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Deliverable 5.5

Report on SbD strategies

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The statements made herein do not necessarily have the consent or agreement of the DIAGONAL consortium.

Abbreviations

CHP: combined heat and power

CSS: Chemicals Strategy for Sustainability

CNTs: Cabon nanotubes

EG: ethylene glycol

EoL: end of life

GNPs: graphene nanoplatelets

GS: graphene sheet

HARNs: High Aspect Ratio Nanoparticle(s)

HBA: hyperbranched aromatic polyamide

HC: hard Chromium

HPUs: hyperbranched poly(urea-urethane)s

MCNMs: Multi-Component Nanomaterial(s)

MWCNTs: multi-walled carbon nanotubes

NMs: Nanomaterial(s)

NPs: Nanoparticles(s)

OSH: Occupational Safety and Health

PC: Physicochemical

PCL: Poly(e-caprolactone)

PGMs: platinum group metals

PLA-PEG:poly(lactide)-poly(ethylene glycol)

PPE: Personal Protective Equipment

PU: polyurethane

PVK: poly(N-vinyl carbazole)

PVP: polyvinylpyrrolidone

RMM: Risk Management Measurements

SbD: Safe-by-design

SbMD: Safe-by-Material-Design

SbPD: Safe-by-Process-Design

SDS: sodium dodecyl sulfate

SLNs: solid-lipid nanoparticles

SSbD: Safe and Sustainable by Design

SusbD: Sustainability-by-design

SVHC: substances of very high concern

SWCNTs: single-walled carbon nanotubes

WP: Work Package

Figures

Tables

Table of contents

1. Scope and goal of the deliverable

Deliverable 5.5 aims to collect the work conducted within task 5.3 “Safe by design strategies development”, in particular subtask 5.3.1 (safe by material design strategies) and subtask 5.3.2 (safe by process design strategies). For subtask 5.3.1, we did an extensive literature review in order to come out with a library of well-balanced safe by material design strategies applied to different types of nanomaterials. Based on these general strategies, specific strategies that could be applied to the materials developed in DIAGONAL project have been proposed with the aim of being implemented later under the framework of task 5.4 “Safe by design strategies demonstration.” Similarly, the work conducted under subtask 5.3.2 “Safe by process design strategies” focused on the exhaustive analysis of the production processes as well as the results obtained from the monitoring campaigns. According to this analysis, the proper safe by process design strategies have been proposed also considering, where applicable, the recommendation for implementing risk management measures (RMM) identified also in WP6. These strategies would be used as well as an input for the activities covered by Task 5.4, related to the demonstration of the SbD strategies within DIAGONAL case studies, as well as a base for the work that is being conducted in Task 5.5 “SbD best practices guidelines”.

It is worth to mention that the activities conducted in this task and the results reported in the current deliverable, are related to the work done before, specifically to the results reported in deliverable D5.1 “DIAGONAL SbD and SusbD implementation framework” in the third month of the project which was aimed at implementing a theoretical framework for the subsequent development of *Safe-by-Design* (SbD) and *Sustainability-by-Design* (SusbD) strategies under the scope of *High Aspect Ratio Nanoparticle* (HARN) and *Multi-Component Nanomaterial* (MCNM) production.

Therefore, the *Safe by design strategies* proposed in this deliverable are based on the work conducted earlier in WP5 and WP4 (Experimental risk assessment) and consequence of the coordinated work from different points of view and research fields, including the industrial partners perspective.

The suggestion of *Sustainability by design strategies* for the case studies is out of the scope of this deliverable since they will be evaluated in Task 5.2 and reported in D. 5.4. However, the proposed strategies were included in the questionnaires to offer to the demonstrators both perspectives and actions that could effectively increase the safety and sustainability of the materials involved. The actions related to sustainability will be reported in M36, within the related deliverable.

Figure 1 shows how every WP and their tasks have related each other:

