Ref. Ares(2020)6241067 - 02/11/2020

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 862419. This publication reflects only the author's views and the European Union is not liable for any use that may be made of the information contained therein.

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

Identification and selection of existing SbD strategies to reduce or mitigate NF/NEP risks

WP	4	Towards SAFER PRODUCTS (NFs/NEPs): Managing risks along the NF/NEP life cycle applying SbD strategies and other RMM		
Dissemination level[a]	PU		Due delivery date	31/10/2020
Nature[b]	R		Actual delivery date	02/11/2020

Lead beneficiary	CEA
Contributing beneficiaries	ISTEC, LEITAT, IOM, ALLIOS, LATI, NOUR

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

Version	Date	Author	Partner	Email	Comments[c]
A	31/08/2020	S. Clavaguera, B. Pellegrin	CEA	simon.clavaguera@cea.fr	Creation
B	08/10/2020	S. Clavaguera, B. Pellegrin	CEA	simon.clavaguera@cea.fr	Modifications from wp4 partners
C	29/10/2020	S. Clavaguera, B. Pellegrin	CEA	simon.clavaguera@cea.fr	Final version reviewed by SC

[c] Creation, modification, final version for evaluation, revised version following evaluation, final

Deliverable abstract

The Safe by Design (SbD) concept refers to identifying the risks and uncertainties concerning human and environmental safety at an early phase of the innovation process so as to minimize uncertainty, hazard(s) and/or exposure. The aim of task T4.1 was to identify, map and sort the existing strategies used to reduce or mitigate risks associated with the use of NFs/ NEPs and their implementation in different application areas taking into account all the life cycle stages. The current deliverable D4.1 compiles the results of T4.1.

Safe-by-Design strategies were identified from publications in scientific journals and projects deliverables. The selected resources were mapped and sorted according to a set of criteria in order to point out the gaps that could be filled during the project. For this purpose an Excel file was built and used to list exiting resources in several groups (reviews, publications, reports and industrial know-how). This database will be further developed in WP4. The list of identified resources (Oct. 2020) is added to the section 6 (annexes) of this deliverable.

The literature survey identified 75 document results (2010-2020) with approximately ¾ of these published in the last three years. Among those articles, we have separated review, concept articles and position papers (35 documents) from research articles (54 SbD approaches). A total of 19 SbD approaches reported from projects (deliverables) were also gathered. Our analysis protocol using the Excel spreadsheet was applied to the selected 46 most relevant research articles and to the 19 approaches reported from projects. We proposed an analysis of the identified resources and emitted some advices for the SAbyNA upcoming activities.

Table of Content

1. Introduction

The objective of SAbyNA is to simplify and distil safety-by-design (SbD) approaches into methods that industry can adopt. Criteria for selecting these approaches should be established on the basis of this aim.

The main objective of the WP4 is to propose and evaluate design strategies towards safer nanoforms (NFs) and nano-enabled products (NEPs), by reducing exposure and/or hazard potential in critical scenarios identified throughout the product (NF or NEP) life cycle.

SbD strategies will be proposed to minimize the release / exposure / hazard of NFs from NEPs, without impairing their performances and functionalities. SbD strategies will be product oriented, meaning that the solutions will imply tuning of the NF physico-chemical properties, or the matrix composition (potential interactions between NF and the matrix), and/or the NEP characteristics. Strategies will aim at:

- Reducing the NF/NEP hazard (e.g. replacement, surface modification…)
- Reducing the NF exposure potential before incorporation in NEP (e.g. granulation, encapsulation…)
- Reducing the NF release / exposure from the NEP (e.g. NF/matrix compatibility & interactions, NF load & dispersion…)

The aim of task T4.1 is to identify, map and sort the existing strategies used to reduce or mitigate risks associated with the use of NFs/ NEPs and their implementation in different application areas taking into account all the life cycle stages. Several sources of information (European and national projects, literature review and industrial partners know-how) will be used for that purpose. The current deliverable D4.1 compiles the results of T4.1.

2. Description of the tasks

The first sub-task related to the completion of T4.1 is to define criteria for selecting SbD approaches to be compiled in D4.1. This sub-task was associated with the milestone M4.1 that was released on July 2020. The second sub-task was to create an inventory of existing resources and identify existing strategies. The last sub-task was to identify, analyse and sort the existing strategies in order to identify the gaps that could be filled during the project.

For this purpose an Excel file was built and used to list exiting resources in several groups (reviews, publications, reports and industrial know-how). This database will be further developed in WP4. The list of identified resources (Oct. 2020) is added to the section 6 (annexes) of this deliverable.

3. Description of the work and main achievements

Several initiatives to define the concept of safe-by-design (SbD) with regards to NFs and NEPs have emerged over the last decades. The terminology around the concept encompassed *safe-by-design*, *safer-by-design* or *safety-by-design* approaches among others. The SbD concept refers to identifying the risks and uncertainties concerning human and environmental safety at an early phase of the innovation process so as to minimize uncertainty, hazard(s) and/or exposure. We further develop those concepts in the following section.

3.1 Conceptual approaches

3.1.1 Prevention through design approach

Prevention through design (PtD) is a set of principles that emerged around the 1970's from the NIOSH[d], which includes solutions to mitigate potential hazards to workers and strategies to eliminate exposure in facilities and consequently minimize risks at the workplace.

PtD rely on the traditional hierarchy of controls by focusing on hazard elimination through the application of engineering controls (collective protective equipment), administrative controls, and the use of personal protective equipment applied during design, redesign and retrofit activities. Those measures participate in control risk to workers at an acceptable level and have been applied to various sectors over the years.

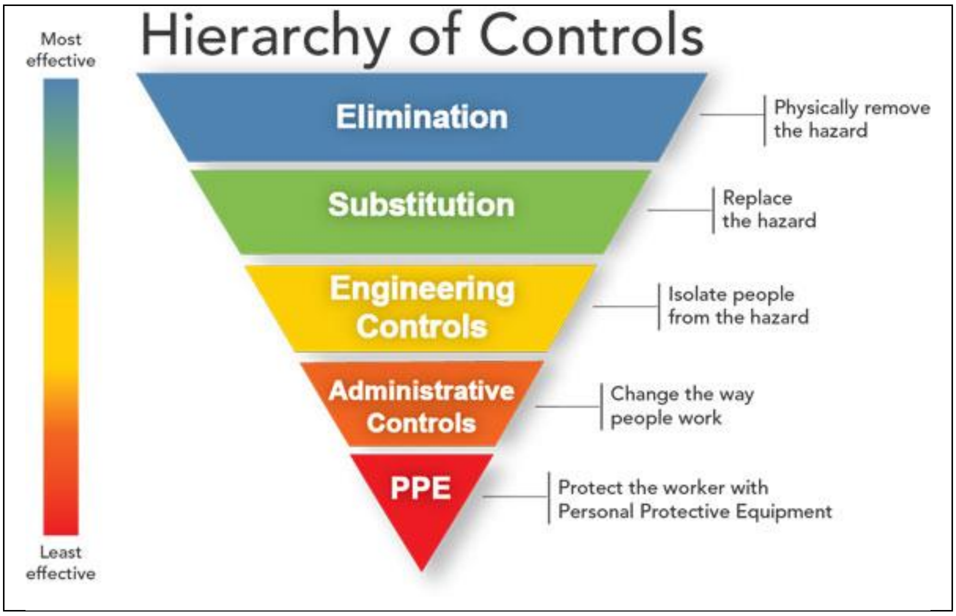

Figure 1. NIOSH[e] representation of the hierarchy of controls

Within the construction industry where PtD approaches were implemented, there has been an emphasis on design modification as a way to prevent injuries on the work floor and reduce negative health effects for those constructing, using or maintaining a product.

PtD is applicable to nanotechnology by including the design of nanomaterials and strategies to eliminate exposures and minimize risks over all the stages of the life cycle of NFs and NEPs. The application of such approaches with a strong focus on prevention would allow the community to avoid the repetition of the history of harmful substances that have been used before illnesses appeared (asbestos, lead, silica etc.).

The most effective approach from the hierarchy of control is to eliminate or to design out hazards. For obvious reasons, elimination is not an option and substitution of a NF to another material is often unlikely. The preferred strategy aims at modifying specific physico-chemical parameters (e.g. size, shape, surface functionalization, surface charge, factors leading to aggregation...) of the materials that alter its biological and environmental activity. The idea is that by modifying the nanomaterial its technical functions and commercial utility could be maintained while the potential hazard is reduced or mitigated. Therefore, the understanding of the mechanisms that control material formation and functionalization is essential to identify future production methods that permit more sophisticated and multiple functionalities without increasing waste from production. Our understanding of

[d] National Institute for Occupational Safety and Health
[e] https://www.cdc.gov/niosh/topics/hierarchy/default.html

transformations and surface reactivity of nanomaterials is in its infancy, and will also be important for understanding, and predicting, product performance, as well as impacts on organisms and the environment.

The recent development of high-throughput screening techniques participated in the more rapid identification of nanomaterial hazards and the mechanisms of nanomaterial toxicity. Predictive modelling relies on those findings and will be one of the key factors to designing inherently safer products and greener nanotechnology.

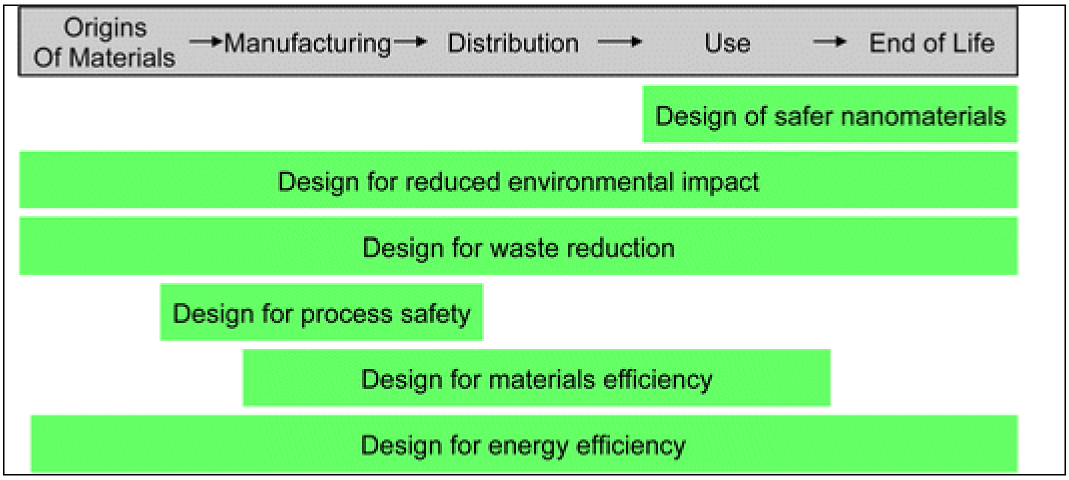

Figure 2. Mapping of the green nanoscience / nanotechnology design principles across the stages of the lifecycle of products. Collectively, the design principles address the challenge of reducing hazards, enhancing material and process efficiency and maximizing the net environmental benefit of NEPs.

3.1.2 Stage Gate process

Within the NANoREG project, emphasis has been placed on SbD as a way to develop new products where functionality and safety are tested in an integrated way during product or material development. In its approach to the concept, the NANoREG project has chosen to link SbD to a "stage gate model of innovation". The model for SbD from this EU funded project presents the innovation process as consisting of various stages, each with its own requirements that need to be met in order for development to move on to the next stage. A gate then represents a "decision" or a "control" point, at which evaluation needs to occur, in this case focusing on safety considerations and risk potentials, before product development can continue.

