Safe-by-design and EU funded NanoSafety projects

Contribution of the EU NanoSafetyCluster (NSC), supporting the SbD-study of the European Commission, March 2021

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Content

1. Safe by Design nanomaterials (R&I landscape)

Safety aspects are amongst others very important to be addressed in the research, development and innovation (R&D&I) along the entire development chain, and specifically already from the earliest possible stages onwards. Considerable experience and knowledge have been gained in recent years tailored to nanomaterial related safety aspects. This enables the entire development and manufacturing areas to reduce delays to market launch of a product while extending their design processes to Safety and Sustainability by design (SSbD). Safety-by-Design concepts and solutions developed in the nanotechnology area have the potential to become an essential asset in the future SSbD approach. Hence, several EU-funded projects in the frame of H2020 have already begun to integrate such aspects into their activities. Besides application and/or product oriented frontrunner-projects (e.g R2R Biofluidics-project[1]) has already incorporated sustainability aspects [in relation to the UN SDGs][2]). In other projects case studies[3,4] have been performed and initial discussions on safe innovation approach[5] took place. In a few ‘closer-to-the-market’ projects (e.g. OITBs[6]) this has been included specifically. Of course, it is needed to further advance current SbD tools and models to be future proof. Thus, the H2020 projects that address SbD aspects either on materials and models[7]-level, as well as on complex systems[8], have to support the further development by implementing this in the standard development process, and in parallel, shall contribute to the establishing a nano risk governance council[9] and a sustainable nanofabrication community[10]. Furthermore, a key issue to implement SbD is data. To enable SbD-implementation, all the knowledge needs to be handled according to the “FAIR”-principles[11] to secure its access and use in the long-run, connected with European initiatives (e.g. EOSC[12], EUON[13]), made operational via an umbrella infrastructure (i.e. NanoCommons[14]) that shall be the organisational center to include or make accessible all data from finished and/or ongoing H2020 (e.g. PROCETS[15], caLIBRAte[16], ACEnano[17], Purenano[18], Hi-Accuracy[19], etc.) as well as future projects that will be funded under Horizon Europe.

In the following paragraph, an overview is presented of the activities related to the safe-by-design concepts and is based on both recently finished and ongoing H2020 nanosafety projects connected to the EU NanoSafety Cluster.

[1] R2R Biofluidics project www.r2r-biofluidics.eu
[2] Schimpel et al. (2018) https://doi.org/10.1016/j.jchas.2017.06.002
[3] NanoReg2 project; EC4SafeNano project; Hi-Response project; Smart4Fabry project
[4] GRACIOUS; PATROLS;
[5] Shandilaya et al. (2020) https://doi.org/10.1016/j.impact.2020.100258
[6] Open innovation test bed projects; e.g.: NextGenMicrofluidics; FlexFunction2Sustain;
[7] NMBP-15-projects: ASINA; SABYDOMA; SbD4Nano; SAbyNA
[8] NMBP-16-projects: DIAGONAL; HARMLESS; SUNSHINE
[9] NMBP-13-projects: Gov4Nano; NanoRigo; RiskGone
[10] NMBP-12-projects: NanoFabNet; SusNanoFab
[11] Wilkinson, M., Dumontier, M., Aalbersberg, I. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* **3,** 160018 (2016). https://doi.org/10.1038/sdata.2016.18
[12] EOSC portal https://eosc-portal.eu/
[13] European Observatory Nano https://euon.echa.europa.eu/
[14] NanoCommons project www.nanocommons.eu
[15] PROCETS https://cordis.europa.eu/project/id/686135
[16] caLIBRAte http://www.nanocalibrate.eu/home
[17] ACEnano http://www.acenano-project.eu/
[18] Purenano https://www.purenano-h2020.eu/
[19] Hi-Accuracy https://www.hi-accuracy.eu/

Acronym	Coordinator	SbD features	Start	End
Calibrate	Keld Alstrup Jensen	x	05-2016	10-2019
SmartNanoTox	Vladimir Lobaskin		03-2016	02-2020
Lorcenis	Christian Simon		04-2016	03-2020
ModCOMP	Costas Charitidis		04-2016	03-2020
ACEnano	Eva Valsami-Jones	x	01-2017	12-2020
npSCOPE	Tom Wirtz / Tommaso Serchi		01-2017	12-2020
GRACIOUS	Vicki Stone	x	01-2018	06-2021
PATROLS	Shareen Doak		01-2018	06-2021
Evo-Nano	Igor Balaz		10-2018	09-2021
NanoCommons	Iseult Lynch		01-2018	12-2021
M3DLoC	Costas Charitidis		01-2018	12-2021
NanoFabNet	Steffi Friedrichs		03-2020	02-2022
NanoExplore	Athena Progiou		10-2018	03-2022
Purenano	Luca Magagnin	x	06-2019	05-2022
Gov4Nano	Monique Groenewold		01-2019	12-2022
RiskGone	Maria Dusinska		01-2019	02-2023
NanoRigo	Janeck Scott Fordsmand		01-2019	02-2023
NanoSolveIT	Antreas Afantitis		01-2019	02-2023
NanoinformaTIX	Miguel A Banares		01-2019	02-2023
Hi-Accuracy	Alexander Blümel	x	04-2020	03-2023
Nanoharmony	Thomas Kuhlbusch		01-2020	12-2023
Nanomet	Anne Gourmelon		01-2020	12-2024
ASINA	Anna Costa	x	01-2020	12-2024
SAbyNA	Socorro Vázquez	x	01-2020	12-2024
SABYDOMA	Andrew Nelson	x	01-2020	12-2024
SbD4Nano	Carlos Fito	x	04-2020	04-2024
HARMLESS	Tobias Stöger	x	01-2021	01-2025
SUNSHINE	Danail Hristozov	x	01-2021	01-2025
DIAGONAL	Juan Antonio Tamayo Ramos	x	01-2021	01-2025

Table 1: screening of SbD-relevant EU-funded projects (non taxative list).

1.1 Activities in Europe, and outside, which are related to sustainability requirements (including policies, standards, labelling schemes, etc.)