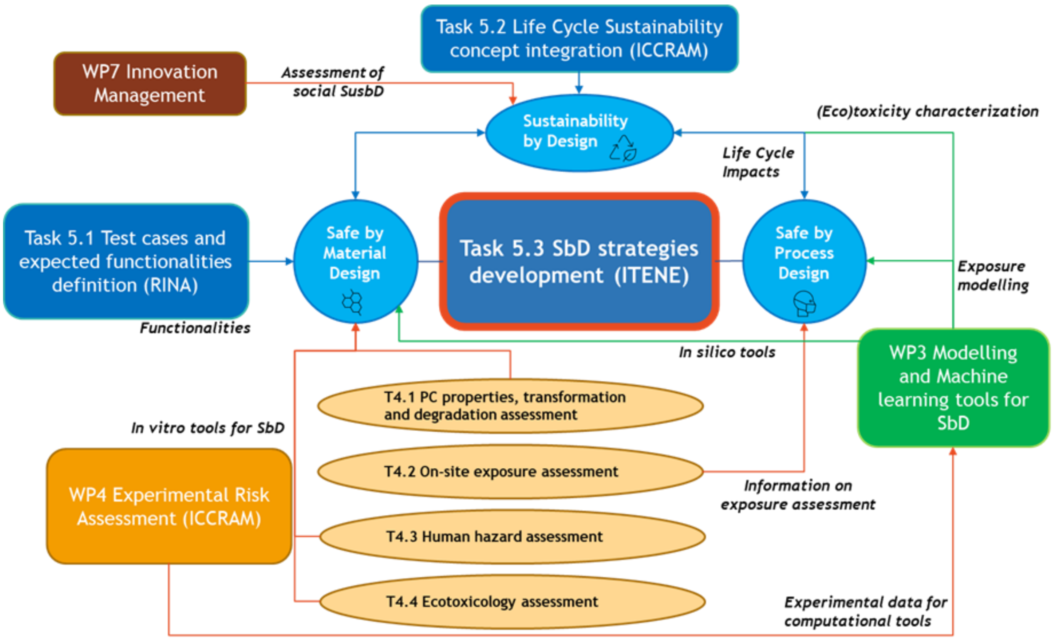

Figure 1 - Flow of information for SbD and SusbD

2. Introduction

2.1. Task description

Task 5.3 SbD strategies development (M1-M42).

Leader: ITENE; Participants; NovaM, RINA-C, QSAR Lab, ICCRAM, CNRS, BNN, ISQ, 4n, IRIS, MON, CNANO, OCSiAl, DTI, GXT

DIAGONAL will develop a SbD framework with strategies and tools for the development of safer, but equally functional, MCNMs and HARNs considering existing SbD concepts developed in previous projects for safer nanomaterials (NMs), safer production and safe use of NMs (e.g. NanoReg2, RiskGONE). Adaptation of SbD approaches to MCNM and HARN specificities will be based on the *in silico* and *in vitro* tools and methods developed, adapted and implemented in DIAGONAL WP3 and WP4.

Subtask 5.3.1 Safe by material design strategies*. (M12-M36) Subtask leader: ITENE*

In this subtask a systematic study will be carried out to design and apply surface engineering approaches, adapted to the chemical nature of the MCNMs and HARNs, and the relevant nano-based formulations. Strategies to produce safer products, such as doping, coating and functionalization will be tested in cooperation with the companies involved in the consortium, to validate the stability under common operative conditions at industrial level and the reduction of the toxic behavior. CNRS will provide inputs based on its long-term experience with SdD modifications of HARNs aimed to improve their biodegradability and safe use. The performance of the modified MCNMs and HARNs will be studied in detail, including the alteration on the primary particle size, shape and surface area. The **main output** of this subtask will be a **library of well-balanced surface engineering approaches to reduce hazards**, validated in case studies to ensure functionality, and therefore market uptake.

Subtask 5.3.2 Safe by process design strategies. *(M12-M36) Subtask leader: ITENE*

ITENE will work on the characterization of relevant factors that may influence the release and emission potential of MCNMs and HARNs in indoor workplaces by means of laboratory-based studies in exposure chambers and pilot studies in companies, where appropriate monitoring devices according to the properties of MCNMs and HARNs and the operational factors of relevant occupational processes will be considered. A range of surface modifications at increasing particle agglomeration/aggregation to reduce the emission and defined in cooperation with the companies involved in the project will be tested following two dustiness testing set-ups (i.e., continuous drop and rotating drum). The links between the surface modifications and dustiness indexes will be used as data input for building evidence-based safe by design approaches. In addition, a range of scoping visits will be conducted to identify exposure hotspots (T4.2) **where applicable risk management measures** (from WP6) will be **recommended for implementation** in T5.4, including **engineering Controls, administrative controls, and Personal Protective Equipment (PPE).**

2.2. Subtasks implementation

a. Safe by Material Design

Within the DIAGONAL framework, the Safe-by-Material-Design (SbMD) approach is focused on the adequation of the physicochemical (PC) nature of the MCNMs and HARNs, and the relevant nano-based formulations with the aim of designing new and safer NMs from earlier stages without damaging their functionality. PC characterization is crucial since this method tries to enhance safety with physical changes such as alteration on the primary particle size, shape, and surface area, or chemical transformation with surface engineering approaches.[1] The SbMD approach is based on the concept that safety is not an intrinsic property of material but can be built in through the manufacturing chain from raw materials to finished products, by adding SbMD criteria to quality assurance and good manufacturing practice specifications.[2]

Different strategies based on the modification of the materials could be applied, for instance, strategies based on modification of the particle morphology (size, shape, and structure) and surface chemistry modification. Although size-related properties of NMs are linked with toxicity and exposure, focusing chemical modification on surface by doping[3], coating, or functionalization will be more interesting, due to physical changes could alter the “high-aspect ratio” of these special nanoparticles.

The implementation of ST5.3.1 happens by the coordination and collaboration of different partners: in one hand ITENE, which is leading the task with the support of CNRS and ICCRAM and, in the other hand the industrial partners within the DIAGONAL consortium, these are: IRIS, Phornano, Monolithos, Creative Nano, GXT, OCSiAl and DTI.