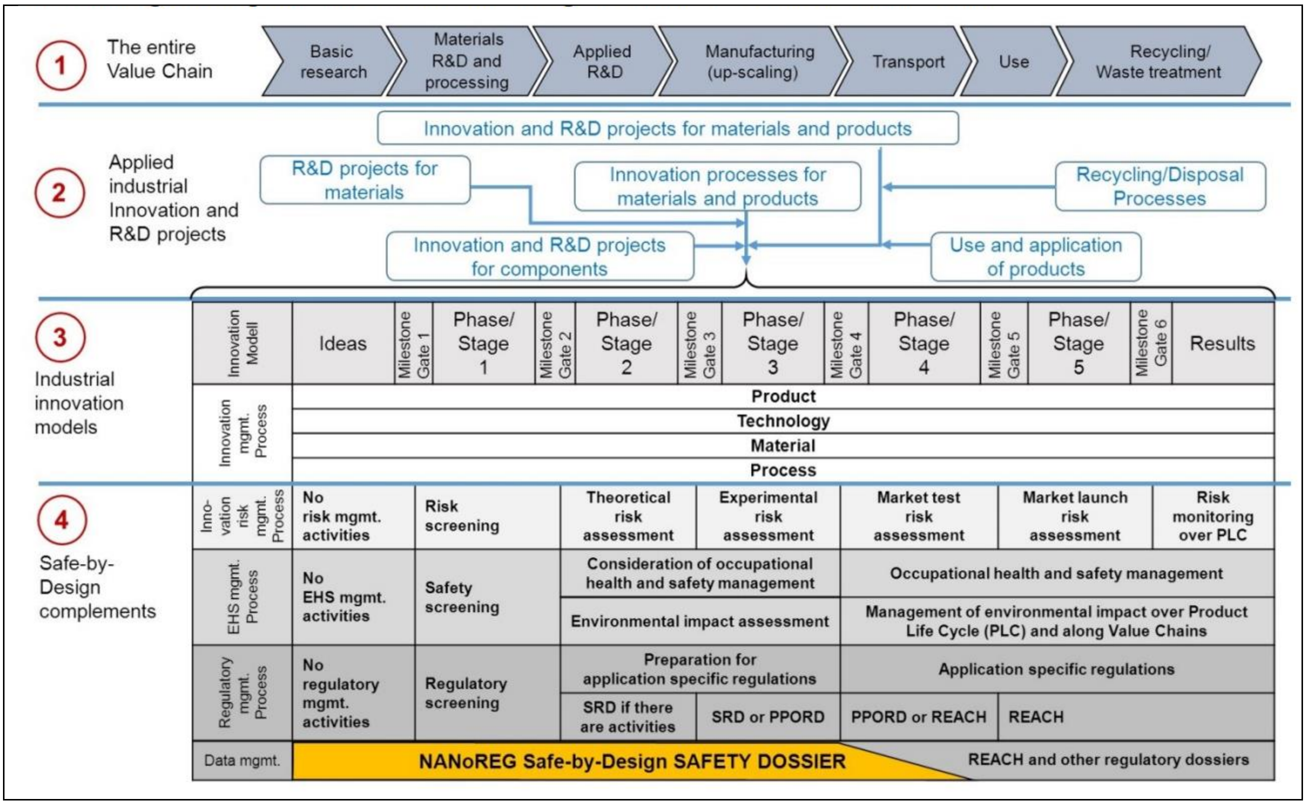

Figure 3. The NANoREG SbD concept based on the stage to gate innovation model.

3.1.3 Three pillars approach

In the NanoReg 2 project, three pillars of safe design, safe production, and safe use underpin a “safe innovation” approach in which the SbD concept is combined with “regulatory preparedness”. The latter is said to refer to a timely interaction between innovators and regulators, with the idea being that through focusing on safety issues early in the production and design process, as well as throughout the innovation chain, innovators are prepared with the information and knowledge they need to meet any regulatory requirements.

Creating safe ENMs in pillar 1 (safe materials and products for human health and the environment) is described as being achieved through understanding factors that influence “risk potential” and assessing knowledge on these using “non-testing” tools such as structure activity relationships, grouping strategies and high throughput screening of *in vitro* and *in vivo* tests to find “less hazardous NFs”. Release, emission, exposure and fate are also factors influencing “risk” and therefore have to be considered both in pillar 1 and pillar 3 (safe use and end-of-life for preventing exposure during use and having adapted recycling and disposal routes). Pillar 2 (safe production for occupational health) will be investigated through SAbyNA WP5 activities.

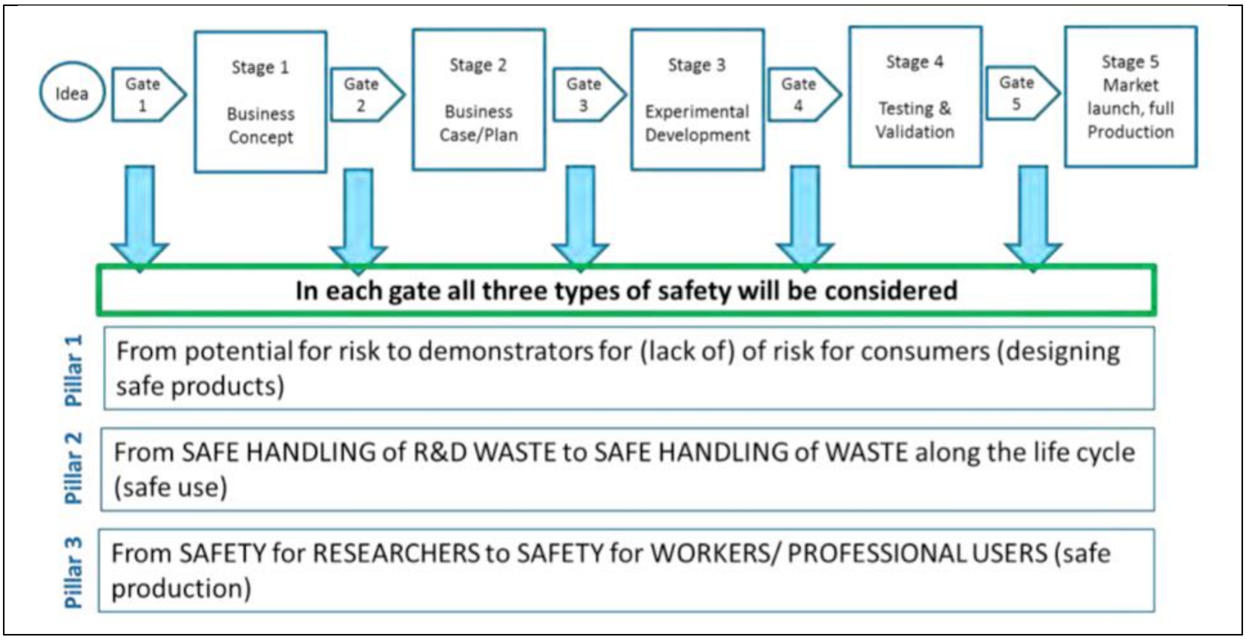

Figure 4. The Nanoreg 2 three pillars approach.

The SbD approach addresses safety of the materials/products and associated processes from the early innovation process and through the whole life cycle: from the research and innovation phase to development, production, use, recycling and/or disposal. This approach is beneficial for industry since this may increase the efficiency of the innovation process and may enable the elimination or reduction of human health and environmental risks from the material or product without losing its functionality. Additional benefits include increased economic viability, consumer trust, responsible innovation, improve sustainability, a better reputation and interdisciplinary collaboration and transparency. SbD aims at balancing safety, functionality, regulatory and cost aspects.

The scope of T4.1 is on SbD approaches applied to NFs and NEPs to minimize the determinants of risks (hazardous properties and/or emission potential) of the nanoform or nano-enabled product while maintaining their technical function (performance). Process safety will be evaluated specifically in WP5.

3.2 Defining criteria for selecting SbD approaches

We have formulated criteria for selecting SbD approaches and guidelines not as rigid rules but as aspects, or important characteristics, that must be considered when selecting a given approach. In other words, the final selection will be the result of a general evaluation of the usefulness of a SbD approach for the goal of the SAbyNA platform, and not the automatic outcome of a rigid decision rule: a SbD approach will still enter the final selection also when, in its current status, it is underdeveloped and/or does not satisfy all the criteria, but it is considered potentially useful and flexible enough to be used, and perhaps improved, within the SAbyNA platform.

3.2.1 Criteria

- Priority will be given to approaches that have been validated, tested, and implemented at a pilot scale. SbD approaches should not be just an “exercise” on how to lower the biological risks (i.e., combination of hazard and exposure for both humans and the environment) of a certain NF/NEP, but should have a focus on nano-risks along the complete life cycle of real nano-enabled products. As an indication of their effectiveness, these approaches must have quantified parameters and characteristics relevant for nano-risk before and after modification/re-design, and long term stability of the SbD solution evaluated. The chemistry involved in the SbD solution must be environmentally stable.

- Selected SbD solutions must be suitable for (or adaptable to) industrial manufacturing of large volumes (e.g., implementation and monitoring should be possible with common equipment.) The possibility, for a given SbD approach, to estimate potential costs and economical sustainability will be considered.
- Many available, and potentially useful, SbD approaches target specific sections of the life-cycle: some focus on the hazard of nanoforms, some other on the safety of a nano-enabled-product, and few of them on the environmental fate. If some of these partial approaches satisfy the other criteria and are judged to be useful for industrial applications, they can enter the final selection, and be the object of further improvement within SAbyNA platform. Obviously, if a given approach already covers the whole life cycle of a NF/NEP, it will enter the final SAbyNA selection.
- Type of source: Priority will be given to approaches that are available as open access information: research articles; official guidelines (National and EU projects, OECD, EPA-USA).

3.3 Contributing factors to risk

To achieve meaningful worker protection, material design must consider the relationships among molecular design, particle properties and the biological activity screening of ENMs; if the biological activity is considered in the molecular design, downstream characterization approaches can be tailored to the specific properties of the materials, enabling more streamlined, economic, and effective screening protocols. Libraries populated with nanomaterial data obtained from relevant biological assays (including high throughput screening techniques etc.) will aid both the predictive and practical aspects of nanomaterials characterization. Further investigation into the pathways through which and the mechanics by which nano-sized objects interact with cells will enable a clarified and more focused approach to the above mentioned techniques.

Addressing fate and exposure in design considerations (in addition to the currently predominating focus on hazard reduction) should also have a high priority.

The OECD recently published a report (ENV/JM/MONO(2019)12) entitled “physico-chemical decision framework to inform decisions for risk assessment of manufactured nanomaterials”. This document provides information regarding physico-chemical parameters that drives risks and on which SbD approaches could be applied.