- The Nanomaterials Expert Group (NMEG) of **European Chemicals Agency** (**ECHA**) aims to provide information and advice on scientific and technical issues regarding the implementation of REACH (registration, evaluation, authorization and restrictions), CLP (classification and labelling) and BPR (biocidal products regulation) legislation in relation to nanomaterials. The activities include: preparing new and updated guidance documents; sharing experience with, and generating consensus among, Member State Competent Authorities and members of the risk assessment and Member State committees, concerning safety information for nanomaterials in REACH registration dossiers; providing feedback and advice to companies that register nanomaterials; participating and contributing to ongoing international regulatory activities (such as the OECD Working Party on Manufactured

Nanomaterials or the Malta Initiative for developing test guidelines); webinars to inform and discuss the latest developments regarding REACH and CLP processes related to nanomaterials, and to help registrants prepare and submit dossiers that involve nanomaterials; hosting the European Union Observatory for Nanomaterials to increase transparency of information on nanomaterials. https://echa.europa.eu/regulations/nanomaterials

- The **Organisation for Economic Co-operation and Development** (OECD) work on environment helps countries design and implement effective policies to address environmental problems and sustainably manage natural resources.[20]
- The **Malta Initiative Towards safer nanomaterials** brings together a group of EU member states, the European Commission (notably the DG RTD, DG ENV, DG GROW and JRC), ECHA, industry and other institutions committed to the aim of adapting/developing Test Guidelines (TG) and Guidance Documents (GD) for testing nanomaterials.[21]

The work that will be performed in SAbyNA will leverage data that can support the standards/ guidance documents currently under development, and potentially generate novel candidate test guidelines and standards to the relevant committees.
SAbyNA will contribute to the different European Regulatory and Standardization Initiatives with the outcomes to help to accelerate their goals. Several SAbyNA partners are participating in relevant technical committees (TC) and will inform and raise awareness of the generated knowledge to the following initiatives:

- OECD- Working groups on Manufactured Nanomaterials
- OECD project 4.95 (Guidance Document on the adaptation of in vitro mammalian cell-based genotoxicity TGs for testing of manufacturing nanomaterials)
- OECD test guidelines to determine the particle size and size distributions of nanofibers and nanoparticles
- ISO/TC 229-Nanotechnologies
- ISO 22293- Evaluation of methods for assessing the release of nanomaterials from commercial, nanomaterial-containing polymer composites
- ISO/ TC 146/SC 2/ WG8- Assessment of contamination of skin and surfaces from airborne chemicals
- CEN/TC 352-Nanotechnologies: Projects:PWI00352047 "prCEN/TS Safe-by-Design concept dedicated for nano scale materials (MNM) and products containing nanomaterials"PWI00352046 "prCEN/TS Risk Assessment and Life Cycle Assessment of Nanomaterials: Synergistic use of data for efficient and effective evaluations"
- CEN/TC 137-Assessment of workplace exposure to chemical and biological agents
- OECD Malta Initiative (participating in different projects)
- ECHA and EFSA expert groups dealing with Nanomaterials

GRACIOUS is generating a framework to allow practical application of grouping and read-across for nanoforms. This approach will reduce the need to assess every nanoform on a case by case basis, thereby reducing animal use, reducing resource (chemicals, cells and energy) use, time and costs.
The activities of GRACIOUS feed into the following European activities:

- OECD working groups on Manufactured Nanomaterials, Integrated Approaches to Testing and Assessment, and Test Guidelines.
- OECD Malta Initiative
- ECHA REACH contributions to nanomaterials expert group.

[20] https://www.oecd.org/environment/
[21] https://www.nanosafetycluster.eu/international-cooperation/the-malta-initiative/

Further activities mentioned:

- Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008)
- Regulation (EC) No 1907/2006 – REACH
- Regulation (EC) N° 1223/2009 on cosmetic products
- Regulation (EU) 2017/745 on medical devices
- PPE directive
- EU standards on PPE certification: UNE-EN 149:2001+A1:2010 / UNE-EN 13274-7 / UNE-EN 143 / UNE-EN 13274-5 / UNE-EN 148-1 / UNE 0064-1 / UNE 0064-2 / UNE 0065 / UNE-EN 14683:2019+AC:2019
- General Product Safety Directive (GPSD) 2001/95/EC
- European directives on safety and health at work
- EU Ecolabel Regulation http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:027:0001:0019:EN:PDF
- CEN/TS 17276:2018 Nanotechnologies - Guidelines for Life Cycle Assessment - Application of EN ISO 14044:2006 to Manufactured Nanomaterials
- Revision of CEN ISO/TS 13830:2013 Nanotechnologies - Guidance on voluntary labelling for consumer products containing manufactured nano-objects (ISO/TS 13830:2013)

1.1.1 General and/or national initiatives:

- The **European Green Deal** is the European action plan to make the EU's economy sustainable.[22]
- Springer Publisher has launched **Nature Sustainability**, a new scientific journal dedicated to sustainability.[23]
- The proceedings of the American National Academy of Science **(PNAS)** has a section dedicated to sustainability science.[24]
- The **United Nations Agenda 2030** for Sustainable Development.[25]
- **LabEx SERENADE** (French program): Laboratory of excellence for safe(r) ecodesign research and education applied to nanomaterial development and it is a safe by design project.[26]

Private sector SbD and sustainability initiatives e.g.

- "We create chemistry for a sustainable future" – BASF (https://www.basf.com/gb/en/who-we-are/sustainability.html)
- "A successful, sustainable business" - Unilever (https://www.unilever.co.uk/sustainable-living/)
- "Committed to a sustainable future"- Nouryon (https://celluloseethers.nouryon.com/sustainability/)

1.2 Outputs of initiatives, enabling progress beyond the state-of-the-art

- There has been growing research into SbD methods and tools that could support the implementation of a safe innovation approach and the meeting of regulatory matters. Some examples of recent European research projects include **ProSafe, NanoMile, EC4SafeNano,**

[22] https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en
[23] https://www.nature.com/natsustain/
[24] https://www.pnas.org/portal/sustainability
[25] https://sdgs.un.org/2030agenda
[26] http://www.labex-serenade.fr/labex-serenade

NANoREG and **NANoREG2**. Using the Cooper's Stage-Gate [27]innovation methodology as the basis, a SbD process addresses three pillars of development (safe product, safe production and safe use) and three risks elements (timely identification of uncertainties, exposure assessment and hazard characterisation). Despite this progress, the majority of RA and RM methods and tools employed in SbD processes, still mainly focuses on the pristine or simplified nanomaterials. The **OECD** series of frameworks and data collection focused on the development of safe nanomaterials.[28]