Indeed, the role of the demonstrators is crucial for the development of this subtask as well for the development of the upcoming ones, specifically task 5.4 in which the demonstration of the selected SbMD strategies will be addressed.

For this purpose, different online meetings (7 in total) were initially arranged by ITENE in collaboration with CNRS and ICCRAM with the aim of evaluating the feasibility of the suggested SbMD strategies together with each industrial partner.

During these meetings, a coherent outline was presented by following this structure:

- Subtask reminder
- SbD concept and purpose
- Background on toxicity results (based on the results reported in D4.5)
- Proposed SbMD strategies
- Company feedback and discussion

Once the meetings were concluded, the presentations and other relevant files were prepared and distributed among the industrial partners.

As an outcome of these initial meetings, and based on the companies’ feedback, several cases studies were prioritized for implementing the recommended strategies in agreement with the industrial demonstrators. At this point it is expected to arrange new meetings to coordinate and concrete the next steps regarding the implementation of such strategies. In addition, after having these meetings we delivered a questionnaire to each industrial partner to collect their feedback and commitment to the implementation of the proposed SSbD strategies. In these questionnaires we include, in addition to SbMD strategies, SbPD and SusbD strategies. SusbD strategies are not contemplated in this deliverable since they were addressed in Task 5.2. Nonetheless, the company feedback regarding the sustainability strategies have been collected in the SSbD questionnaires (see ANNEXES).

Despite the implementation of the proposed strategies is out of the scope of this deliverable, in Sections 4 and 5 we provide an overview of each company need and interest of the implementation of SbMD strategies based on their feedback.

b. Safe by Process Design

Within SSbD Framework[4], processes are addressed in Step 2: Human health and safety aspects in the chemical/material production and processing phase. This step evaluates the occupational safety and health (OSH) aspects in the life cycle of the chemical/material prior to its final application. It refers to the production process from the raw material extraction (from natural resources) to production (e.g., substance manufacturing, mixing) of the chemical/material including the recycling or waste management.

The goal is to assess whether the production and processing of the chemical/material poses any risk to workers. The assessment covers all the hazards of the chemicals/materials used in the process (raw chemicals/materials, processing aids…) and the potential for exposure of workers to them.

For the evaluation, it is important to identify all the production and processing steps, the chemicals used in each of them (raw chemicals/materials, processing aids…), the ones that may be produced during the processes (welding fumes, etc.), and identify their hazards. The operational conditions (how the substance is used, duration, concentration in a preparation, outdoor/indoor use, close/open process) together with the potential of release (Volatility, dustiness, fugacity, temperature, pressure) and the Risk Management Measures (RMMs) in place (e.g. Local Exhaust Ventilation) will identify the likelihood of the exposure to the chemical/material as well as the potential route (inhalation, dermal, ingestion) of exposure.

The risk should be estimated as a combination of the chemical/material hazards and the exposure during the different processes and the RMMs already in place to control the risks. A tiered approach can be applied, depending on whether the assessment refers to a new or to an existing chemical or material and the availability of the data in the different cases.

Figure 2 illustrates a hierarchy for tiered risk assessment depending on the data availability for each of the aspects.

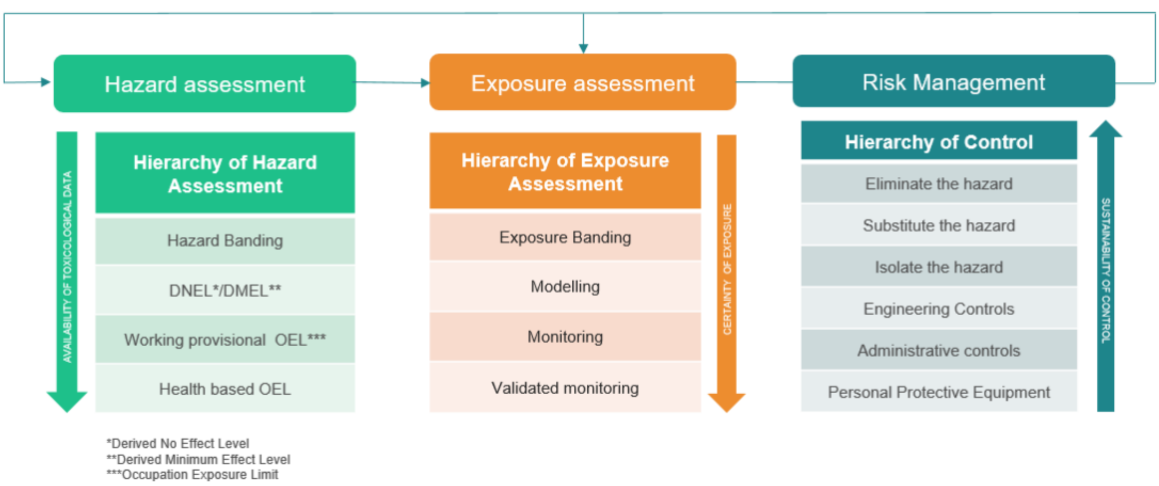

Figure 2 - Hierarchy for a tiered risk assessment depending on the data availability for each of the aspects[5]

There are different qualitative/simplified models available (also known control banding models) for the safety assessment and management at the workplace. These models are designed to characterize the risk at the workplace in a Tier 1 approach, when the whole set of data to perform a quantitative assessment is not available. These models are based on assigning scores or levels to some of the different variables *(Hazards of chemicals; exposure frequency and duration; amount of chemical used or present; physical properties of the chemical like volatility and dustiness; operational conditions; type of existing RMMs; etc.)* to be considered during the risk characterization. The result is a categorization into different risk levels, which determine whether the risk is acceptable or not, and sometimes, the type of preventive measures to be applied.