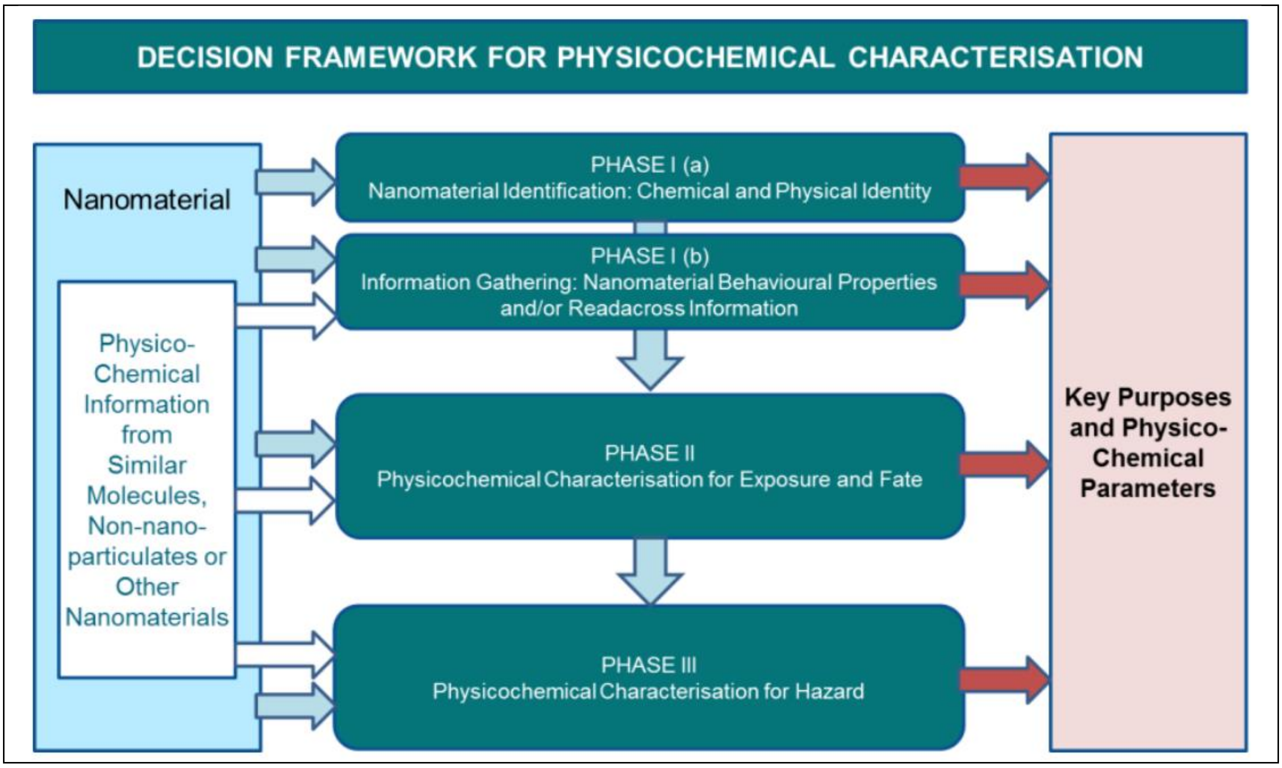

Figure 5. Overview of the decision framework for physico-chemical characterization.

From this work, we have selected the following key physico-chemical parameters driving toxicity mechanisms (Table 1) and mechanisms of concern (Table 2).

Table 1. Key physico-chemical properties

Aspect ratio - shape
Length, diameter - size
Surface layer thickness
Surface area
Porosity
Crystallinity
Surface charge
Hydrophobicity / hydrophilicity
Zeta potential
Hamaker constant
Conduction band energy level
UV-Vis absoption
Chemical composition
Surface chemistry
Surface reactivity
Chemical surface affinity
Chemical stability
Dissolution rate
Aggregation / Agglomeration state
Dustiness potential
Particle density

Bulk density
Dispersion stability
Sedimentation kinetics
Redox properties

Table 2. Mechanisms of concern

Fiber-like toxicity
Surface reactivity
Reactive oxygen species generation
Interference with intracellular redox processes
Photocatalytic activity
Trojan horse phenomena
Affinity to aquatic and terrestrial organisms
Soluble compound release

We have used this information (Table 1 and Table 2) to structure a spreadsheet to analyze the different SbD approaches identified and look for trends and gaps. Besides those key parameters, we have decided to look for information such as the identification of NFs (chemical composition, main properties, physical state…), the intended use of the NFs/NEPs (life cycle stage, industrial sector, application and targeted technical function), the hazard mechanism, and the relevant exposure route. We have then tried to look for the SbD modifications that have been implemented and the consequences in terms of risk reduction and performance.

The Excel spreadsheet (see appendix in section 6) will be further developed during the project in order to pursue the collection of resources and the assessment of the reported approaches.

3.4 Existing resources and SbD strategies

The entire lifecycle of NFs or NEPs needs to be considered to ensure minimal and known human health and environmental impact. The identified resources were screened regarding this aspect.

3.4.1 Approaches developed or implemented through European and National projects

European projects that claimed they were dealing with SbD approaches were identified through the NanoSafetyCluster and CORDIS. We have approached the SAbyNA partners that were involved in some of the projects and contacted additional colleagues involved in the other projects to have a broad view of the current approaches. From National projects, we have identified the LABEX serenade (http://www.labex-serenade.fr).

The following projects were identified but not all of them were working on SbD strategies to reduce NF/NEP risks and hence, have not all produced exploitable deliverables:

Table 3. EU projects in which Safe-by-Design is mentioned

ACEnano	Analytical and characterisation excellence in nanomaterial risk assessment: a tiered approach	http://www.acenano-project.eu/
MODCOMP	Modified cost effective fibre based structures with improved multi-functionality and performance	http://modcomp-project.eu/
NANOGENTOOLS	Developing and implementation of a new generation of nanosafety assessment tools	http://www.ubu.es/iccram
NANoREG	A common European approach to the regulatory testing of nanomaterials	
ProSafe	Promoting the implementation of Safe by Design	http://www.h2020-prosafe.eu/

NanoReg 2	Development and implementation of grouping and Safe-by-Design approaches within regulatory frameworks	http://www.nanoreg2.eu/
SmartNanoTox	Smart tools for gauging nano hazards	http://www.smartnanotox.eu
FutureNanoNeeds	A framework to respond to regulatory needs of future nanomaterials and markets.	http://www.futurenanoneeds.eu/
HISENTS	High level integrated sensor for nanotoxicity screening	https://hisents.eu/
OpenRiskNet	Open e-infrastructure to support data sharing, knowledge integration and in silico analysis and modelling in risk assessment	https://openrisknet.org/
SKHINCAPS	Skin healthcare by innovative nanocapsules	http://skhincaps.eu/
GOV4Nano	Implementation of risk governance: meeting the needs of nanotechnology	https://www.gov4nano.eu/
NanoExplore	Integrated approach for exposure and health effects monitoring of engineered nanomaterials in workplaces and urban areas	https://www.lifenanoexplore.eu/
NanoFabNet	International hub for sustainable industrial-scale nanofabrication	http://www.nanofabnet.net
SusNanoFab	Integrated EU strategy, services and international coordination activities for the promotion of competitive and sustainable nanofabrication industry	https://susnanofab.eu/
NanoInformatics	Development and implementation of a sustainable modelling platform for nanoInformatics	http://www.nanoinformatix.eu/
NanoSolveIT	Innovative nanoinformatics models and tools: towards a solid, verified and integrated approach to predictive (eco)Toxicology	https://www.nanosolveit.eu/
SANOWORK	Safe nano worker exposure scenarios	
Guide Nano	Assessment and mitigation of nano-enabled product risks on human and environmental health: Development of new strategies and creation of a digital guidance tool for nanotech industries	https://www.guidenano.eu/
NanoLeap	Nanocomposite for building constructions and civil infraestructures: European network pilot production line to promote industrial application cases	http://www.nanoleap.eu/
SUN	Sustainable Nanotechnologies	http://www.sun-fp7.eu/
Calibrate	Performance testing, calibration and implementation of a next generation system-of-systems risk governance framework for nanomaterials	http://www.nanocalibrate.eu/
Biorima	Biomaterial risk management	https://www.biorima.eu/
CeraSafe	Safe production and use of nanomaterials in the ceramic industry	http://www.cerasafe.eu/
Scaffold	Innovative strategies, methods and tools for occupational risks management of manufactured nanomaterials (MNMs) in the construction industry	http://scaffold.eu-vri.eu/
Basmati	Bringing innovation by scaling up nanomaterials and inks for printing	http://www.basmati-project.com/

The following table gathers some information about the SbD approaches that have been developed in projects. The related information has been summarized and added to the Excel spreadsheet[f] for further exploitation. A total of 19 approaches were entered and processed.

[f] "Identified SbD approaches – ressources.xlsx" that can be consulted from the SAbyNA doc repository.

Table 4. European / National project SbD approaches

Project (providing partner)	Known SbD approaches	Reference
SANOWORK (LEITAT, CNR-ISTEC)	Following a safety by design approach, surface engineering of NFs (surface coating, purification process, colloidal force control, wet milling, film coating deposition and granulation) were proposed as risk remediation strategies to decrease hazard (toxicity end points), emission potential (dustiness) and persistence at the end of life within real processing lines. • The PlasmaChem ZrO_2 manufacturing, the colloidal force control applied to the washing of synthesis reactor, allowed to reduce ZrO_2 contamination in wastewater, performing an efficient recycling procedure of ZrO_2 recovered. • ZrO_2 NM was investigated in the ceramic process owned by CNR-ISTEC and GEA-Niro; the spray drying and freeze drying techniques were employed decreasing NM emissivity, but maintaining a reactive surface in dried NM. • Considering the handling operation of nanofibers obtained through Elmarco electrospinning procedure, the film coating deposition was applied on polyamide non-woven to avoid free fiber release. For TiO_2 the wet milling was applied to reduce and homogenize the aspect ratio, leading to a significant mitigation of fiber toxicity. • In the Colorobbia spray coating line, Ag and TiO_2 nanosols, employed to transfer respectively antibacterial or depolluting properties to different substrates, were investigated. Ag was subjected to surface coating and purification, decreasing NM toxicity. TiO_2 was modified by surface coating, spray drying and blending with colloidal SiO_2, improving its technological performance. • In the extrusion of polymeric matrix charged with carbon nanotube (CNTs) owned by Leitat, the CNTs used as filler were granulated by spray drying and freeze drying techniques, allowing to reduce their exposure potential.	**SANOWORK deliverables and PhD Thesis Camilla (Delpivo, Camilla** (2015) *Safety by design: production of engineering surface modified nanomaterials*, [Dissertation thesis], Alma Mater Studiorum Università di Bologna. Dottorato di ricerca in Chimica, 27 Ciclo. DOI 10.6092/unibo/amsdottorato/6969)

GUIDE Nano (LEITAT, LATI)	*Production stage:* During the activity/ES of extrusion, the likelihood of risk was hypothesized to be high for worker exposure, with the possible inhalation of the released NM and low for the environmental compartments. For this case study, the likelihood of risk to appear during the production process was assumed to be high for the worker, as the worker was supposed to handle manually large amounts of nanomaterials in powder form. Thus, in order to avoid unnecessary exposure to workers during the scoping visit a SbD strategy was anticipated and nanomaterials in masterbatch form, in which the additive is concentrated into a polymeric matrix, were made available for the trials along with powder ones. The measurement campaign carried out at LATI's premises performed during the extrusion activity, confirmed an unlikely worker exposure. The measurement has been carried out during the extrusion of MWCNT enabled products. However, the results may be extended to other nanomaterials handling due to the nature of the process involved. The impact of the industrial waste that can be generated during the production process is low since scrap material is recycled in the facility. On the other hand, only cleaning/cooling water has to be considered as significant source as well as residual powder in empty packaging as solid waste. *Use and end-of-life stages:* The initial assumption was right, TiO_2 NFs can be released from the nanocomposites and even more in the case of climatic aged samples containing a great amount of anatase crystalline TiO_2. This is due to the high reactivity of these type of nanoparticules with UV light that leads to the degradation of the organic matrix. The initial assumption was wrong, polyamide 6.6 with glass fiber and different carbon nanofillers did not show an important amount of released material. The FTIR study indicated no migration of nanofillers to the polymer surface. On the other hand, thermal study corroborated the last result. However, a protective effect of ageing was found on the degradation temperature. TiO_2 coated with SiO_2 has been investigated in end-of-life stage, other aspects considered in end-of-life (incineration): UV stabilization of PP, effect of aging. "Best" compromise between mechanical & thermal properties for SbD: 3% TiO_2 NPs. PA 66 loaded with MWCNTs investigated, but with no conclusive results. TiO_2 NPs coated by SiO_2 or Al_2O_3. This reduces surface activity of the NMs avoiding TiO_2 photocatalytic effect when it is used as a UV filtering in polymeric nanocomposites as compared to tests done with TiO_2 anatase or rutile as an additive for PP.	