NSC project	Outputs of initiatives, enabling progress beyond the state-of-the-art
NANoREG II	A **Safe Innovation Approach (SIA)** Toolbox has been developed that should support decision making in developing nano-enabled technology.[29] SIA toolbox (see https://www.siatoolbox.com/tool), which was the result from the NanoReg2 project.
NanoCommons	A nanosafety knowledge infrastructure is offered, that organizes and visualises data and data relationships, integrating computational tools for risk assessment and decision support.[30]
GRACIOUS	A framework has been developed that supports the use of grouping and read-across throughout all innovation stages of a nanoform or nano-enabled product. The GRACIOUS Framework includes tiered testing, so that simple in vitro, in silico or in chemico tests can be prioritised for data generation if required, only moving to animal testing if required at the later stages of product launch. Using grouping and read-across during innovation reduces the need to generate data for all nanoforms during their development, can allow identification of high risk nanoforms at an early stage without the need for testing and therefore can streamline the decision making process.
SANOWORK	SbD strategies have been applied to NM and processes and tested in pilot processing lines.
SUN	**S**afer by design strategies in order to open new possibilities for innovators to**-** design greener nanotechnologies.[31]
GUIDEnano	a web-based tool has been made available for supporting decision making about safety of nanoforms and nano-enabled products.[32]
HARMLESS	SbD will be based on the framework of **NanoReg2**, but also in the framework of **Guidenano** and **SUN** projects. All three projects arrived to a general conclusion that, of course, you can arrive to safer nanomaterials through design but it is difficult to establish general design rules that permit to decrease the toxicity of NMs or increase their safety. In the particular case of **NanoReg2** three pillars have been considered for Safe-by-Design (safer industrial processes, safer products containing NMs, safer NMs). Considering these three pillars, in the case studies[33] of **NanoReg2** the industrial partners have arrived to a safer production. The comparison of the information generated in terms of ecotoxicity, physico-chemical

[27] https://www.researchgate.net/publication/4883499_Stage-Gate_Systems_A_New_Tool_for_Managing_New_Products
[28] http://www.oecd.org/chemicalsafety/nanosafety/
[29] https://www.rivm.nl/en/about-rivm/mission-and-strategy/international-affairs/international-projects/nanoregii/introduction-sia-toolbox
[30] https://www.nanocommons.eu
[31] http://www.sun-fp7.eu/
[32] https://tool.guidenano.eu/
[33] NanoImpact 20 (2020) 100267, https://doi.org/10.1016/j.impact.2020.100267.

	properties and structural features of nanomaterials used in Harmless will also give important clues for safe(r) by design approaches
SUNSHINE	Will transfer SbD and Safe Innovation approaches from previous projects (**NANoREG, NanoReg2, and NanoMILE)** as a basis for the SUNSHINE Safe Innovation Approach (SIA) e-infrastructure. The SIA e-infrastructure will be developed in a close collaboration with the ongoing **SbD4Nano** project and on the basis of the NanoReg2 Safe Innovation Implementation Platform. There will a connection with NMBP-15-2019-projects SbD4Nano, ASINA, SAbyNA and SABYDOMA to align SUNSHINE with the activities in the area of Safe-by-Design of nanomaterials to be developed in these projects. The H2020 projects **SUN, GUIDEnano** and **SANOWORK** will provide data on specific surface modification Safe-by-Design strategies for nanomaterials (e.g., doping, coating, functionalisation, passivation, agglomeration) and safe process design strategies, while **NanoMicex** will contribute information on the efficacy of risk management measures for nanomaterials to use as starting points for the respective activities in **SUNSHINE**. **SUNSHINE** also participates to all Safe-by-Design initiatives of the European Nanosafety Cluster.
caLIBRAte	**caLIBRAte** SbD tools - **SUN/caLIBRAte** Decision Support System (DSS) (nanoriskgov-portal.org/Public/Index (nanoriskgov-portal.org))

Table 2: Output of EU-funded projects relevant to SbD (non taxative list).

1.3 Application oriented projects and/or initiatives dedicated to SbD including sustainability requirements in the private sector

NSC project	Description
PRISMA	Piloting responsible research and innovation in industry, delivers Frameworks and physical facilities for piloting responsible research and innovation in industry.[34]
HARMLESS	Case studies of the **NanoReg2** project with industrial partners (e.g. Grupo Antolin, **Avanzare, Nanomakers, Nanogap, HIQ-NANO**, etc. Detailed information about these case studies and safe(r)-by-design approaches in NanoImpact 20 (2020) 100267, https://doi.org/10.1016/j.impact.2020.100267 The global "responsible care" initiative of the chemical industry includes projects on nanomaterials, but is not limited to them. SbD process tools are not specific to nanomaterials, and already routine in project portfolio management https://cefic.org/our-industry/responsible-care/ .
SABYDOMA	The main applications of the project output are a technological platform which manufactures safe nano at source requiring a minimum of further testing. Another application of the project output is a complete reworking and subsequent synthesis of the SbD philosophy which can be applied to all Safety issues in Society. Implicit in both the Lead Demonstrator and the philosophy which underwrites it, there is a commitment to sustainability throughout.
SAbyNA	will have an impact on the United Nations Sustainable Development Goals, in particular in SDG3- health and well-being, SDG6-Clean water, SDG7-clean Energy; SDG9-Industry innovation and infrastructure and SDG12-responsible

[34] https://www.airi.it/prisma-piloting-responsible-research-and-innovation-industry/

	consumption and production; contributing to these goals by enabling sustainable, safe and fair industrialization of NEPs.
PROCETS, Purenano	some coating sector companies, electroplating and thermal spraying, have applied or are applying SbD in their production lines.
DIAGONAL	SbD and SustbD will be applied to nanomaterial production companies.
LightMe	covers Environmental (LCA and Resource efficiency), economic (LCC), circularity.

Table 3: Application areas in EU-funded projects relevant to SbD (non taxative list).