On the other hand, a set of criteria can be defined to assess the hazard and exposure aspects to estimate the risks from all the processes along the life cycle. The criteria will address the use of hazardous chemicals/materials as well as the process related potential of exposure. The application of such criteria will give additional information on the worker safety in the different processes along the life cycle (e.g., extraction, production, recycling, waste treatment) that will contribute to the overall sustainability indicators.

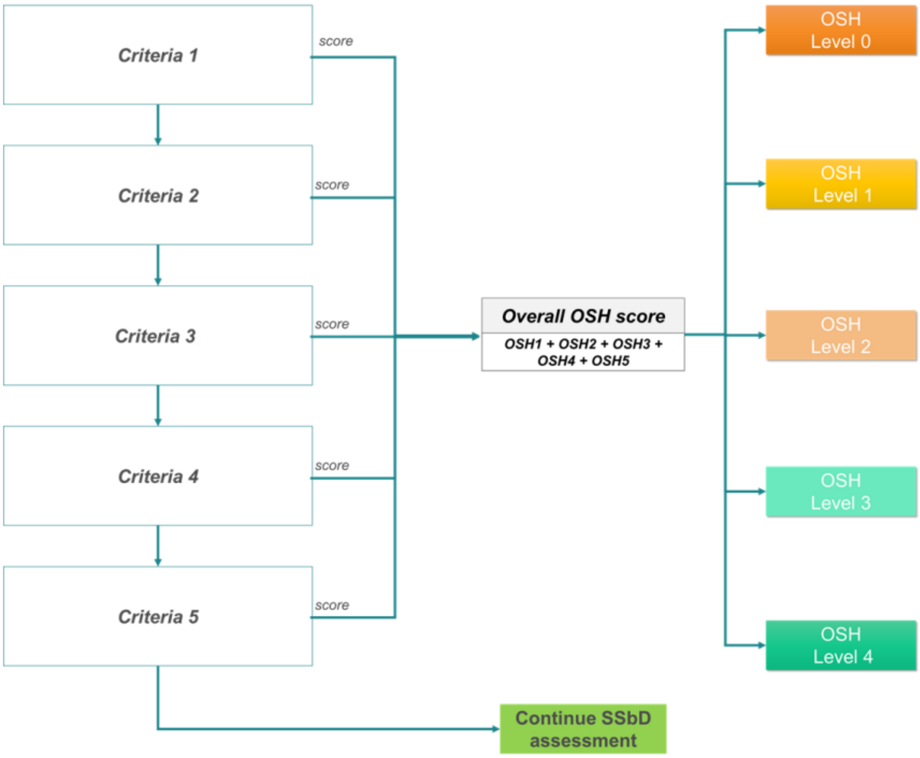

Figure 3 - Workflow relevant to Step 2 of the SSbD framework

The implementation of ST5.3.2 acts as a parallel task to Safe-by-Material-Design covered in ST5.3.1. ITENE, with the previous work of ISQ on monitoring campaigns, has prepared a batch of general strategies to design safer processes, which has been offered to demonstrators. Furthermore, the contribution from Task 6.1 about risk management approaches has been considered within SbPD scope. Therefore, although RMMs will be addressed in detail in T6.1, they have been also included within the SbPD approaches.

In the questionnaires mentioned before, a general approximation has been proposed, allowing the companies to choose the best option for them according to their economic and technical feasibility. Therefore, regarding the different feedback from the companies, we will address the efficiency of each strategy.

3. Safe by design strategies: overview

3.1. EC recommendations on SSbD framework

The European Green Deal has established four interlinked policy goals for the transition to a sustainable economy and society: climate neutrality, biodiversity protection, circular economy and a zero-pollution ambition for a toxic-free environment. To achieve these objectives, the Chemicals Strategy for Sustainability (CSS) calls for the transition to a Safe and Sustainable by Design (SSbD) approach for chemicals. The transition to chemicals and materials that are 'safe and sustainable by design' requires a common understanding of safety and sustainability aspects to be successful. Therefore, it was necessary to develop a European assessment framework for 'safe and sustainable by design' chemicals and materials, that can assist in the definition of safety and sustainability criteria.

In December 2022, the European Commission adopted the "COMMISSION RECOMMENDATION, establishing a European assessment framework for 'safe and sustainable by design' chemicals and materials". This Recommendation proposes that a European framework for 'safe and sustainable by design' chemicals and materials be established for R&I activities. It is based on the technical reports published by the Commission's Joint Research Centre (JRC)[6,7].