NanoReg 2 (IOM, CEA)	**Increasing the hydrophilicity** to decrease the potential to cross biological membranes, since the degree of particle hydrophobicity appears to directly correlate with their penetration to the cell monolayer (Petla, 2009, 2014). **Changing the oxidation state** to reduce surface reactivity or masking the reactivity by coating the NM as long as this does not affect the desired functionality. As a principle, catalyst residues and other impurities that that can contribute to the redox activity should be eliminated (e.g. elimination of Polycyclic Aromatic Hydrocarbons on carbon based NMs). **Decreasing the length of HARNs.** There is evidence of length-dependent toxicity since these long materials prevent complete ingestion by the macrophages contributing to a build-up of the dose (Poland et al. 2008; Donaldson et al. 2010; Shi et al., 2011). The key length appeared to be between 15-20 µm, beyond which macrophages cannot stretch and enclose the fibre eliciting frustrated phagocytosis (Donaldson et al. 2010). **To reduce their biopersistence** high surface energy that leads to aggregation and higher solubility and dissolution rate is desired (Casals et al. 2012). **Coating the NM to reduce dustiness.** Nanomakers NanoReg2 case study successfully reduced the dustiness of silicon from 1,163 mg/kg to 150 mg/kg by coating the nanoparticles with an amorphous layer of carbon. Coating of Si NPs with C induced better homogeneity of the battery anode active layer but did not reduce particle emission during calcination in air (mimicking a potential accidental scenario of a defective device). These approaches can negatively impact the functionality and therefore require careful consideration. **Adding a liquid intermediate to reduce exposure**. Avanzare NanoReg2 case study. The emissivity during abrasion tests of the water-based coatings manufactured with the dispersion of the graphene powder in a liquid phase was not altered. The identification of hot spots and need for testing was described in NanoReg 2 D2.2. In this deliverable, the results obtained in the testing are included and those results are used in different nanospecific RA models. In the identified hot spots Avanzare implemented SbD which included a liquid intermediate that can be useful for some of the applications (paints) and that will reduce the exposure of the workers by the inhalation route. It also includes the installation of a Local Exhaust ventilation system that will increase the air exchange in the room and the automation of the step with most risk of exposure, namely the packaging of the graphene powder. These changes have been evaluated with the same RA models used previously and described in D2.2 and with a more specific model that is the Weight of Evidence approach. All the models indicate an improvement in the safety of the process by a decrease in the exposure levels. From the toxicology results obtained, both NMs (the graphene powder and the liquid intermediate), are very similar. However, a more extensive testing should be needed to give a complete profile of their hazardous nature.	Sanchez Jimenez et al. 2020. Safe by Design guidelines for the nanotechnology industry: the NanoReg2 case studies ; NanoReg 2 D2.2
WEAREND (CEA)	Project aims at developing a nanostructured tungsten carbide composite (nanoWC-Co) powder and the associated post-processing (thermal spray), to generate coatings presenting enhanced wear resistance compared to conventional WC-Co coatings. The developement of the nanoWC-Co powder will be conduced with a double objective of improving wear resistance of the final coating and **limiting the dustiness** of the nanoWC-Co powder. Low dustiness is targeted throughout the material development to reduce the occupational exposure during powder post-processing.	WEAREND2 - High-end wear-resistant WC-Co materials EIT – Raw Materials Duration : 01.2020-

NANOLEAP (CEA)	Several samples including variations were produced by NanoLeap partners to be evaluated for both their performances and their potential to release airborne particles that could lead to occupational, consumer or environmental exposure. Three case studies have been identified with the participation of UCLM, ACCIONA and IMDEA: • Dustiness studies on agglomerated materials: the goal was to evaluate and improve the ability of micron-sized granules to reduce the release of free unbounded nanoparticles in workplace air. Several batches of spray dried granules from various partners and processes were characterized in terms of dustiness to identify the safer product and promote it for further processing. • Assessment of aging and release of ACCIONA intumescent paints incorporating UCLM agglomerated silica: the goal was to characterize the behaviour of functionalized nanoparticles dispersed in various matrices in simulated use. Accelerated weathering and abrasion tests were performed to evaluate the release of free nanoparticles from coated panels that might lead to occupational, consumer and/or environmental exposure. • Development of a new class of bactericidal material with a reduced amount of nanoparticles while maintaining high bactericidal properties thanks to moth-eye mimetic patterned surface	NanoLeap D8.8 - Report on the implementation and effectiveness of safe-by-design approaches
SERENADE (CNRS-CEREGE, CEA, ALLIOS)	**SafeTiPaint project:** To mitigate potential risks associated to the use of these nano-objects, a safer by design strategy to develop a photocatalytic paint containing TiO_2 nanoparticles taking into consideration safety aspects at each step of the value chain was implemented during SafeTiPaint project. New types of TiO_2 nanoparticles were synthesized and their photocatalytic activities were tested in different conditions. These nanoparticles were then incorporated into an organic paint matrix. Liquid paints applied on standard Leneta and Taber substrates underwent artificial weathering. For this purpose, paints were placed in an accelerated weathering chamber with controlled parameters (irradiance, temperature, relative humidity). Photocatalytic efficiency towards airborne VOCs was measured for pristine and aged paints. Mechanical solicitation through abrasion was performed to assess potential emission of airborne particles that could lead to human or environmental exposure. In parallel, toxicology studies were conducted to assess the hazard associated to these species (pristine particles, formulated paints and emitted debris). As the result of the implemented safer by design strategy to manufacture new generation of paints, we succeeded to decrease the TiO_2 paint content while keeping a good photocatalytic efficiency and reducing the nanoparticles release. It appeared that the synthesized TiO_2 nanoparticles integrated in the paints were less prone to degrade the matrix in comparison to reference TiO_2 nanoparticles. Although some TiO_2 based photocatalytic paint presented promising results, a further optimization is still needed to make them more efficient and mitigating their risks on human and environmental.	A. Rosset et al. manuscript under preparation
GRACIOUS (LEITAT)	**Increase the NEP product matrix resistance** or use stronger matrix toward aging factor to reduce the NMs release. **Increase the binding of NMs and product matrix** to reduce the NMs release **Improve NMs dispersability in product matrix**	

3.4.2 Approaches developed or implemented through internal projects by SAbyNA industrial partners

SAbyNA industrial partners involved in WP4 were approached to describe the SbD approaches implemented that were not reported in the identified articles or deliverables. Allios and Nouryon provided some information that is summarized below. Allios refered to the SERENADE project for which publications and deliverables were produced are reported in the list of resources.

Table 5. Internal project SbD approaches

Lead partner	Known SbD approaches
ALLIOS	SafeTiPaint 1 & 2 projects under the frame of Labex SERENADE – reported above
NOURYON	One obvious SbD strategy is to use closed and wet processes if applicable since this is a very efficient way to minimize exposure via inhalation. Used in production of colloidal silica (water-based silica nanoparticles). When a certain nanomaterial has been chosen from a cost, sustainability and safety perspective there can still be room for reduction of hazard of the nanomaterial considering surface modification. There are indications that surface modifications reduce hazard but there is lack of a systematic understanding how this tool can be used. An interesting question is how low the surface coverage needs to be and still have a positive impact from a hazard perspective and avoid having the surface modifying agent acting as a "pollutant" and negatively affecting the performance in an industrial application. Aluminium or silane modification of silica seem to reduce toxicity. Silica can also be used as dispersant for pigments/fillers. Can adsorption of silica reduce the toxicity of for example TiO_2?

3.4.3 Approaches identified through literature search

A literature survey using Scopus and Web of Science and the terms "Safe-by-Design" and "Nano" within title, abstract and keywords identified 75 document results (2010-2020). 55 of these were published in 2017-2020, indicating that Safe-by-Design approaches applied to NFs and NEPs is a growing topic.

Among those articles, we have separated review, concept articles and position papers from research articles. Our analysis protocol using the Excel spreadsheet was applied to the 46 research articles selected following initial screening.

3.5 SbD strategies mapping and identification of gaps

From the different sources of information (literature, projects & partners), the identified SbD approaches were screened according to a common template in an Excel spreadsheet.

3.5.1 Life cycle stage

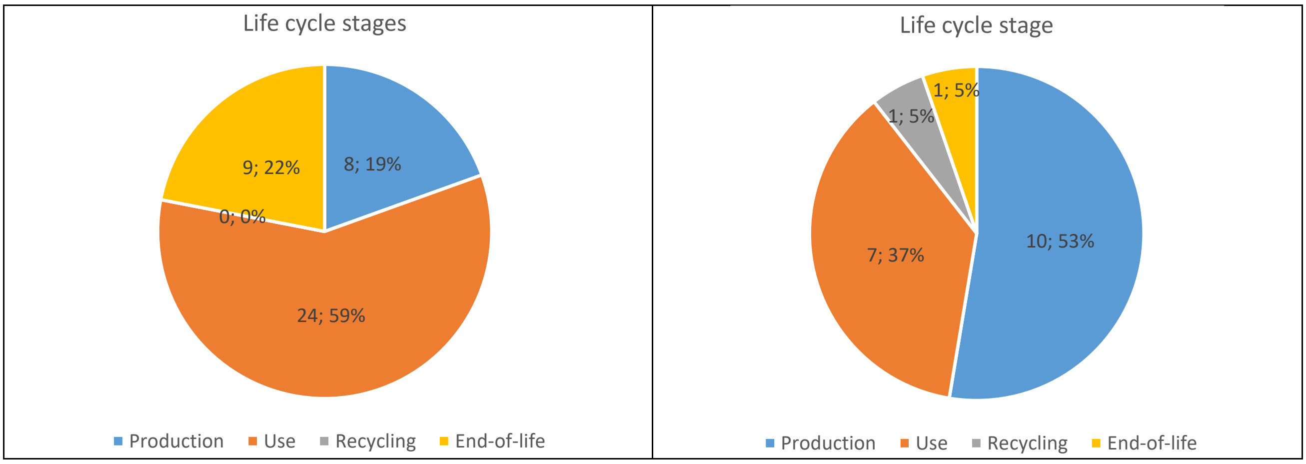

Figure 6. Targeted life cycle stages for the implemented SbD approaches (left literature survey, right projects survey).

More than half of the research articles were focused on the use stage while approaches reported from projects were mainly focused on the production. It appears that the end-of-life is not the main concern for the reported approaches and consequently, we would advise the SAbyNA consortium to fill this knowledge gap by developing long term studies on the environmental impact related to the NEPs end-of-life for instance.

3.5.1 Exposure route

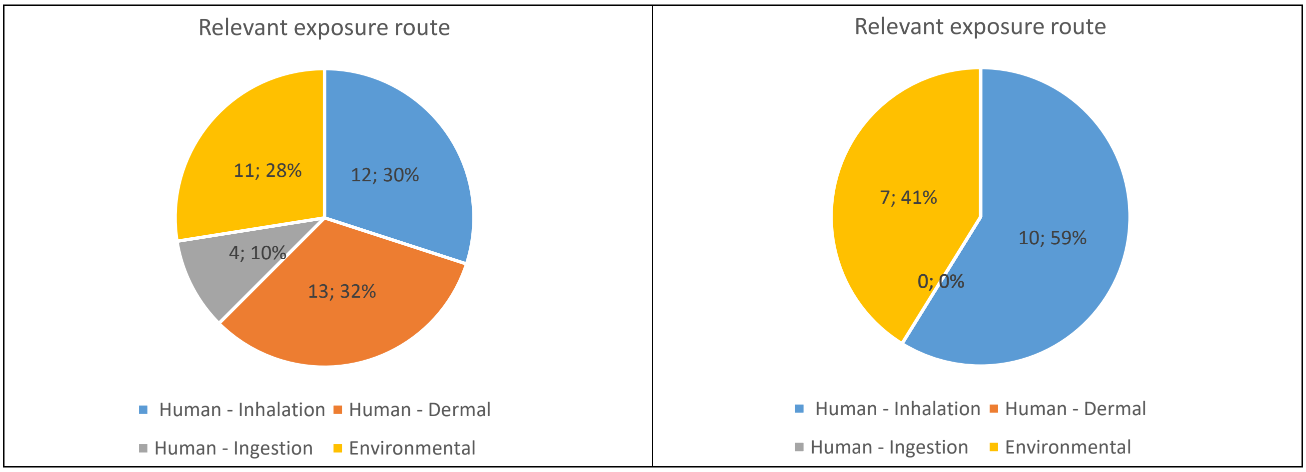

Figure 7. Exposure routes related to the SbD approaches (left literature survey, right projects survey).