2. H2020 projects

2.1 NMBP-15 – “Safe by design, from science to regulation: metrics and main sectors”[35]

NSC project	Description
ASINA	Development of a Management Scheme, driven by ASINA Expert System (data management tool) that nano-manufacturers may adopt to implement Safe-by-Design approach. Two value chains are considered (antimicrobial coatings, nano-encapsulating systems (antimicrobial and antiaging active components) for cosmetics)[36]
SABYDOMA	Development of a technology to design safe nanomaterials at source and running this technology in four case studies (nanomaterials and nanocoatings production).[37]
SAbyNA	Development of a web-based platform that includes and manages existing tools, in support to small and medium enterprises for the development of safe nano-based technology.[38]
SbD4Nano	Development of an infrastructure which consist of two parts; one part in which the user can access basic information on SbD, data on hazard, exposure, pchem and regulatory requirements; and then a second part in which the user can describe their own case study and get scores based on existing models from current or former projects.[39]

Table 4: Metrics and Sectors of NMBP-15-projects.

[35] https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/nmbp-15-2019
[36] https://www.asina-project.eu/
[37] https://www.sabydoma.eu
[38] https://www.sabyna.eu/
[39] https://www.sbd4nano.eu

2.2 NMBP-16 – “Safe by design, from science to regulation: multi-component nanomaterials”[40]

Project	Description
DIAGONAL	Efforts on the study of MCNM forms or NMs with heterogeneous morphology, required to meet specific functionalities (MCNMs and HARNs). DIAGONAL will advance the SoA in following directions: 1) Expand the application of SbD approaches to integrate issued related to MCNMs and HARNs; 2) Define processes to facilitate the coordination between different parties involved in the process: modellers, experimentalist, industrial demonstrators. 3) Integrate the RA and RM under a SbD approach; 4) Unification of terminology and knowledge transfer to industry and civil society (consumers); 5) Acquire a holistic perspective by including LCSA methodologies, integrating the SusbD principles. The later will be achieved through two different aspects, i) integrating the new experimental knowledge into the LCA system via characterisation factors, ii) developing a full LCSA including env-LCA, LCC and SOLCA methodologies. Previously available and newly produced hazard and exposure data, considering NMs and NEPs fate along their life cycle, will be integrated in novel multi-scale modelling tools, such as exposure modelling, physiologically-based kinetic modelling, and structure-activity prediction networks, which will be able to determine the joint toxicity action of MCNMs, HARNs and their transformation products.
HARMLESS	Fish acute toxicity and fish bioaccumulation assays using selected nanomaterials (NMs). These assays will be performed following the OECD Test Guideline 203 (TG 203, Fish acute toxicity) and OECD TG 305 (Bioaccumulation in fish). Both TGs have been originally set up for chemicals and there is a need to compile data to ensure their applicability to NMs. Our partners are now working at the OECD level (together with the Spanish competent authorities) in order to confirm the applicability of these TGs to NMs and, if deemed necessary, propose some adaptations. Furthermore, test development will be carried out related to the algal growth inhibition test (OECD TG 201). Here collaboration with the NanoHarmony project has been initiated in PATROLS and will be continued in Harmless. Furthermore, we follow the principles of the EC Chemicals Strategy for Sustainability, which again tightly links us to the safe-by-design (SbD) principles.
SUNSHINE	Safe and sustainable by design (S&SbD) strategies to be developed in SUNSHINE will consider also environmental and socioeconomic aspects. Specifically, SUNSHINE will propose criteria and guiding principles to be delivered as practical guidance for sustainable by design. These sustainability criteria and guiding principles[41] will be derived from Prospective Lifecycle Analysis (LCA) studies following the ISO 14040 standard as well as economic and social cost-benefit analysis studies. With these activities SUNSHINE aims to contribute to

[40] https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/nmbp-16-2020

[41] Details are provided in the answer to question 6

	the European policy ambitions for Circular Economy as in The Green Deal and in the Circular Economy Action Plan.

Table 5: Multi-Component nanomaterials addressed in NMBP-16-projects.

2.3 Scope and application area of nanomaterials within H2020-SbD-projects (NMBP-15 & NMBP-16)

The following section contain – self-reported information by project coordinators

2.3.1 ASINA

Although ASINA pursues an as general as possible development of an approach to the implementation of Safety-by-Design processes for the production of nano-enabled products, the project will focus on:

a. ANTIVIRAL NANOSTRUCTURED COATINGS (reusable PPE or photocatalytic air filters for the sanitation of indoor environment);
b. NANO-ENCAPSULATING SYSTEMS carrying antimicrobial or antiaging ingredients at liquid or powder state (lotion, spray, gels).

Given the current COVID-19 EMERGENCY, ASINA has been included within EU projects tackling corona virus and aims to improve the design and validate nano-enabled technologies (nano-Ag, nano-TiO_2, essential oils) along the entire value chain.

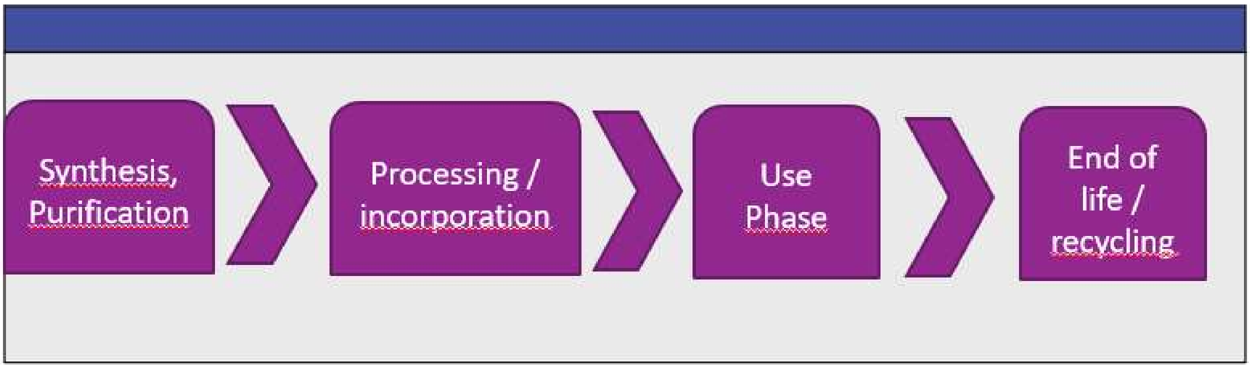
ASINA considers SbD for the addressed value chains (VCs) through the whole nanomaterials (NMs) and nano-enabled products (NEPs) life cycle by applying a modular approach. This is done through the identification of four main stages in the life cycle, corresponding to four analytical modules:

- NMs synthesis and purification
- NMs processing and incorporation
- Use phase
- End of life (for linear models) /recycling (for circular models).