Since this framework was not published when DIAGONAL proposal was prepared, neither when deliverable D5.1 was submitted (July 2021) the team considers necessary to apply and test it through DIAGONAL case studies, to be able to report on the implementation of the framework.

The current SSbD framework can be applied either to the development of new chemicals and materials or to the re-assessment of existing ones. This safety and sustainability assessment is composed of **four steps** (a **fifth step** would be **recommendable** but not mandatory) and follows a hierarchical approach in which safety aspects are considered first, before moving on to sustainability aspects. In this manner, the first three steps mainly cover different aspects of the safety of chemicals or materials. The fourth step covers the environmental aspect of sustainability. Moreover, depending on how the SSbD framework is applied, it might also be beneficial to evaluate socio-economic sustainability factors, for example as a supplementary component to the major safety and sustainability assessments in the framework's use in the future.

Therefore, in this deliverable we follow the current framework recommendations. In particular by promoting the selection of most relevant re-design principles for each of the studied test cases (in agreement to the Stage 1 of the EC Recommendation).

3.2. Concept and purpose

Safe by design (SbD) can be described as an approach that focuses on providing functional materials/products, while avoiding damage to human health (and/or the environment) because of their fabrication process, use or disposal. In other words, SbD approaches aim at the **reduction of NMs hazard and exposure**, the reduction of NMs **migration and release**, and the controlled degradation of these once they are released from their matrices.

The need to develop commercial products that are at the same time useful and safer, starts at the very beginning of their conception. The objective is to establish safer by design selection rules and synthetic approaches that can be used for the reduction of nanotechnology-associated risks. Taking into consideration all stages of the life cycle of these products, these rules should protect the safety of workers, users and consumers and the product end of life. In detail, SbD approaches aim at the reduction of NMs hazard and exposure, the reduction of NMs migration and release, and the controlled degradation of these once they are released from their matrices. Traditionally, several strategies have been employed toward these aims:

Reducing toxicity of the employed materials: i) avoiding the use of intrinsically toxic elements or substances where possible ii) modifications in the size and shape to reduce the toxicity of the NMs in a specific biological system iii) increase in hydrophilicity to decrease the potential to cross biological membranes, or iv) changing the oxidation state to mitigate NP reactivity.

Reducing the release of NMs from the matrix during their life cycle. Normally, NPs are components embedded in a solid or liquid matrix forming part of different products. It is possible to reduce the release of NM from the matrix by controlling van der Waals, ionic, coordination and covalent bonding between NP and matrix using ligands and compatibilizers. In the case of inorganic NPs, not only the release of the NP should be controlled but also the release of its constituent ions, since toxicity of NPs has been often attributed to their leached ions rather than the NPs themselves. In this case, **encapsulating the NMs** makes it possible to preserve the properties of the core material along with protecting it from dissolution, as in the case of ZnO NPs coated with a nano-thin amorphous silica.

Reducing the persistence of NMs. If NPs are used massively in consumer products, they will inevitably end up in the environment. Thus, developing strategies that control the end of life of the NPs are needed. As NPs have a high surface energy, they are prone to both **aggregation and dissolution**. Thus, NPs can be irreversibly aggregated (and easily sintered) until they reach bulk sizes of well-known materials that we know how to deal with safely, or otherwise, NPs can be corroded into ionic species where our knowledge to safely deal with them is broad.

Decisions made during the product design stage affect the impact of the product on both worker and consumer exposure and safety. Therefore, Safe by-design strategies are used to guide decisions during the product design stage to address particular design objectives.

3.3. Safe by material design

3.3.1. General design principles for safer nanomaterials

Here we propose five material-design principles that can be used as starting point during the design stage of nanomaterials and products containing NMs[8]. By using these design principles, the health risk of the nanoparticle may be mitigated by potentially lowering the hazard and/or the exposure potential of the nanoparticle. The type of nanoparticles used in products, as well as the way they are incorporated into products, is vastly diverse. Therefore, the **guidelines to reduce the risks of nanoparticles must be general and practical** enough to cover the wide spectrum of nanoparticles contained in products.

