available/missing information. Assessments should try to adapt, as much as possible to the type of data available, but as long as the main goal of the assessment can still be met. So, if key properties of different nanoforms under comparison are missing, and these could influence their hazard ranking, such information should be asked to the user, or at least should be informed that no conclusion can be drawn without such data.

  We need to differentiate between 'non-existing information' and 'existing but not willing to use in a website' information. As part of interaction with stakeholders this should be evaluated and need for a downloadable version should be evaluated.

Further considerations regarding the scope of the assessment that we will need to decide:

- Whether the tool allows assessments of multiple scenarios (to compare NFs or processes) in parallel or a single scenario is evaluated in each 'run' and later on compared.

- Whether we allow comparisons of conventional substances vs. nano. Chemical safety or NF safety only? If we are going to include cost considerations and LCA, it would seem logical than a chemical safety assessment also considers other chemicals. Chemical safety assessment for conventional substances could rely on existing external resources (even in this case, it would make the assessments much more complex).

  E.g., right now, only the hazard of the NF itself is considered and not potentially toxic by-products resulting from a specific production process. In the case study example for CNTs, chemical vapour deposition indicates potential exposure to volatile substances, but the flow as presented does not consider the toxicity of these substances. Also nickel and sulphur have toxic properties.

  So, this is about whether we want to compare NF to conventional substances, but also whether we want to consider exposure to conventional substances involved in nanoprocesses (when comparing overall risks of two nanoprocesses for instance).

5. Benchmarking versus similar resources at the end of the SAbyNA project

The need to organize and facilitate access to resources that can support SbD and risk assessment of nanomaterials has been recognized since many years, and the creation of portals/platforms streamlining access to SbD/RA resources been the focus of several calls in the H2020 Framework Programme.

The project NANoREG 2 created the Safe-by-design implementation platform, and the Safe Innovation Approach Toolbox. The project caLIBRAte created the Nanorisk Governance Portal. The projects Gov4nano, Nanorigo, and Riskgone (all funded under the NMBP-13 call), as well as the projects NanoinformaTIX and NanoSolveIT (NMBP-14 call), at least one of the sister projects in our call SBD4nano, and the project that was funded under NMBP-16 are all including within their activities the generation of some type of Portals/Platforms.

The following table summarizes the scope of these different platforms/portals, based on the information available at this point. Several of these projects are still in their early stages and it is difficult to anticipate the details of the Portals/Platforms that will be generated in each of them. However, considering that the actual resources (e.g., tools, guidance documents, etc) that all of these projects will consider is a (not so long) finite list, it is to be expected that all these Portals/Platforms will have a large degree of overlap.

Table 9. Overview of Platforms/Portals developed or under development in NMBP projects.

Project	Scope
NANoREG 2 (finished)	*"Safe-by-design implementation platform"* It is a web-based tool that supports the specific elaboration of safety dossiers and safety profiles. It contains an Inventory of concepts, links to tools or procedures as well as databases and data sources. It covers the following two property categories of nanomaterials and products: 1. Law based requirements (if a regulation is chosen): Nano-relevance, substance identity, hazards, exposures, risk management and 2. Further needs and information (non-regulatory): Precaution, applications (functionalities and properties), chemical safety documentation, sustainability and life cycle assessment, management processes, balancing of benefits, costs and risks/safety, governance aspects and soft regulations such as social responsibility, labels, codes of conduct, etc. Derives a report on the risk profile.