Inhalation and environmental exposure routes are reported significantly both in published articles and in projects related activities. Ingestion is underrepresented and dermal exposure is described only in research articles.

3.5.1 Physical state

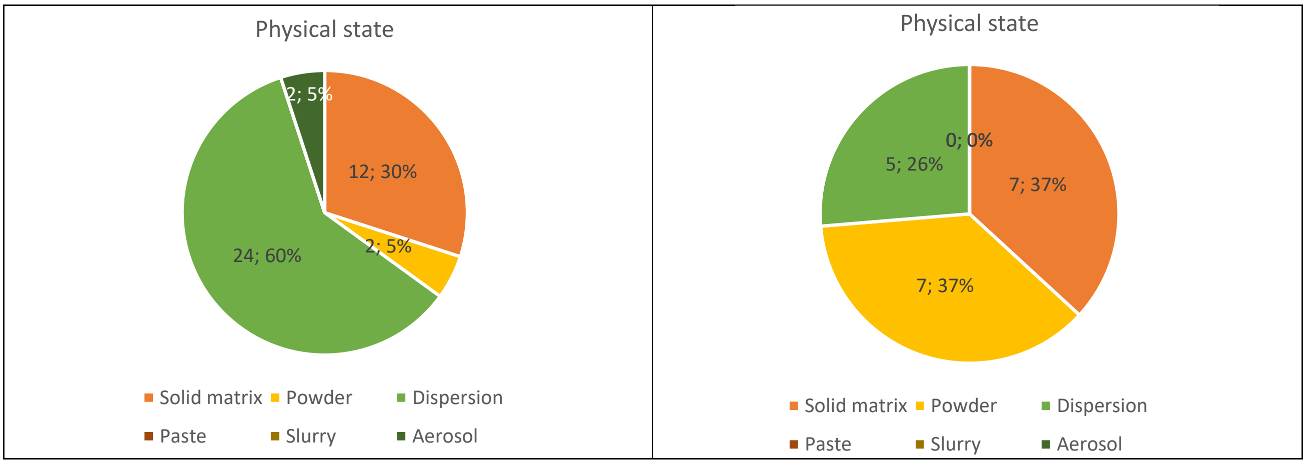

Figure 8. Physical state of the NFs (left literature survey, right projects survey).

NFs and NEPs involved in reported SbD approaches are mainly under the form of dispersions, bulk solid or divided solid. Dispersions appears to be more represented in research articles compared to the other physical states. This could reflect how NFs are currently used in NEPs life cycle or could also reflect a more accessible way to implement changes on NFs to evaluate their impacts.

3.5.1 Industrial sector and application of NFs and NEPs

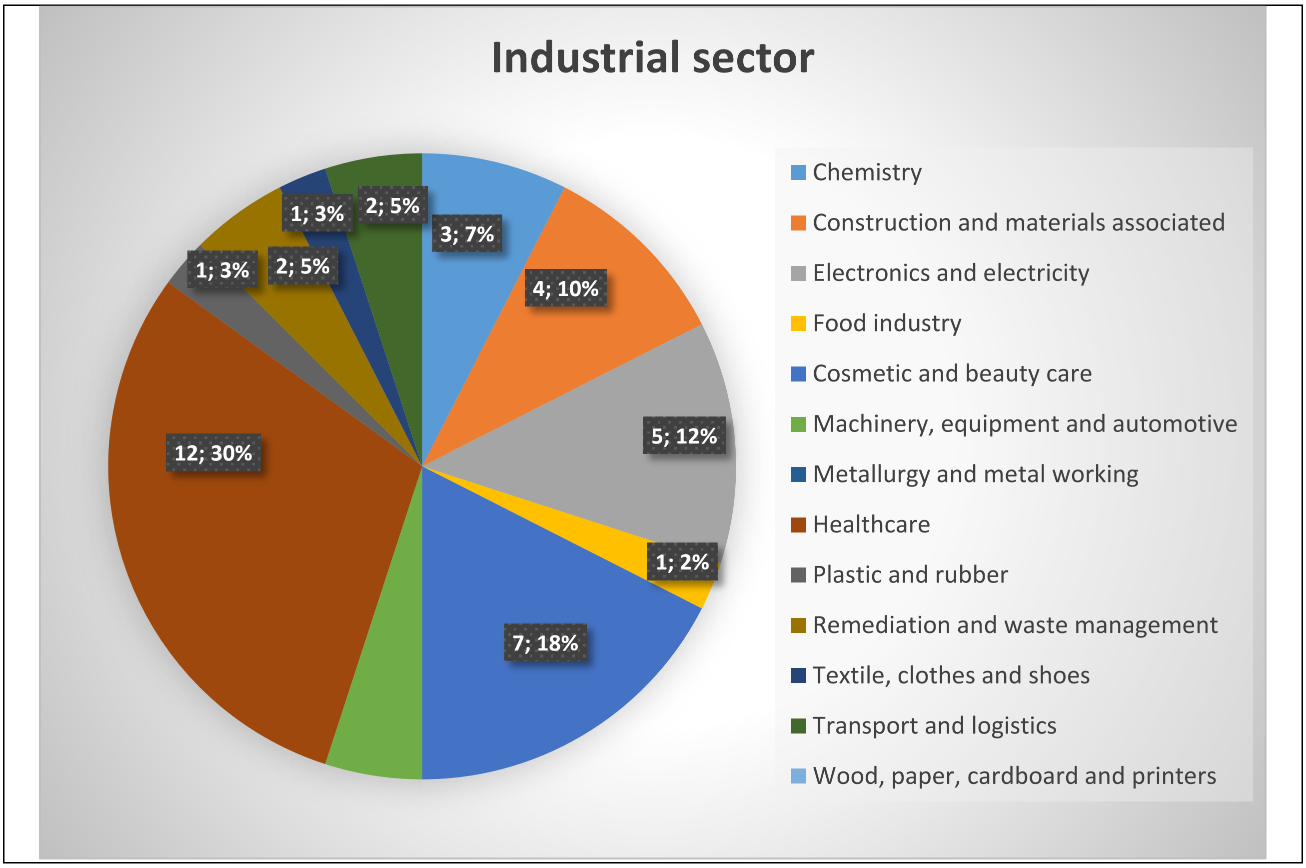

Figure 9. Industrial sector related to the implementation of the identified SbD approaches (litt. survey).

Healthcare (nanomedicine applications) appears to be the main sector followed by cosmetic and beauty care (sunscreens). Biocide applications are also mentioned significantly.

The project survey showed the construction sector in the first position but this might be influenced by the limited number of case studies from EU projects.

The reported NFs are mainly metal oxides (TiO_2, ZnO, CeO_2, SiO_2 …), metals (Ag, …) and carbon-based (CNTs …).

3.5.1 Mechanism of concern

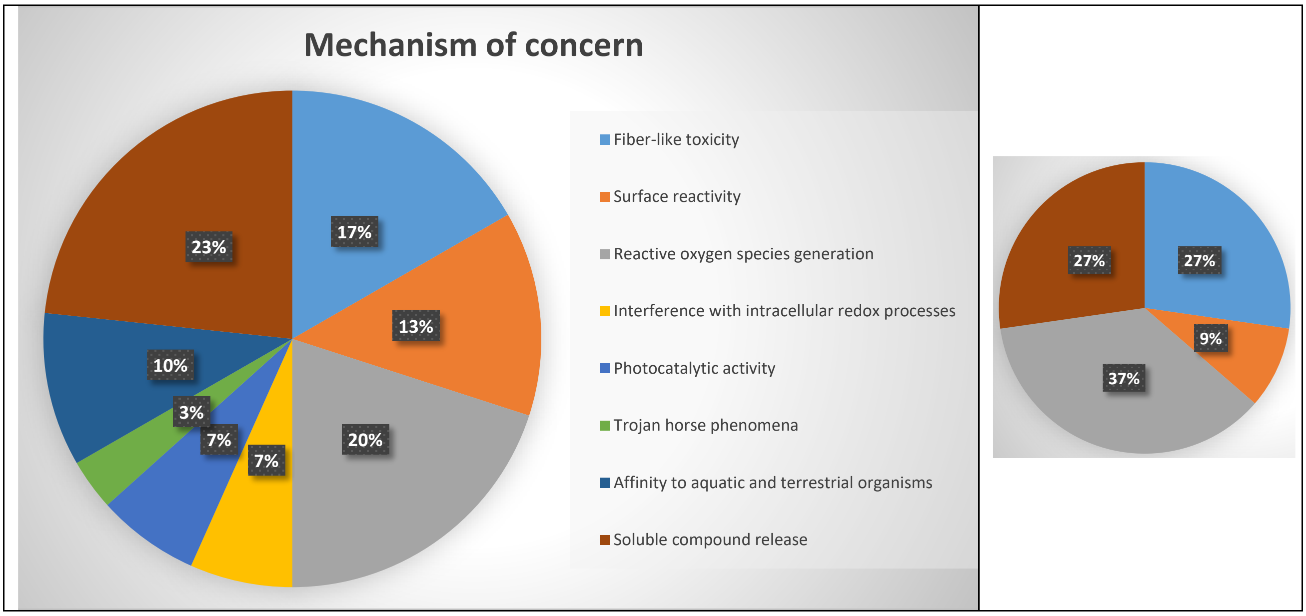

Figure 10. Mechanism of concern related to the NFs (left literature survey, right projects survey).

The results from literature survey and projects are indicating that ROS generation, release of soluble ions, fiber-like toxicity and surface reactivity are the main mechanisms of concern.