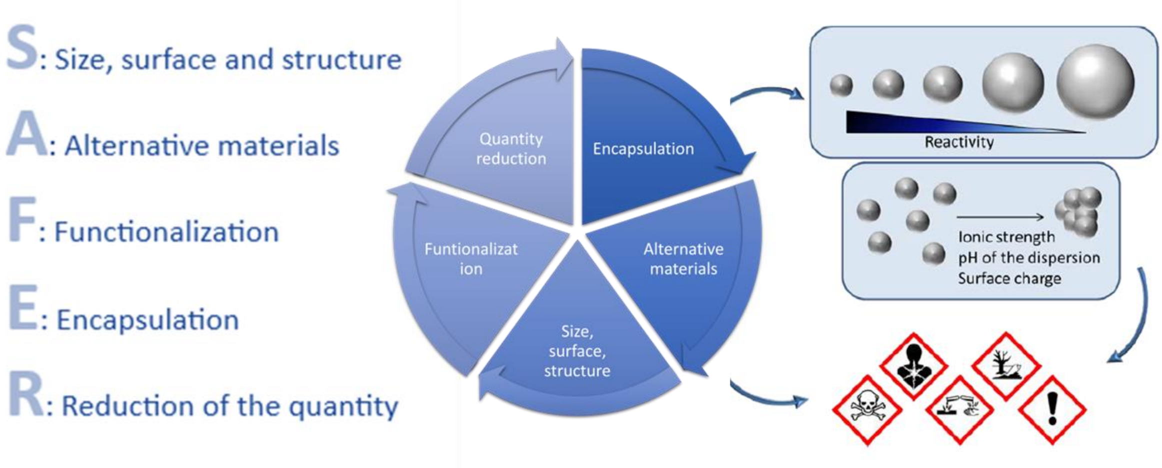

Figure 4 - General principles design for safer nanomaterials.

The following are five general principles that product designers can use as an **initial framework** to address the risks of nanoparticles during the product design stage.

Principle 1: size, shape and structure.

There are three major characteristics of nanoparticles (size, surface, and structure) that if changed, can affect fundamental nanoparticle properties (color, conductivity, melting temperature, and reactivity). The objective for this design principle would be to change the size, surface, or structure of the nanoparticle so that the desired product functionality is preserved, but the hazard and/or exposure potential of the nanoparticle is diminished.

Size: The size of a nanoparticle includes the dimensions for diameter, length, width, etc. which affect the fundamental properties of the nanoparticle. Research on the toxicity of nanoparticles has revealed there is a relationship between toxicity and particle size, in general, the smaller the size, the more reactive the nanoparticle as the contact surface is increased.

Regarding hazards linked to human skin permeation of inorganic and carbonaceous nanoparticles, the size of nanoparticles is important. Guidance for control of size to minimize penetration of the human skin may be based on a paper by Filon et al.[9] These authors review the related literature and concluded that **nanoparticles with a diameter <20 nm can permeate both the intact and damaged skin**, that nanoparticles with a **diameter between 20 and 45 nm can only permeate the damaged skin** and that nanoparticles with a **diameter >45 nm cannot permeate** the skin. Increased size of nanosilica is linked to a reduction of surface area per unit of mass. Reducing the surface area has been proposed as a safe(r)-by-design strategy for amorphous silica nanoparticles in products that may be ingested. Increasing the size of amorphous nanosilica would be in line with the design strategy proposed by Chatterjee et al.[10]. Hazards linked to the dissolution of substances from inorganic NMs may be reduced when nanoparticulate size increases[11].

An important point is reported in the case of non-biodegradable inorganic fibers longer than 10 µm where macrophages cannot engulf them, setting then a defense action well known as frustrated phagocytosis. In these cases, the NPs cannot be completely phagocytosed inducing thus chronic inflammation and consequent carcinogenicity (asbestos-like effect).

Differences in physicochemical properties between NPs and larger particles determine their behavior as aerosol, their biodistribution in the body following translocation from the portal of entry, their cellular interactions, and their effects. Whereas many of the effects at the organ of entry, the respiratory tract, can be the same for both particle sizes, secondary organs are affected differently.

Surface: The surface characteristics affect the fundamental properties of the nanoparticle and include surface chemistry, surface charge, surface morphology, surface roughness, and surface contamination. For example, the greater the surface area per mass possessed by particles with the same chemistry, the greater the resultant biological (i.e., inflammatory or pro-oxidant) activity[12]. Further, oxidation of the surface of nanoparticles may influence their cytotoxic effects.

Structure: The structure (crystal structure, shape -sheet, fiber, tube, sphere, cube, and sharp edges-, porosity, chemical composition, aggregation, etc.) of the nanoparticle can also affect the properties of the nanoparticle. For carbon nanotubes, structural differences include the wrapping angle (degree of twisting) of the lattice structure, or the presence of single or multi-walled nanotubes. The researchers state that ‘‘carbon materials with different geometric structures exhibit quite different cytotoxicity and bioactivity *in vitro*’’[13]. Further, the structure of a nanoparticle also includes the degree that the nanoparticles are joined together by aggregation or agglomeration to form larger particles.

For example, a study by Jiang et al.[14] showed that **crystal structure** can have a significant impact on NP reactivity, using as model TiO_2 NPs. Results showed a **ranking from highest to lowest activity** as amorphous > anatase > anatase ⁄ rutile mixture > rutile.

Concerns had been raised earlier that NPs of fibrous shape and dimensions and of high biopersistence, resembling asbestos, may induce adverse effects like those known to be caused by asbestos exposure, i.e., lung fibrosis, lung carcinoma, and mesothelioma.

In addition, Bottero et al.[15] compared **different shapes of rutile and anatase**, varieties of photocatalytic nano-TiO_2, and concluded that small compact cubes of anatase TiO_2 were the best compromise to minimize negative impacts by reactive oxygen species while retaining photocatalytic activity. These are just a couple of examples in which the importance of the NM structure is highlighted.