	"Safe Innovation Approach Toolbox" The SIA Toolbox is a set of tools, guidances and checklists to be used by innovators and regulators along the innovation chain. Tools are organized according to the innovation process phase to which they support, and according to the scope of their assessments, namely: risks, costs, and benefits.
caLIBRAte (finished)	*"Nanorisk Governance Portal"* Portal including tools for Horizon Scanning, Identification of nanomaterials, Risk Assessment, Risk Management, Decision Support and Workplace Monitoring, which were thoroughly tested and, when possible, validated during the project. Databases: caLIBRAte developed a tailored e-NanoMapper database that include all the parameters requested by the different tools and models selected in the project to be calibrated. Access to case studies and qualified material, hazard and exposure measurement data for direct access information and specially as guidance documents to support user in running the nano-risk governance tools. Guidance and good practice information relevant for research and development as well as established industrial production of nanomaterials and products containing them. The Portal does not have any suggestions on SbD strategies, it was really focused on SELECTED models/ tools for exposure, hazard and risk assessment that have been revised in depth in the project.
Gov4nano (NMBP13)	Gov4Nano, Nanorigo and Riskgone, all funded under the same call, aim towards the generation of a single Governance Council, and are currently discussing whether at how their Portals will be aligned. Gov4nano will explore FAIR databases, data-hackathons, blockchain technology and implementation of Safe-by-Design to achieve adaptive and resilient risk governance. Gov4nano portal builds upon caLIBRAte. It will likely become an incremental version of caLIBRAte. It is still not clear yet whether or which tools/ models will be added on top of those considered in caLIBRAte.
Nanorigo (NMBP13)	The framework involves several stages: Preassessment, Scientific (technical) RA, Perception, opinion and concern assessment, Risk evaluation, Risk management, monitoring and feedback. A web-based platform that includes tools/models/guidelines for the different stages is being developed. This will guide different types of stakeholders through the framework according to their needs. Nanorigo includes a specific focus on socioeconomic aspects. It is also developing a tool on prospective early risk assessment (human and environment, including mass flow simulations along the life cycle).
Riskgone (NMBP13)	Riskgone will develop a platform that will also include tools and models for Risk-benefit analysis, risk management and risk transfer and integrating Safer by design concepts. The project will develop pre-validated draft guidance for the characterisation, fate, and dosimetry of ENMs, for human hazard assessment and for environmental hazard assessment. Special focus on developing SOPs and guidance /prevalidated test methods.
NanoinformaTIX (NMBP14)	The project aims at creating a comprehensive, sustainable, multi-scale modelling framework for exposure and (eco)-toxicity of Engineered Nanomaterials (ENM) to facilitate cost-effective risk assessment, less reliant on animal testing, and to support the design of safer materials and products. Models for prediction of human health and environmental hazard and exposure. Flow of data out of databases for use in these models. There are no specific considerations or models for SbD. Identification of descriptors and model them to avoid experimental work. Prioritizing in silico, but experiments are also performed when needed for model validation. Dose-response modelling. In vitro, in vivo. Systems biology. PBPK. Fluid dynamics.
NanoSolveIT (NMBP14)	E-platform will implement and integrate approaches for testing and assessment (IATAs). In silico prediction of NF toxicity (QSAR); exposure assessment. Includes development or updating of exposure models (NRCWE for occupational models, UKCEH for environmental models). Focuses on both human and environment.

SbD4Nano (NMBP15)	The SbD4Nano project is funded under the same call as SAbyNA. Its primary goal is to develop an online e-Infrastructure to support different actors in the nano enabled product supply chain to conduct SbD approaches in an cooperative manner. The e-Infrastructure should assist in assessing (initial) exposure, hazard, risk, functional performance and propose SbD or RMM strategies. For each SbD iteration step aspects like risk reduction, functional performance and related costs are determined. Finally, these iteration steps can be compared and use to establish an overall score. There is a high risk of overlap, and actions should be coordinated to minimize such overlap.
SABYDOMA (NMBP15)	The SABYDOMA solution is technological and involves screening at the point of production and feeding back screening results to modify design. Complementarities are foreseen in the SbD solutions proposed by SABYDOMA could be potentially included in the SAbyNA Guidance platform (collaboration is already in progress).
ASINA (NMBP15)	Will not create a platform, but written guidance on how to implement SbD focused on the cosmetic sector and on antiviral/antibacterial. ASINA is not only focused on the technical part – also management part on implementation – focused on antiviral/antibacterial (textiles) and cosmetics. From safe design to implementation.
Sunshine (NMBP-16; starts early next year)	Nanoreg 2 approach – Web-based platform – adapting SIA toolbox for multicomponent NMs. The call was particularly asking to focus on modelling and on implementation of the concept of Safe-by-design for much more complex materials (multicomponent nanomaterials)
Harmless (NMBP-16; starts early next year)	We do not have information on the specific approach of this project, but the call was particularly asking to focus on modelling and on implementation of the concept of Safe-by-design for much more complex materials (multicomponent nanomaterials)

SAbyNA differentiates from some of the existing platforms by proposing SbD solutions. However, that is also the approach of some of the other ongoing projects. Sector-specific efforts may be additional ways to provide differentiated and complementary solutions. Coordination and open discussions with other projects will be crucial to avoid major overlaps and optimize resources.

6. Next steps

As described in the DoW, the first release of the SAbyNA Guidance Platform is scheduled at month 24, and this will be the ultimate goal of the activities in T6.4 during the coming period.

A meeting with the Advisory Board took place the last week of October, and targeted interviews with selected stakeholders (mostly potential users) are currently being conducted (as a joined effort from T6.1, T7.2 and WP8). Several of the discussion points raised in this current deliverable were presented during the Advisory Board meeting and are also addressed during the stakeholder interviews. On the basis of this feedback, the scope and specifications of the SAbyNA Guidance Platform will be revised.

The databases on activity lists, material functionalities, hazard warnings, and the decision flows on how these will link to early safety recommendations will continue to be the focus of T6.4 activities in the coming months.

It is foreseen that WP2 and WP3 will soon finalize the analysis of existing CB/RA tools and their suitability and limitations for SbD purposes. This analysis will be extremely useful in refining and extending in detail the initial workflows that were presented in Section 3.3 per each type of user case. We also expect that WP4 and WP5 will soon finalize the compilation and categorization of resources for SbD and that this will allow associating specific SbD solutions to different type of user cases.

Efforts to align nomenclature are still necessary. Definitions for some key concepts, such as nano-enabled product will be discussed and agreed in the coming weeks.

Altogether, activities will converge into the generation of the first version of the SAbyNA Guidance Platform.