SbD will be applied to all stages of the life cycle.

- specific focus on the occupational safety will be given within the first two modules. Modelling and experimental sampling will be performed in order to identify the most critical conditions for occupational exposure to NMs.
- For the use phase, end user exposure and environmental safety will be considered specifically for the use options and potential misuse of NEPs.

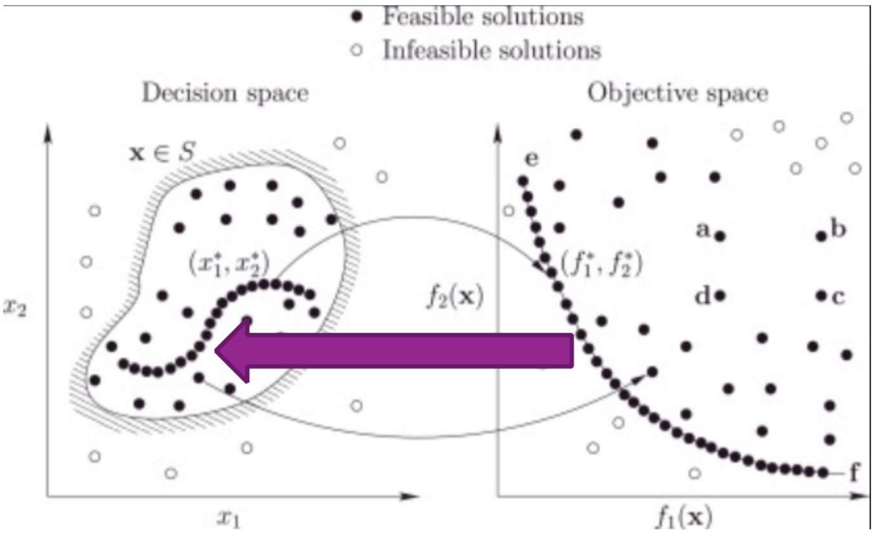
- For the end of life and recycling, specific disposal protocols will be considered in compliance to the operators safety and manufacturer requirements to avoid dispersion of NMs and maximise NEPs duration.



For all modules the potential risk of NMs will be assessed by starting from exposure, dose/response approach, followed by the study of potential Adverse Outcome, Pathways (AOPs).

Each module will be analysed by identifying the most relevant parameters, characterising NMs synthesis, processing and incorporation features, which have major impact on performances attributes: safety, functionality, LCA and LCC impact (determining sustainability). By applying the grouping theory, safety will be corelated to relevant features and behaviour of the employed NMs and NEPs such as the physical-chemical (pchem) characteristics and in turn the processing parameters determining such features.

ASINA Expert System (ASINA-ES) will generate response functions that link material and process variables to performance attributes such as those related to safety, functionality but also cost, life-cycle impact, overall sustainability. NMs engineers and product designers to select the parameters which lead to the safe/sustainable domain in the parameters hyperspace. Calibration hypersurfaces will be obtained by literature data and from the ASINA project experimental work in order to associate specific processing (synthesis, incorporation) parameters values to NEPs performance attributes.



Response functions generated by ASINA Expert System will assist the decision process

Criteria areas of sustainability covered beyond safety (e.g. environmental, circular, governance, economic and social)

ASINA will cover Environmental and Managerial aspects of the development of safer nano enabled products
In particular for the four identified a.m. modules the safety, environmental, economic and functional dimensions are simultaneously considered.

Design means “design for-X (DfX)”, whose “X” stands for: costing (Design for costing), for functionality, with ASINA DfX is enriched of the new safety dimension. Therefore ASINA SbD is intended in the broadest sense and aims at simultaneously complying with

- Low environmental and cost impacts
- Maximum efficiency and safety.

This task is addressed through the multy criteiria decision modelling (MCDM), which allows obtaining a subset of efficient solutions providing simultaneous compliance with (functional, environmental, economic and safety) performance constraints.

2.3.2 DIAGONAL

DIAGONAL will develop SbD strategies (including the three pillars -Safe products by design, Safe production, and Safe use) integrated with a sustainability dimension (SusbD) for or distinct MCNMs/HARNs and NEPs, produced by seven selected Industrial Cases offering a portfolio of products of widespread use in different sectors, such as automotive, pharma, cosmetics, textile, electronics and industrial flooring.

DIAGONAL will contribute expanding the knowledge on MCNMs, HARNs and their transformation products along their whole lifecycle (from cradle to grave) through extensive physicochemical, hazard ((eco)toxicology), and exposure assessment. All results will be used to build new or refine existing computational models based on machine learning that will be able to predict these features, in turn reducing the R&D time and cost. Experimental information will provide specific knowledge to develop characterisation factors that will support the environmental Life Cycle Assessment integrating new, experimental information valorising the risk assessment.

The NEPs will be subjected to Life Cycle Sustainability Assessment (LCSA) studies, expanding the concept of SbD into SusbD. Three types of assessment are combined to cover the three pillars: environmental LCA, social-organisational SOLCA and LCC.

2.3.3 HARMLESS

As explained above Safe-by-Design in the area of NMs needs to consider at least three different perspectives, which are the safer industrial processed (1), safer products (2) and safer NMs (3). Within HARMLESS we will tackle safer products and safer NMs. Typically safer NMs means to choose or to design less hazardous NMs. Concerning the hazards the focus within HARMLESS is mainly on toxicity/adverse outcomes following inhalation/pulmonary exposure. Relevant endpoints include inflammation, cancer, fibrosis, cardiovascular disease, based on respective Adverse Outcome Pathways. Furthermore, focus will be to establish relationships between physico-chemical properties of ENM and toxicological outcomes for SbD approaches and as benchmark for in vitro toxicity testing. However, within the industrial SbD case studies that will conducted within HARMLESS, we will also address safer products. Of course, safer products can be achieved by choosing a less hazardous NM for that product, and equally important, a potential NM release from that product. It might not always be feasible to substitute a hazardous compound for different reasons. In that sense it might be equally important to look at the product matrix and into the details how the NMs is embedded in that matrix. This is very much connected to the fundamentals of risk assessment where possible health risks can be reduced/ eliminated by reducing the hazards and as well by reducing the exposure, which in this case means reducing the release.
HARMLESS covers several industry sectors: Packaging, Paints & coatings, Photovoltaics, Chemical production, and Construction