Additional physicochemical properties of the NMs, related to size, surface, and structure, that might be relevant for toxicology are:

- Size and size distribution
- Shape
- Agglomeration/aggregation
- Surface properties
    - Surface area and porosity
    - Surface charge
    - Surface reactivity
    - Surface chemistry
    - Defects
- Solubility
- Crystallinity

Principle 2: alternative materials

This approach involves identifying an alternative material (nano or bulk), that can be used to replace the hazardous nanoparticle. Also, the hazardous nanoparticle could be replaced by a combination of alternative materials. The alternative material(s) should provide the desired functionality without the attendant toxicity issues. The use of alternative materials requires careful analysis, including the investigation of the potential effect that the replacement may have on product functionality, hazards, and costs. There are several tools and methodologies available, such as **P2Oasys** and the SSbD frameworks, to help product designers to assess the potential alternative materials. If no alternative materials are available, then it may be necessary to eliminate the hazard by no longer using the nanoparticle in the product. This involves redesigning the product so that the functionality requirements that led to the initial choice of the hazardous nanoparticle is either significantly changed or eliminated.

Principle 3: functionalization

Functionalization is the intentional bonding of atoms or molecules to nanoparticles to change the properties of the nanoparticles. The objective for this design principle would be to functionalize the nanoparticle in a manner such that the desired product properties are preserved, but the hazard and/or exposure potential of the nanoparticle is reduced or eliminated.

The surface functionalization of NMs involves a process that aims to improve and/or add functional properties to these NMs to be used in diverse applications. Different types of NMs have characteristic chemical properties and functional groups exposed on their surface to be used in the first steps of functionalization. Often the first step of the functionalization is based on the use of homo- or hetero-bifunctional cross linkers to the aim to add an organic functional group ($R\text{-}NH_2$, R-COOH, etc.), useful to bind biological molecules. For instance, aminosilanes can introduce an amino group to the surface of *silica nanoparticles* in preparation for the upcoming bioconjugation[16]. Crosslinkers containing -SH or -NH2 groups can be used to functionalize noble metals, such as *gold or silver*, by reacting with the metal and creating a covalent bond. Thio-carboxylic acids are an example of a bi-functional linker that has functional groups at the other end that can be used to bind ligands[17]. *Metal oxides* NMs are often modified by using a ligand exchange strategy based on the substitution of the original surfaces with functional groups such as diol, amine, carboxylic acid, and thiol useful for the next steps[18]. The *carbon-based* NMs contain a significant fraction of sp^2 hybridized carbon atoms that can be used to generate functional groups. Through the oxidation it is possible to generate -COOH, -OH, and -C = O on the NPs surface[19]; through halogenation, it is possible to obtain halogenated carbon that can be further modified[20,21].

The functionalization will depend as well on the final application of the NM, for example, for biomedical applications, it is important to inhibit tissue accumulation of the nanoparticle, and instead promote the urinary excretion of the nanoparticle. This can be accomplished by increasing the solubility of the nanoparticle as well as preventing nanoparticle aggregation[22]. A study showed that covalently functionalized multi-walled caron nanotubes (MWCNTs) exhibited rapid urinary clearance, as opposed to non-covalently functionalized MWCNTs that accumulated in the liver[23].

Table 1 - Resume of the most common strategies used to modify NPs surface related to the nanomaterials.

Material	Usable functional/chemical groups	Example of chemical compounds/ processes suitable for surface modification
Silica	–SiOH	X-Si$(OC_2H_5)_3$
Noble metals	–Au; –Ag (plasmonic metals)	X-SH, X-NH_2
Metal oxide	MO_x	X-COOH; X-$(OH)_n$; X-NH_2 (adsorption)
Carbon based	sp^2 hybridize carbon	Oxidation; halogenation, cycloaddition . . .

Principle 4: encapsulation or coating

Encapsulation is a method used to completely enclose a nanoparticle within another material. The intent of this principle is to enclose a potentially hazardous nanoparticle within a material that is less hazardous. The use of the encapsulation strategy should include certainty that the hazardous nanoparticle remains encapsulated during the relevant product life cycle stages where exposure may be an issue.

We can find many examples of NMs coatings in the literature, for instance: coating inorganic nanoparticles with silica and (bio)polymers can reduce nonspecific interactions with biomolecules and improve aqueous stability, which may improve the performance of nanopharmaceuticals, in this case, long term stability of these material would be mandatory[24,25]. Coating of rare earth-oxide nanoparticles with phosphonates or rare earth phosphates has been suggested as a safer-by-design technology to reduce damage caused by phosphate stripping of cellular components[26,27]. Coating with phosphonates has also been suggested as a SbD strategy for metal oxides because such a coating can reduce the dissolution of metal ions and the generation of reactive oxygen species at the nanomaterial surface[28]. Coating MCWNTs with Pluronic F 108 (a nonionic triblock copolymer) may reduce the lung fibrosis hazard of such nanotubes[29].