3.5.1 Key physico-chemical parameters that are targeted

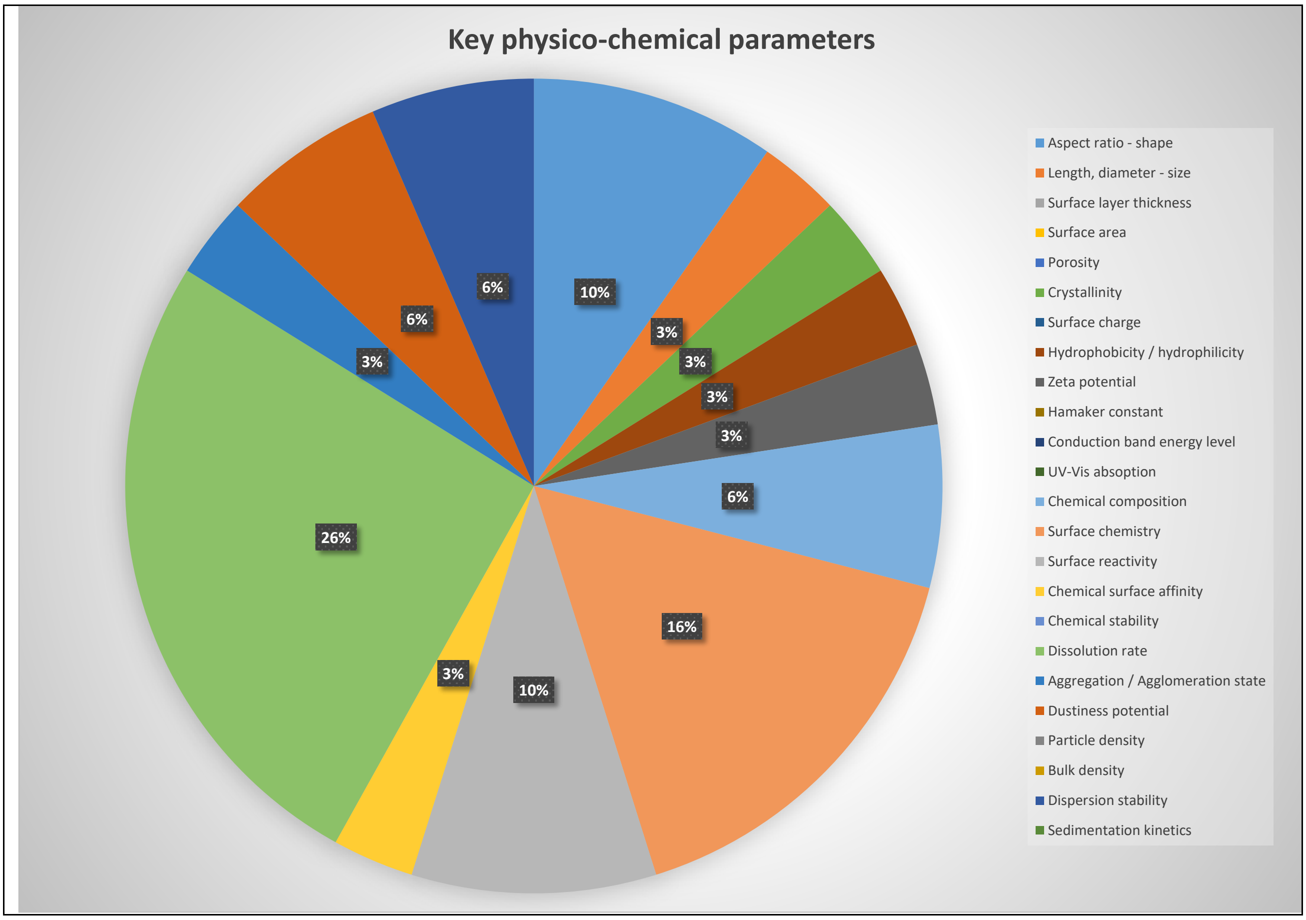

Figure 11. Key physico-chemical parameters reported in the research articles.

The results from literature survey and projects are indicating that there is a large diversity of parameters to be targeted for the implementation of SbD approaches. Factors governing dissolution rate and surface-related properties appears to be of prime interest.

3.5.1 Identified SbD strategies

We proposed to gather the identified SbD strategies in families targeting hazard, exposure and/or reducing biopersistence. Some the implemented SbD measures from the different resources that were identified are provided in the following table.

Table 6. Identified Safe-by-Design strategies over the last decade

SbD strategy	Targeted key determinant for risk	Implemented measure
Design out hazard	Several factors governing hazard	Substitution / replacement Nanoparticle doping Surface passivation / modification / functionalisation Reduction of photocatalytic efficiency Formation of composites Modification of particle size / shape Post-synthesis treatment (spheroization …)
Reduce exposure	Several factors driving exposure	Nanoparticle doping Selection of nanofiller

SbD strategy	Targeted key determinant for risk	Implemented measure
		Compatibilization matrix & nanofiller (Surface passivation / functionalisation) NF load and dispersion in the matrix Modification of particle size / shape Flocculation strategy Improve brittleness and tendency to break into smaller pieces Control dustiness indices through morphological parameters tuning (granulation …) Packaging, encapsulation strategies
Reduce bio-persistence		Nanoparticle doping Solubility tuning Minimize matrix decomposition / surface reactivity

4. Deviations from the work plan

No deviation to be reported.

The Excel spreadsheet will be further expanded and detailed over the course of the SAbyNA project.

5. Conclusions

Safe-by-Design strategies were identified from publications in scientific journals and projects deliverables. The selected resources were mapped and sorted according to a set of criteria in order to point out the gaps that could be filled during the project. For this purpose an Excel file was built and used to list exiting resources in several groups (reviews, publications, reports and industrial know-how).

The literature survey identified 75 document results (2010-2020) with approximately ¾ of these published in the last three years. Among those articles, we have separated review, concept articles and position papers (35 documents) from research articles (54 SbD approaches). A total of 19 SbD approaches reported from projects (deliverables) were also gathered.

Our analysis protocol using the Excel spreadsheet was applied to the selected 46 most relevant research articles and to the 19 approaches reported from projects. This database will be further developed in WP4. The list of identified resources (Oct. 2020) is added to the section 6 (annexes) of this deliverable.

From the gathered resources, it appears that there is a gap regarding the impact of the SbD measures over time throughout the whole life cycle. Most of the identified approaches reports short term studies taking into account few stages of the life cycle (production and use mainly). Long term studies taking into account the whole life cycle allowing transformation mechanisms are very limited.

NFs and NEPs involved in reported SbD approaches are mainly under the form of dispersions, bulk solid or divided solid. Dispersions appears to be overrepresented in research articles. The reported NFs are mainly metal oxides (TiO_2, ZnO, CeO_2, SiO_2 …), metals (Ag, …) and carbon-based (CNTs …). TiO_2 is the most investigated compound – which is coherent with the production level of those NFs. Healthcare (nanomedicine applications) appears to be the main sector followed by cosmetic and beauty care (sunscreens). Biocide applications are also mentioned significantly. The project survey showed the construction sector in the first position but this might be influenced by the limited number of case studies from EU projects.

The results from literature survey and projects are indicating that ROS generation, release of soluble ions, fiber-like toxicity and surface reactivity are the main mechanism of concern. But since, we were focusing our analysis on SbD approaches, it is possible that these mechanisms were highlighted as they are easier to manipulate through modifications (e.g. surface reactivity can be changed by coating particles).

The results from literature survey and projects are indicating that there is a large diversity of parameters to be targeted for the implementation of SbD approaches. Factors governing dissolution rate and surface-related properties appears to be of prime interest. We would recommend to further investigate approaches targeting those parameters during the course of SAbyNA without eliminating any underrepresented areas that might be of interest. SAbyNA project offer also the opportunity to test strategies with various materials and different physical forms and evaluate the impact of those modifications on the technical functions.

We would advise to take into account the amount of NFs which is often partially reported. Approaches that demonstrates that the technical function is maintained with a lower amount of NFs could be added to the resources identified so far.

6. Annex

[Annex 1]

All Safe-by-design approaches used in GUIDEnano

Relevant Endpoints	Effect with possible inherent risk	Proposed SbD approach	Specific proposed cases to be tested
Size	Dissolution (minimization)	NM that could release relatively toxic ions in different sizes to test if bigger NPs are less reactive and dissolve slower, releasing less ions. This can also have an effect on release	Ag NPs in sizes from 5 to 200nm. Nevertheless, from sizes above 50nm we follow a dilution steps approach, reducing by 1-5 orders of magnitude the concentrations (and thus the total amounts) that can produce for big AgNPs. AgNPs of 10nm and 50nm to test if lower dissolution rates yield to lower toxicity with the same mass of Ag. *The Safer-by-design strategy in this case would be tuning the size of NPs to reduce its toxicity while keeping (at least partly) its properties: use the less toxic particles with enough antimicrobial activity.*
Size	Agglomeration (to minimize)	Conjugation of NM prone to agglomeration (metal oxides such as TiO_2 and ZnO) with PEG or other coating molecules to avoid formation of aggregates/agglomerates.	a) Ag 10nm NPs with without PVP (though silver is not very prone to agglomeration) b) TiO_2 4nm NPs with/without PVP *It is important to note that isoelectric point for TiO_2 NPs is about pH 7. So, if any toxicity test is to be performed at this pH, it could lead to agglomeration/precipitation of both NPs with/without PVP.*
Surface Charge	Toxicity due to cationic surface charge (to avoid)	Formation of Albumin-based protein corona (albuminization) to change cationic surface charge of NPs to anionic, and thus more biocompatible, surface charge.	*Cationic NPs are known to be biologically toxic, due to its "stickiness" with proteins, cell membranes and other biologically relevant structures. In the case of cell membranes, they can be heavily disrupted when in contact with cationic NPs.*

Relevant Endpoints	Effect with possible inherent risk	Proposed SbD approach	Specific proposed cases to be tested
			Cationic Ag nanoparticles, synthesized with chitosan and the same Ag(+) NPs conjugated with albumin to form an anionic protein corona.
Oxidation	Complete Oxidation/Corrosion of NP into ions	Protect the NPs from corrosion by engineering a selective oxide passivation layer. It has also an effect over exposure.	This endpoint was thought for nZVI. Magnetite (Fe_3O_4) NPs and old Magnetite NPs oxidized to Maghemite (Fe_2O_3). Nevertheless, we do not find it very relevant, being both oxides known to have a very low toxicity, if any. Fe(II) oxides NPs could be tested in nanoremediation We additionally propose 10nm AgNPs with/without a selective AgO passivation layer to test if controlled oxidation of metal nanoparticles could lead to mitigate its corrosion, and thus the release of ions.
Traceability	If the NM cannot be detected, the risk would be very high	NM doping will allow tracing materials that present an extremely high background	SiO2 doped with lanthanides, and they are studying the doping of TiO2 NM.
Release reduction	Photocalytic effect (reduction)	Avoid TiO2 photocatalytic effect when it is used only for UVfiltering (LATI case study – reduction of polymer degradation)	TiO2 coated by SiO2 or Al2O3. This reduces surface activity of the NM.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 862419. This publication reflects only the author's views and the European Union is not liable for any use that may be made of the information contained therein.

[Annex 2]

Reviews, concept articles, position papers and general guidelines

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2020	A Methodological Safe-by-Design Approach for the Development of Nanomedicines	Schmutz M, Borges O, Jesus S,Borchard G, Perale G, Zinn M, Sips ÄAJAM, Soeteman-Hernandez LG, Wick P, Som C	Front. Bioeng. Biotechnol.	8		258	
2020	Safe-by-Design part I: Proposal for nanospecific human health safety aspectsneeded along the innovation process	Dekkers S., Wijnhovena S.W.P., Braakhuisa H.M., Soeteman-Hernandez L. G., Sips A. J. A. M., Tavernaro I., Kraegloh A., Noorlander C.W.	NanoImpact	18		100227	
2020	Nanotoxicology and Nanosafety: Safety-by-Design and Testing at a Glance	Zielinska A., Costa B., Ferreira M.V., Miguéis D., Louros J.M.S., Durazzo A., Lucarini M., Eder P., Chaud M.V., Morsink M., Willemen N., Severino P., Santini A., Souto E.B.	Int. J. Environ. Res. Public Health	17		4657	
2020	Nanotoxicology and Nanosafety: Safety-by-Design and Testing at a Glance	Aleksandra Zielinska, Beatriz Costa, Maria V. Ferreira, Diogo Miguéis, Jéssica M. S. Louros, Alessandra Durazzo, Massimo Lucarini, Piotr Eder,Marco V. Chaud, Margreet Morsink, Niels Willemen, Patrícia Severino, Antonello Santini and Eliana B. Souto	Int. J. Environ. Res. Public Health	17		4657	
2020	Assessing Sunscreen Lifecycle to Minimize Environmental Risk Posed by Nanoparticulate UV-Filters – A Review for Safer-by-Design Products	Labille J., Catalano R., Slomberg D., Motellier S., Pinsino A., Hennebert P., Santaella C. Bartolomei V.	Frontiers in Environmental science	8		101	
2020	Property-Activity Relationship of Black Phosphorus at the Nano-Bio	Qu G., Xia T., Zhou W., Zhang X., Zhang H., Hu L., Shi J., Yu X.-F., Jiang G.	Chemical Reviews	120	4		2288-2346