HARMLESS case studies on advanced materials enabled by nanomaterials are:

- Papermaking uses very small (sub-10-nm diameter) silica additives of elongated morphology. The SbD design space comprises the morphology and surface doping of the silica particles.
- Paint formulations (Nouryon) are complex mixtures of both dissolved and particulate components, both organic and inorganic. Their mutual colloidal interaction may modify in turn the biological interactions. The design space for SbD comprises the size and surface modification of silica particles, and the on-nano components.
- Ag-wires (NanoLund) can result in record low haze (optical transparency) at sufficient conductivity to serve as electrode on displays of photovoltaic panels. The design space for SbD comprises the diameter and length of the fibers (with direct correlation to the performance), their doping and polymer functionalization.
- Perovskites (BASF) represent both model catalysts (where a real catalyst includes the internally porous support, the ceramic-particle washcoat and precious-metal nanoscale active sites) and record efficiency solar panels. They are also tunable emitters of light. The design space for SbD consists of the stoichiometry of multiple metals, some of them leaching, and their particle sizes, but has direct implications on the key performance indicators of catalytic or electro-optical functionality.
- Aerogels (Harvard, BASF) can be synthesized directly onto glass fiber mats, thus providing a multicomponent material that is further complicated by additional water glass and hydrophobizing organics. The release of fragments can contain nanoscale particle aggregates and fibers. The design space for SbD comprises the fractional dimension and pore sizes of the aerogel, and the diameter and composition of the fibers and other non-nano-components.
- Imogolites (CEA) are developed as environmentally friendly alternative in the treatment of vine leaves against fungus (in particular downy mildew). In the current state of development, the product contains multi-components (nanotubular framework, polymer, oxidative molecules).

Of course different life cycle stages will be considered, which is the synthesis of the NMs, the production of the products, the use phase of that product as well as the end-of-life scenario. Not every case study will target all life cycle stages as this pretty much also depends on the industrials needs. All HARMLESS case studies have been suggested by industrial partners and will also be conducted by the industry partners, but will be accompanied by other HARMLESS partners. In that way HARMLESS can ensure that various different life cycle stages will be addressed.
The HARMLESS SbD principles will be applied to all life-cycle stages. It is important that the HARMLESS framework will support safety throughout all life-cycle stages and not only to the safe production.

HARMLESS has mainly focused on safe-by-design so far while sustainable-by-design still needs to be discussed in our project.

2.3.4 SABYDOMA

SABYDOMA is committed to sustainability. Sustainability is implicit in the SABYDOMA philosophy whereby both nanomaterial screening and production will be developed as online flow through technologies and coupled together so that the screening results feedback to nanomaterial design as a control system. This step development minimises manual handling and waste, encourages recycling and increases speed in manufacturing safe nano. SABYDOMA will transfer its technology to four Case Study companies respectively in Spain, France, Greece and Ukraine so propagating its philosophy and technology throughout Europe for a long time to come.

The predominant output of SABYDOMA is a technical demonstrator which consists of a flow through online multiple screener coupled to a flow through online nanomaterial production line. This appropriately named Lead Demonstrator addresses the Safe-by-Design issue "head on" with a technological solution. The demonstrator is underwritten by a specific philosophy which revolutionises the Safe-by-Design paradigm and has general applications ranging from environmental challenges to the current Covid-19 epidemic. This overall Safe-by-Design philosophy will be developed and aligned with the Lead Demonstrator throughout the project.

Research output to date:
Zeng, T.; Gautam, R.; Barile, C. J.*; Li, Y.*; **Tse, E. C. M.*** Nitrile-Facilitated Proton Transfer for Enhanced Oxygen Reduction by Hybrid Electrocatalysts. ACS Catalysis, **2020**, 10, 13149-13155.
EU H2020 – SABYDOMA (GA 862296) acknowledged in paper.

The nanomaterials developed in SABYDOMA are very specific and are a test-bed for demonstrating novel ideas and technologies. We list them under the four case studies as follows: Case Study 1: Ag and CuO nanoparticles manufacture and screening; Case Study 2: SiC/ceramic composite coatings for medical implants stability and toxicity; Case Study 3: SiC/Ni composite electroplated coatings stability and toxicity and; Case Study 4: TiO_2 nanoparticles manufacture and screening.

Case Studies 1 and 4 which cover safe nanoparticle manufacture applies SbD mainly to safe nano production. Case Studies 3 and 4 which deal with the stability and toxicity of composite coatings apply SbD to both the short and long term stability and toxicity of the coatings which will include later periods in their life-cycle.

As stated above SABYDOMA covers all issues related to sustainability. This is exemplified in the following. The SABYDOMA philosophy of a control system approach to SbD can be applied to environmental, governance, economic and social issues. The circular economy is built into the SABYDOMA technological platform whereby screening is directly coupled to production and the screening signal is used to moderate the production process.

2.3.5 SAbyNA

The SAbyNA Guidance Platform will consider the purposes and constrains for the implementation of SbD approaches in any industrial innovation process and based on those, establish optimal workflows to identify risks and propose solutions to reduce or mitigate them as early as possible in the innovation process. SAbyNA Guidance Platform will be designed for general use by all industries, but it will include advanced functionalities tailored to two main sectors: Paints and Additive Manufacturing (3D Printing).
SAbyNA Guidance Platform will propose SbD strategies to address risks as early as possible in the innovation process, that eliminates or reduces hazard and/or exposure, considering the occupational, consumer and environmental risk domains at all life cycle stages of nanotechnology-based products, and balancing product functionality and overall sustainability.

SAbyNA’s Guidance Platform will help the industries to save costs and time by avoiding unnecessary tests and recommending SbD measures at early stage of the innovation process. The Platform will provide estimations of costs as well as overall sustainability associated with the implementation of SbD strategies via the integration of LCA and LCC tools. Furthermore, SAbyNA includes explicit RRI study actions that both engage stakeholders’ directly in constructing knowledge and ethical insights and provide reproducible tools to allow future projects and researchers across the world to add a societal database initiated in SAbyNA.

2.3.6 SbD4Nano

SbD4Nano covers 4 main markets, including functional and structural ENMs, coatings, cosmetics and food supplements, and pharma and health. We focus on manufacturing and formulation. The criteria areas of sustainability Governance, economic and social are covered by SbD4Nano.