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
	Interface: From Molecules to Organisms						
2019	Guiding the development of sustainable nano-enabled products for the conservation of works of art: proposal for a framework implementing the Safe by Design concept	Semenzin E., Giubilato E., Badetti E., Picone M., Volpi Ghirardini A., Hristozov D., Brunelli A., Marcomini A.	Environmental Science and Pollution Research	26			26146-26158
2019	A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines	L. Yan, F. Zhao, J. Wang, Y. Zu, Z. Gu, and Y. Zhao	Adv. Mater.	31	45		1 - - 33
2019	Guiding the development of sustainable nano-enabled products for the conservation of works of art: proposal for a framework implementing the Safe by Design concept	Semenzin E., Giubilato E., Badetti E., Picone M., Volpi Ghirardini A., Hristozov D., Brunelli A., Marcomini A.	Environmental Science and Pollution Research	26	25		26146-26158
2019	Safe innovation approach: Towards an agile system for dealing with innovations	Soeteman-Hernandez L.G., Apostolova M.D., Bekker C., Dekkers S., Grafström R.C., Groenewold M., Handzhiyski Y., Herbeck-Engel P., Hoehener K., Karagkiozaki V., Kelly S., Kraegeloh A., Logothetidis S., Micheletti C., Nymark P., Oomen A., Oosterwijk T., Rodríguez-LLopis I., Sabella S., Sanchez Jiménez A., Sips A.J.A.M., Suarez-Merino B., Tavernaro I., van Engelen J., Wijnhoven S.W.P., Noorlander C.W.	Materials Today Communications	20		100548	
2018	Implementation of safe-by-design for nanomaterial development and safe innovation: Why we need a comprehensive approach	Kraegeloh A., Suarez-Merino B., Sluijters T., Micheletti C.	Nanomaterials	8	4	239	
2018	Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need aComprehensive Approach	Kraegeloh A., Suarez-Merino B., Sluijters T., Micheletti C.	Nanomaterials	8		239	
2018	Current approaches for safer design of engineered nanomaterials	R. Hwang, V. Mirshafiee, Y. Zhu, and T. Xia,	Ecotoxicol. Environ. Saf	166			294-300

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2018	Nanomaterials Safer-by-Design: An Environmental Safety Perspective	Lin S., Yu T., Yu Z., Hu X., Yin D.	Advanced Materials	30	17	1705691	
2018	Nanomaterial exposure and sterile inflammatory reactions	Leso V., Fontana L., Iavicoli I.	Toxicology and Applied Pharmacology	355			80-92
2018	Engineered NanoMaterials interactions with living plants: Benefits, hazards and regulatory policies	López-Moreno M.L., Cassé C., Correa-Torres S.N.	Current Opinion in Environmental Science and Health	6			36-41
2018	Engineered NanoMaterials interactions with living plants: Benefits, hazards and regulatory policies	López-Moreno M.L., Cassé C., Correa-Torres S.N.	Current Opinion in Environmental Science and Health	6			36-41
2017	Making nanomaterials safer by design ?	Schwarz-Plaschg C., Kallhoff A., Eisenberger I.	Nanoethics	11			277-281
2017	What can nanosafety learn from drug development? The feasibility of “safety by design"	Hjorth R., van Hove L., Wickso F.	Nanotoxicology	11	3		305-312
2017	Saved by Design? The Case of Legal Protection by Design	Hildebrandt M.	NanoEthics	11	3		307-311
2017	Towards a New Paradigm in Nano-Genotoxicology: Facing Complexity of Nanomaterials’ Cellular Interactions and Effects	Gonzalez L., Cundari E., Leyns L., Kirsch-Volders M.	Basic and Clinical Pharmacology and Toxicology	121			23-29
2017	Toxicity Effects of Functionalized Quantum Dots, Gold and Polystyrene Nanoparticles on Target Aquatic Biological Models: A Review	Libralato G., Galdiero E., Falanga A., Carotenuto R., De Alteriis E., Guida M.	Molecules	22	9	1439	
2017	Effects of nanoparticles in species of aquaculture interest	Khosravi-Katuli K., Prato E., Lofrano G., Guida M., Vale G., Libralato G.	Environmental Science and Pollution Research	24	21		17326-17346
2017	Safer by design strategies	Cobaleda-Siles M., Guillamon A.P., Delpivo C., Vázquez-Campos S., Puntes V.F.	Journal of Physics: Conference Series	838	1	12016	
2017	Proactive approach for safe use of antimicrobial coatings in healthcare settings: Opinion of the cost action network AMiCI	Ahonen M., Kahru A., Ivask A., Kasemets K., Kõljalg S., Mantecca P., Vrček I.V., Keinänen-Toivola M.M., Crijns F.	International Journal of Environmental Research and Public Health	14	4	366	

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2017	SERENADE: safer and ecodesign research and education applied to nanomaterial development, the new generation of materials safer by design	Bottero J.Y., Rose J., De Garidel C., Masion A., Deutsch Th., Brochard G., Carrière M., Gontard N., Wortham H., Rabilloud T., Salles B., Dubosson M., Cathala B., Boutry D., Ereskovsky A., Auplat C., Charlet L., Heulin T., Frejafon E., Lanone S.	Environmental Science: Nano	4	3		526-538
2017	Strategy for identification of nanomaterials' critical properties linked to biological impacts: Interlinking of experimental and computational approaches	Lynch I., Afantitis A., Leonis G., Melagraki G., Valsami-Jones E.	Challenges and Advances in Computational Chemistry and Physics	24			385-424
2016	The Road to Sustainable Nanotechnology: Challenges, Progress and Opportunities	Hutchinson JE	ACS Sustainable Chem. Eng.	4			5907-5914
2016	In vitro toxicity assessment of oral nanocarriers	Ciappellano S.G., Tedesco E., Venturini M., Benetti F.	Advanced Drug Delivery Reviews	106			381-401
2015	Perspectives on the design of safer nanomaterials and manufacturing processes	Geraci C., Heidel D., Sayes C., Hodson L., Schulte P., Eastlake A., Brenner S.	J. Nanopart. Res.	17		336	
2014	Mechanisms of toxic action of Ag, ZnO and CuO nanoparticles to selected ecotoxicological test organisms and mammalian cells in vitro: A comparative review	Ivask A., Juganson K., Bondarenko O., Mortimer M., Aruoja V., Kasemets K., Blinova I., Heinlaan M., Slaveykova V., Kahru A.	Nanotoxicology	8	SUPPL. 1		57-71
2011	No time to lose--high throughput screening to assess nanomaterial safety	R Damoiseaux, S George, M Li, S Pokhrel, Z Ji, B France, T Xia, E Suarez, R Rallo, L Mädler, Y Cohen, E M V Hoek, A Nel	Nanoscale	3	4		1345-1360
2010	Prevention through design: The effect of European Directives on constructionworkplace accidents	Martínez Aires M.D., Rubio Gámez M. C., Gibb A.	Safety Science	48			248-258
2008	National Prevention through Design (PtD) Initiative	Schulte P.A., Rinehart R., Okun A., Geraci C.L., Heidel D.S.	Journal of Safety Research	39			115-121
2008	Research Issues in Prevention through Design	Gambatese J.A.	Journal of Safety Research	39			153-156

[Annex 3]

Research articles

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2020	Optimizing the dispersion of nanoparticulate TiO2-based UV filters in a non-polar medium used in sunscreen formulations – The roles of surfactants and particle coatings	Catalano R., Masion A., Ziarelli F., Slomberg D., Laisney J., Unrine J.M., Campos A., Labille J.	Colloids and Surfaces A: Physicochemical and Engineering Aspects	599		124792	
2020	The shape of titanium dioxide nanomaterials modulates their protection efficacy against ultraviolet light in human skin cells	Ilić K., Selmani A., Milić M., Glavan T.M., Zapletal E., Ćurlin M., Yokosawa T., Vrček I.V., Pavičić I.	Journal of Nanoparticle Research	22	3	71	
2020	The 3D Design of Multifunctional Silver Nanoparticle Assemblies Embedded in Dielectrics	Bonafos C., Bayle M., Benzo P., Pugliara A., Makasheva K., Carrada M., Chery N., Balout H., Benoit M., Tarrat N., Benassayag G., Pécassou B., Navarro E., Carles R.	Physica Status Solidi (A) Applications and Materials Science	217	6	1900619	
2020	Exposure Assessment During the Industrial Formulation and Application of Photocatalytic Mortars Based on Safer n-TiO2 Additives	Vaquero C., Esteban-Cubillo A., Santaren J., López de Ipiña J., Galarza N., Aragón G., Múgica I., Larraza I., Pina-Zapardiel R., Gutierrez-Cañas C.	International Journal of Environmental Research	14			257-268
2020	Formation of Protein Corona on Nanoparticle Affects Different Complement Activation Pathways Mediated by C1q	Ding T., Sun J.	Pharmaceutical Research	37	1	10	
2020	Challenges of implementing nano-specific safety and safe-by-design principles in academia	L. G. Soeteman-Hernández et al.	NanoImpact	19		100243	
2020	Assessing Sunscreen Lifecycle to Minimize Environmental Risk Posed by Nanoparticulate UV-Filters – A Review for Safer-by-Design Products	Labille J., Catalano R., Slomberg D., Motellier S., Pinsino A., Hennebert P., Santaella C. Bartolomei V.	Frontiers in Environmental science	8		101	
2020	Safe by Design implementation in the nanotechnology industry	Araceli Sánchez Jiménez, Raquel Puelles, Marta Perez-Fernandez, Paloma Goméz, Leire Barruetabeña, Nicklas Raun Jacobsen, Blanca Suarez-Merino, Christian Micheletti, Nicolas Manier, Bénédicte Trouiller, Jose Maria Navas, Judit Kalman, Beatrice Salieri, Roland Hischier, Yordan Handzhiyski, Margarita D. Apostolova, Niels Hadrup, Jacques Bouillard, Yohan Oudart,	*Not yet published*				

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
		Cesar Merino, Erika Garcia, Biase Liguori, Stefania Sabella, Jerome Rose, Armand Maison, Karen S. Galea, Sean Kelly, Sandra Štěpánková, Catherine Mouneyrac, Andrew Barrick, Amelie Chatel, María Dusinska, Elise Rundén-Pran, Espen Mariussen,Christophe Bressot, Olivier Aguerre-Chariol, Neeraj Shandilya, Henk Goede, Julio Gomez-Cordon, Sophie Simar, Fabrice Nesslany, Keld Alstrup Jensen, Martie van Tongeren, Isabel Rodríguez Llopis					
2020	Zeta-Potential Read-Across Model Utilizing Nanodescriptors Extracted via the NanoXtract Image Analysis Tool Available on the Enalos Nanoinformatics Cloud Platform	Dimitra-Danai Varsou Antreas Afantitis Andreas Tsoumanis Anastasios Papadiamantis Eugenia Valsami-Jones Iseult Lynch Georgia Melagraki	Nano-Micro-Smalls	16	21	1906588	
2020	Safer-by-design biocides made of tri-thiol bridged silver nanoparticle assemblies	Marianne Marchioni, Giulia Veronesi, Isabelle Worms, Wai Li Ling, Thomas Gallon, Didier Leonard, Christelle Gateau, Mireille Chevallet, Pierre-Henri Jouneau, Laura Carlini, Chiara Battocchio, Pascale Delangle, Isabelle Michaud-Soret, Aurélien Deniaud	Nanoscale Horiz.	5			507-513
2019	A chemoinformatics approach for the characterization of hybrid nanomaterials: Safer and efficient design perspective	Mikolajczyk A., Sizochenko N., Mulkiewicz E., Malankowska A., Rasulev B., Puzyn T.	Nanoscale	11	24		11808-11818
2019	Towards nano-risk assessment with high throughput screening and high content analysis: An intelligent testing strategy	Mittal D., Kaul G.	Comprehensive Nanoscience and Nanotechnology				343-360
2019	Cytotoxicity of nanomaterials applicable in restoration and conservation	Brzicová T., Remzová M., Žouželka R., Rathouský J., Vrbová K., Rossner P., Topinka J.	NANOCON 2018 - Conference Proceedings, 10th Anniversary International Conference on Nanomaterials - Research and Application	-			548-553