2.3.7 SUNSHINE

SUNSHINE will address the current challenges of implementing safe and sustainable by design (S&SbD) strategies in practice by supporting the prototyping and scale-up of innovative technologies based on multi-component nanomaterials (MCNMs) in the following key industrial sectors:

- Structural and functional materials, including metal and non-metal oxide-based MCNMs, and advanced nanoscale ceramic transition metal complexes (Global market of about €27 billion in 2021 at a CAGR of 20.7% [42]).
- Food and feed technology, including MCNMs in biocidal coatings and high aspect ratio functionalized nanoclays for anti-pest packaging (Global market of about €105 billion in 2016 at a CAGR of 24% for 2018-2023 [43]).
- Energy, including graphene-carbon nanotube hybrids for electrodes and energy storage (Global market estimated to grow from €5 billion in 2018 to reach €9,5 billion by 2023 at a CAGR of 12.0% for the period of 2018-2023[5]).
- Automotive, including multi-walled carbon nanotubes/silica nanocomposites used as fillers in the rubber matrix of tires (EU tire market projected to reach €24 billion by 2024 at a CAGR of 4.5% from 2019 to 2014 [44]).
- Construction, including metal oxide complexes used in advanced paints and scratch/abrasion resistant coatings (Global market expected to reach €14 billion by 2024 at a CAGR of 6.95 % [45]).

Pharma and health technology, including functionalised and carbon nanotube-coated metals and metal-oxides used in diagnostics and therapy (Global market valued at 79,8 billion with an estimated CAGR of 17 % in the field of nanomedicine from 2017 to 2023 [46]).

The SIA e-infrastructure to be developed in SUNSHINE will be designed to facilitate collaboration and information exchange between actors along nanotechnology supply chains (developers, producers, downstream users) operating across all lifecycle stages (synthesis, formulation, use, end-of-life) to promote the development and implementation of S&SbD strategies for MCNM-based materials, products and processes. The SIA e-infrastructure will be tested for its capacity to facilitate the development of such strategies in industry-derived case studies.

The Sustainable by Design strategies to be developed in SUNSHINE will be based on criteria and design principles addressing specific environmental impacts and greenhouse gas emissions as well as the optimisation/reduction in the use of raw materials, energy resources and toxic substances, the adoption of business management practices for selection of reusable components for products that are designed to last longer, be easier to repair, upgrade and recycle. In addition, they will involve product design strategies to minimise the release of nanomaterials in the end-of-life stage (recycling, disposal, incineration).

[42] Nanomaterials Market – Global Opportunity. Analysis and Industry Forecast, 2014–2022 (Allied Market Research, September 2016)
[43] Global Food Nanotechnology Market 2019-2023.
[44] https://www.psmarketresearch.com/market-analysis/europe-automotive-tire-market
[45] https://www.marketwatch.com / nano-paints-and-coatings-market-sizeshare
[46] www.researchandmarkets.com/reports/4092019/global-nanomedicine-market-drivers

2.4 Scope and application area of nanomaterials within H2020-NanoSafety-projects

2.4.1 GRACIOUS

GRACIOUS covers all nanoforms used in consumer and industrial applications, including fillers, pigments and fibers used in composite materials. GRACIOUS does not focus on medical or pharmaceutical or sensing applications. GRACIOUS covers the pristine nanoforms when manufactured, in formulations, in products and after use/end of life. GRACIOUS covers nanoforms that may be inadvertently released into consumer, occupational and environmental settings, into air, water, soil or sediments. For humans GRACIOUS covers nanoforms that may be inadvertently inhaled, ingested or exposed via the dermal route, but does not focus on intentionally administered medical formulations.

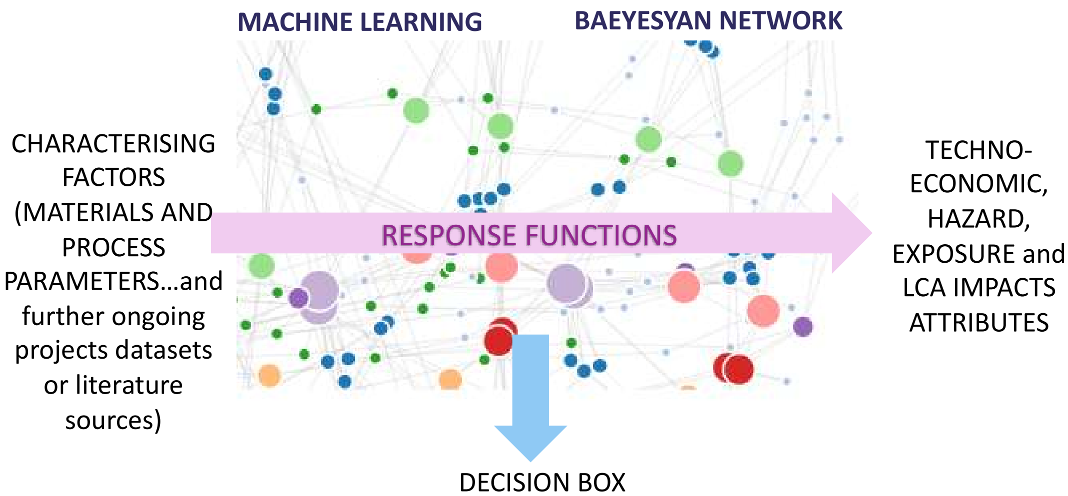
All life cycle stages are covered by GRACIOUS. Safety by design could be applied to any nanoform, or nanoenabled product at any life cycle stage using the GRACIOUS framework.

Inadvertent releases to the environment are assessed. None of the other additional areas are covered by GRACIOUS.

2.5 Main outcomes, supporting the development and applicability of a "(Safe and) Sustainable by Design"-framework

2.5.1 ASINA

ASINA will deliver a data-driven Safe-by-Design Management Methodology (the “ASINA-SMM”) molded on industrial practices currently adopted by industry.
The brain of ASINA-SMM will be the ASINA-ES that will use data management tools to generate response functions and support the decision process.



ASINA-ES generating response functions for linking NMs and process parameters (DECISION SPACE) to performance attributes (OBJECTIVE SPACE)

The strength of the SbD solutions proposed by ASINA relies on the fact that they are developed starting from the production in pilot plants, and not from the elaboration of theoretical concepts that are eventually tested in real scenarios in a second phase.The practical character of the approach developed in ASINA makes it immediately useful for SME.

2.5.2 DIAGONAL

DIAGONAL aims to bring new methodologies to guarantee long-term nanosafety and contribute to fill current gaps in: Risk Assessment (RA), Risk Management (RM) and Risk Governance (RG)research for MCNMsand HARNs along their life cycle, from NM design and production to its application into Nano-Enabled Products (NEPs),the product use, and end of life phases. Emphasis will be made in the interactions between NM constituents, with other particles and the environment, as well as their release rate and fate. The project relies on experimental (in vitro) and modelling (in silico) research to understand and ultimately predict the interactions among the NM components, their transformation products, and between the NMs and the environment, promoting a better understanding of potential adverse effects on human health, and biota. All the knowledge generated will be the basis to create specific RM guidelines and Safe by Design (SbD) tools, integrating Life Cycle Sustainability (Sustainable by Design, SusbD) to make the material not just safer but greener and economically feasible. In order to implement the planned work, the project will be supported by seven industrial demonstrators acting as NM and/or NEP manufacturers, to provide (i) material samples, (ii)industry insight, (iii) application and validation of computational tools and SbD strategies redesigning their products/processes, and (iv) helping mainstreaming safe innovations across their value chains and sectors. All the knowledge, tools and guidelines will be exploited according to the Open Innovation principles. The results will synergize with existing databases and data generated by ongoing projects and companies, while generating all its outputs following the FAIR concept (Findable, Accessible, Interoperable and Reusable Data). DIAGONAL, through its partners' networks, will align its activities with the efforts done by international expert bodies and agencies. DIAGONAL´s consortium will maximise its links with all previous and ongoing research actions and developed standards, driving its work plan to avoid overlapping and contributing to the NMs' safety community.

2.5.3 HARMLESS

The decision support tool that will be developed in the HARMLESS project will assist various stakeholders (industry, regulators, researchers) to apply the SbD and safe innovation principles in their material and product development. The HARMLESS tool will make use of existing models, tools, guidances, and databases to derive SbD decision by making use of machine learning and deep learning techniques.

2.5.4 SABYDOMA

The two main outputs from SABYDOMA are the Lead Demonstrator technical demonstrator and the underlying control system concept both of which have very wide application to Safety-by-Design and sustainability frameworks. Both these outputs can be used for very general application after the project end.

2.5.5 SAbyNA

The main outcome from SAbyNA will be a web-based Guidance Platform to support industry in the implementation of the SbD concept as early as possible in their innovation process. SAbyNA will focus on streamlining or adaptation of existing methodologies, testing strategies, models and tools for human and environmental hazard and exposure assessment into simple, robust, and cost-effective ones to obtain key input data required by the selected SbD support tools integrated in the Platform. Defining optimal workflows and finally generating sector-specific versions (Paints and Additive manufacturing) of models and tools, integrating sector-specific information, including the novo generated datasets in selected case studies.

In SAbyNA a variety of SbD strategies towards safer NFs/ NEPs and safer nanoprocesses will be proposed with a main emphasis on maintaining technical functionality of products.

Real industrial case studies will be used to demonstrate how the SAbyNA Guidance Platform can be implemented. Opportunities to increase the usability of the embedded resources, by considering sector-specific information, will be demonstrated with two selected industrial sectors: Paints and Additive Manufacturing (3D printing).

2.5.6 SbD4Nano

Sbd4nano proposes an overarching integrated software e-infrastructure where scientists, regulators and industries can interact for using, sharing, developing, testing and implementing existing or new SbD strategies. Our main outcomes are:

- Surface engineering approaches developed to meet the needs of the end users and ensure its applicability for reducing toxicity / release while meeting specific functions.
- Easy interfaces for toxicity and exposure modelling based on a crosstalk design to allow the user to operate with available modelling approaches to predict the toxicological profile of ENMs and ENPs and estimate the exposure under specific scenarios of use.
- A community framework to share valuable information for the implementation “Uptake” of SbD approaches by the industry by implementing secure information exchange protocols and by applying tailored designed workflows to operate new and existing models for hazard and exposure profiling.
- A SbD performance index based on the severity, exposure, cost and product functionality scores calculated by running existing and newly developed models
- A complete library of Sbd resources

2.5.7 SUNSHINE

SUNSHINE is an industry-oriented project, where leading research and technology organizations will cooperate with SMEs and large industries to develop and implement simple, robust and cost-effective S&SbD strategies for materials and products incorporating MCNMs. To this end, the project will establish a user-friendly e-infrastructure to foster dialogue, collaboration and information exchange between actors along entire MCNMs supply chains.

We aim to transform the state-of-the-art knowledge, tools and data on the exposure and hazard characteristics of MCNMs, especially those arising from their unique properties, into S&SbD strategies implementable at industrial scale. The S&SbD strategies will modify materials, products and processes to reduce the potential for release of MCNMs, accelerate their degradation in physiological or environmental media, and/or decrease their biopersistence, bioaccumulation and/or hazard. These strategies will be validated on the lab and pilot scales in case studies corresponding to supply chains of real products, provided by our industry partners. The S&SbD approaches that are successful in reducing the environmental and health risks, while retaining the functional performance, economic viability and overall sustainability of the modified materials, products and processes will be proposed for full scale industrial implementation.

2.5.8 GRACIOUS

The main outcome from GRACIOUS will be a Framework that can support the practical application of Grouping and Read-across for nanoforms. This Framework will be delivered as a Guidance Document and as an open access Software blueprint. The software blueprint is accessible via an online testing platform, and will be incorporated into risk assessment software such as the SUN decision support system (SUNDS) and the GUIDEnano tool.

This Framework supports grouping of nanoforms to allow data gaps to be filled at any stage in the innovation or regulatory process. By application of the GRACIOUS Framework during innovation the user can reduce the need to generate data on 'where they go' (fate and behaviour in the environment, and toxicokinetics in the human body) and 'what they do' (hazard to humans and environmental species). This will reduce costs, save time and increase the confidence for decision making by provision of a robust scientific evidence base.

3. Final Remark and Acknowledgement

This document is based on the voluntary contributions delivered by the project consortia of the projects mentioned in chapter 1 and 2. The contributions have been edited without further interpretation or commenting about those inputs. It was delivered to the European Commission to answer their request to contribute to their study on the state-of-the-art and ongoing research in the field of safe-and-sustainable-by-design.

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