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2019	Citrem-phosphatidylcholine nano-self-assemblies: Solubilization of bupivacaine and its role in triggering a colloidal transition from vesicles to cubosomes and hexosomes	Prajapati R., Larsen S.W., Yaghmur A.	Physical Chemistry Chemical Physics	21	27		15142-15150
2019	A toxicology-informed, safer by design approach for the fabrication of transparent electrodes based on silver nanowires	D. Toybou, C. Celle, C. Aude-Garcia, and T. Rabilloud	Environ. Sci. Nano	6	2		684-694
2018	In Vitro Pulmonary Toxicity of Reduced Graphene Oxide-Nano Zero Valent Iron Nanohybrids and Comparison with Parent Nanomaterial Attributes	Wang Q., Masud A., Aich N., Wu Y.	ACS Sustainable Chemistry and Engineering	6	10		12797-12806
2018	Elucidating differential nano-bio interactions of multi-walled andsingle-walled carbon nanotubes using subcellular proteomics	Ndika J.D.T., Sund J., Alenius H., Puustinen A.	Nanotoxicology	12	6		554-570
2018	Nanosilver: An innovative paradigm to promote its safe and active use	Gardini D., Blosi M., Ortelli S., Delpivo C., Bussolati O., Bianchi M.G., Allegri M., Bergamaschi E., Costa A.L.	NanoImpact	11			128-135
2018	High-throughput tool to discriminate effects of NMs (Cu-NPs, Cu-nanowires, CuNO3, and Cu salt aged): transcriptomics in Enchytraeus crypticus	Gomes S.I.L., Roca C.P., Pegoraro N., Trindade T., Scott-Fordsmand J.J., Amorim M.J.B.	Nanotoxicology	12	4		325-340
2018	Nano-engineering safer-by-design nanoparticle based moth-eye mimetic bactericidal and cytocompatible polymer surfaces	Viela F., Navarro-Baena I., Jacobo-Martín A., Hernández J.J., Boyano-Escalera M., Osorio M.R., Rodríguez I.	RSC Advances	8	40		22606-22616
2018	Hierarchical nano ZnO-micro TiO2 composites: High UV protection yield lowering photodegradation in sunscreens	Reinosa J.J., Docio C.M.Á., Ramírez V.Z., Lozano J.F.F.	Ceramics International	44	3		2827-2834
2018	Silica modification of titania nanoparticles enhances photocatalytic production of reactive oxygen species without increasing toxicity potential in vitro	Ortelli S., Costa A.L., Matteucci P., Miller M.R., Blosi M., Gardini D., Tofail S.A.M., Tran L., Tonelli D., Poland C.A.	RSC Advances	8	70		40369-40377
2017	Early Assessment and Correlations of Nanoclay's Toxicity to Their Physical and Chemical Properties	Wagner A., White A.P., Stueckle T.A., Banerjee D., Sierros K.A., Rojanasakul Y., Agarwal S., Gupta R.K., Dinu C.Z.	ACS Applied Materials and Interfaces	9	37		32323-32335
2017	The effect of nanosilica (SiO2) and nanoalumina (Al2O3) reinforced polyester nanocomposites on aerosol nanoparticle emissions into the environment during automated drilling	Starost K., Frijns E., Van Laer J., Faisal N., Egizabal A., Elizetxea C., Nelissen I., Blázquez M., Njuguna J.	Aerosol Science and Technology	51	9		1035-1046

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2017	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach	Mantecca P., Kasemets K., Deokar A., Perelshtein I., Gedanken A., Bahk Y.K., Kianfar B., Wang J.	Environmental Science and Technology	51	16		9305-9317
2017	Approach for in vitro testing of oral nanocarrier toxicity	Tedesco E., Benetti F.	Chimica Oggi/Chemistry Today	35	4		52-55
2017	Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products	López De Ipina J.M., Hernan A., Cenigaonaindia X., Insunza M., Florez S., Seddon R., Vavouliotis A., Kostopoulos V., Latko P., Duralek P., Kchit N.	Journal of Physics: Conference Series	838	1	12018	
2017	Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu-O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos	Naatz H., Lin S., Li R., Jiang W., Ji Z., Chang C.H., Köser J., Thöming J., Xia T., Nel A.E., Mädler L., Pokhrel S.	ACS Nano	11	1		501-515
2017	Characterization of photocatalytic paints: A relationship between the photocatalytic properties-release of nanoparticles and volatile organic compounds	Truffier-Boutry D., Fiorentino B., Bartolomei V., Soulas R., Sicardy O., Benayad A., Damlencourt J.-F., Pépin-Donat B., Lombard C., Gandolfo A., Wortham H., Brochard G., Audemard A., Porcar L., Gebel G., Gligorovski S.	Environmental Science: Nano	4	10		1998-2009
2017	Safer-by-design hybrid nanostructures: an alternative to conventional titanium dioxide UV filters in skin care products	N. Shandilya and I. Capron	RSC Advances	7			20430-20439
2016	Comparing the CORAL and random forest approaches for modelling the in vitro cytotoxicity of silica nanomaterials	Cassano A., Robinson R.L.M., Palczewska A., Puzyn T., Gajewicz A., Tran L., Manganelli S., Cronin M.T.D.	ATLA Alternatives to Laboratory Animals	44	6		533-556
2016	A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies	Azmi I.D.M., Wibroe P.P., Wu L.-P., Kazem A.I., Amenitsch H., Moghimi S.M., Yaghmur A.	Journal of Controlled Release	239			01-sept
2016	Enzymatic oxidative biodegradation of nanoparticles: Mechanisms, significance and applications	Vlasova I.I., Kapralov A.A., Michael Z.P., Burkert S.C., Shurin M.R., Star A., Shvedova A.A., Kagan V.E.	Toxicology and Applied Pharmacology	299			58-69
2016	Targeted polyethylene glycol gold nanoparticles for the treatment of pancreatic cancer: From synthesis to proof-of-concept in vitro studies	Spadavecchia J., Movia D., Moore C., Maguire C.M., Moustaoui H., Casale S., Volkov Y., Prina-Mello A.	International Journal of Nanomedicine	11			791-822
2016	End-of-life thermal decomposition of nano-enabled polymers: Effect of nanofiller loading and polymer matrix on by-products	Singh D., Sotiriou G.A., Zhang F., Mead J., Bello D., Wohlleben W., Demokritou P.	Environmental Science: Nano	3	6		1293-1305

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2015	Effects of amorphous silica coating on cerium oxide nanoparticles induced pulmonary responses	Ma J., Mercer R.R., Barger M., Schwegler-Berry D., Cohen J.M., Demokritou P., Castranova V.	Toxicology and Applied Pharmacology	288	1		63-73
2015	Do nanoparticle physico-chemical properties and developmental exposure window influence nano ZnO embryotoxicity in Xenopus laevis?	Bonfanti P., Moschini E., Saibene M., Bacchetta R., Rettighieri L., Calabri L., Colombo A., Mantecca P.	International Journal of Environmental Research and Public Health	12	8		8828-8848
2015	An integrated methodology for the assessment of environmental health implications during thermal decomposition of nano-enabled products	Sotiriou G.A., Singh D., Zhang F., Wohlleben W., Chalbot M.-C.G., Kavouras I.G., Demokritou P.	Environmental Science: Nano	2	3		262-272
2015	Influence of paints formulations on nanoparticles release during their life cycle	B. Fiorentino, L. Golanski, A. Guiot, J.-F. Damlencourt, and D. Boutry	J. Nanoparticle Res.	17	3		149
2014	Engineering safer-by-design silica-coated ZnO nanorods with reduced DNA damage potential	Sotiriou G.A., Watson C., Murdaugh K.M., Darrah T.H., Pyrgiotakis G., Elder A., Brain J.D., Demokritou P.	Environmental Science: Nano	1	2		144-153
2014	A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells	Movia D., Gerard V., Maguire C.M., Jain N., Bell A.P., Nicolosi V., O'Neill T., Scholz D., Gun'ko Y., Volkov Y., Prina-Mello A.	Biomaterials	35	9		2543-2557
2013	Implementation of alternative test strategies for the safety assessment of engineered nanomaterials	Nel A.E.	Journal of Internal Medicine	274	6		561-577
2013	An in vivo and in vitro toxicological characterisation of realistic nanoscale CeO2 inhalation exposures	Demokritou P., Gass S., Pyrgiotakis G., Cohen J.M., Goldsmith W., McKinney W., Frazer D., Ma J., Schwegler-Berry D., Brain J., Castranova V.	Nanotoxicology	7	8		1338-1350
2013	Biodegradation of iron oxide nanocubes: High-resolution in situ monitoring	Lartigue L., Alloyeau D., Kolosnjaj-Tabi J., Javed Y., Guardia P., Riedinger A., Péchoux C., Pellegrino T., Wilhelm C., Gazeau F.	ACS Nano	7	5		3939-3952
2013	Plasma concentration gradient influences the protein corona decoration on nanoparticles	Ghavami M., Saffar S., Abd Emamy B., Peirovi A., Shokrgozar M.A., Serpooshan V., Mahmoudi M.	RSC Advances	3	4		1119-1126
2013	Towards large scale aligned carbon nanotube composites: An industrial safe-by-design and sustainable approach	P Boulanger , L Belkadi , J Descarpentries , D Porterat , E Hibert , A Brouzes , M Mille , S Patel , M Pinault , C Reynaud, M Mayne- L'Hermite , and JM Decamps	J. Physics Conf. Series	429		12050	

Year	Title	Authors	Source title	Volume	Issue	Art. No.	Page start-end
2011	Decreased dissolution of ZnO by iron doping yields nanoparticles with reduced toxicity in the rodent lung and zebrafish embryos	Xia T, Zhao Y, Sager T, George S, Pokhrel S, Li N, Schoenfeld D, Meng H, Lin S, Wang X, Wang M, Ji Z, Zink JI, Mädler L, Castranova V, Lin S, Nel AE.	ACS Nano	5	2		1223-1235
2010	Use of a Rapid Cytotoxicity Screening Approach To Engineer a Safer Zinc Oxide Nanoparticle through Iron Doping	Saji George, Suman Pokhrel, Tian Xia, Benjamin Gilbert, Zhaoxia Ji, Marco Schowalter, Andreas Rosenauer, Robert Damoiseaux, Kenneth A. Bradley, Lutz Mädler, and André E. Nel	ACS Nano	4	1		15-29
	A safe-by-design tool for functionalised nanomaterials through the Enalos Nanoinformatics Cloud platform	Dimitra-Danai Varsou, Antreas Afantitis, Andreas Tsoumanis, Georgia Melagraki, Haralambos Sarimveis, Eugenia Valsami-Jones and Iseult Lynch	Nanoscale Advances	1			706 - 718

[Annex 4]

Project activities

Year	Title	Authors	Name of the project	Coordinator / WP leader contact details
2017	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products	Jose Luis Muñoz, Camilla Delpivo, Vicenç Pomar, Alejandro Vilchez, Socorro Vázquez, Delphine Boutry, Cecile Phillippot, Carlos Conception, Olga Chybová, Cristiano Citterio	GUIDEnano	LEITAT/ WP3
2017	GUIDENANO (Assessment and mitigation of nano-enabled product risks on human and environmental health: Development of new strategies and creation of a digital guidance tool for nanotech industries)	Project partners	GUiDEnano	LEITAT
2014	D 7.1 – Report on the development of SbyD strategies applied to CuO	Anna L. Costa	SUN	anna.costa@istec.cnr.it
2018	D8.8 - Report on the implementation and effectiveness of safe-by-design approaches	Simon Clavaguera et al.	NANOLEAP	UCLM (Jose Luis Valverde Palomino) / CEA (Simon Clavaguera) simon.clavaguera@cea.fr
2015	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2016	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2017	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2018	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2019	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it

Year	Title	Authors	Name of the project	Coordinator / WP leader contact details
2020	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2021	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2022	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS	Camilla Delpivo	SANOWORK	Anna Luisa Costa, anna.costa@istec.cnr.it
2018	D2.3 Final comparative risk assessment and life Cycle assessment for candidate materials after SbD implementation in “hot spots” along the life cycle	Isabel Rodríguez-Llopis et al.	Nanoreg2	Emeric Frejafon