Principle 5: reduce the quantity

There may be situations where applying the above design principles cannot reduce or eliminate the nanoparticle hazard while maintaining the desired product functionality. In these cases, the continued use of the hazardous nanoparticle may be necessary. If so, we should investigate the possibility of using smaller quantities of hazardous nanoparticle in the product while maintaining product functionality.

To conclude, it is worth to mentioned that there is no intended hierarchy for these general five principles, since they are expected to cover a wide range of nanoparticles and product applications. We could say that they are five general principles that product designers can use as an initial framework to address the risks of nanoparticles during the product design stage, however, it will require more testing, validation, and refinement.

3.3.2. Specific safe by material strategies depending on nanomaterial type

From a point of view of chemical composition, nanomaterials can be generally categorized into organic or carbon-based and inorganic NPs.

Carbon based NMs: The carbon atom, being a more versatile element, has received increased attention from researchers towards taming its different types of hybridization states (sp, sp^2 and sp^3) and synthesizing a lot of its allotropes. These are fullerenes (C60), carbon nanotubes, carbon nanofibers, graphene, and carbon onions. Furthermore, single-walled carbon nanotubes, multiple-walled carbon nanotubes, quantum dots, and zero-dimensional dots have also been synthesized.

Inorganic NPs: among these materials we have metals and metal oxides nanoparticles like aluminosilicates. NPs using inorganic metals like silver, gold, silicon, etc., and metal oxide NPs like iron oxide (Fe_3O_4), titanium oxide (TiO_2), copper oxide (CuO), zinc oxide (ZnO), etc., have been synthesized as well as other forms of gold and silver NPs, like gold nano shells or silver nanorods.

The combination of these two types of nanomaterials (carbon based and inorganics) could result in a third group, that would be ***hybrid nanoparticles.***

In this section we will focus on the safe by design strategies that are often applied **to carbon based and inorganic nanomaterials**. In the case of the hybrid nanomaterials, finding the proper strategy might be most complex since we must consider the properties of both materials. The proper strategy often is a combination of the strategies applied to both groups. Some of the strategies applied to DIAGONAL MCNMs are explained in Section 4 “SbD strategies proposed for the case study materials”.

Strategies for carbon-based materials

Surface functionalization is a proper strategy for carbon-based nanomaterials, including graphene, graphene oxide and CNTs. It can be applied to prevent their agglomeration, but it also can be applied with the aim of achieving new functions, often related with the improved mechanical properties, electrical properties, thermal properties, etc. Currently, the methods for the functionalization of carbon-based materials (CNTs, graphene and graphene oxide) mainly include **covalent bond functionalization**, **non-covalent bond functionalization**, and other **atomic doping functionalization**. In general, covalent modification of carbon-based materials is preferred when seeking to improve the structural properties of graphene oxide whereas non-covalent modification is proper for enhancement of electrical properties. A doping strategy is recommended when seeking improvements of electronic properties[30].

- **Covalent bond functionalization:** Covalent bond functionalization of carbon-based materials involves combining them with newly introduced groups in the form of covalent bonds to improve and enhance its performance. The oxygen-containing groups on the surface of graphene oxide makes covalent bond functionalization easier than that on graphene. The surface of graphene oxide contains a large amount of hydroxyl groups, carboxyl groups, and epoxy groups. These groups can be used for common chemical reactions such as isocyanation, carboxylic acylation, epoxy ring opening, diazotization, and addition. In the case of covalent functionalization, the translational symmetry of CNTs and graphene is disrupted by changing sp^2 carbon atoms to sp^3 carbon atoms, and the properties of nanofillers, such as electronic and transport are influenced. In covalent functionalization, graphene and CNTs are linked with a functional unit through covalent linkage. There are several methods or strategies for covalent functionalization of these carbon nanomaterials, among them:

- *Carboxil functionalization:* The reaction is simple and versatile. It takes place at room T and can be performed using a wide variety of molecules: amino acids, enzymes, polymers, silanes, amine-terminated biomolecules, aliphatic and aromatic amines, nanoparticles, and ionic liquids.
- *Covalent attachment of small biological molecules* such as glycine, glucose or ethylendiamine
- *Functionalization of graphene and CNTs using click chemistry*: Polystyrene-functionalized SWCNTs, Polyurethane-grafted SWCNTs, Hyper-branched polymer-CNT, Poly(e-caprolactone) (PCL) functionalized MWCNTs, PLC-graphene sheet (GS), PNIPAm-grafted graphene sheets (PNIPAm-GS).
- *Functionalization of graphene and using block copolymers* such as polyurethane (PU), Poly(lactide-co-caprolactone) or poly(lactide)-poly(ethylene glycol) (PLA-PEG) among others.
- *Functionalization of CNTs and graphene using dendritic polymers* such as hyperbranched poly(urea-urethane)s (HPUs) or Hyperbranched aromatic polyamide (HBA).

- **Non-covalent bond functionalization:** non-covalent functionalization of carbon nanomaterials through aromatic compounds, surfactants, biomolecules and polymers are connected by π-π stacking or hydrophobic interactions, electrostatic interaction, and hydrogen bonding. In these approaches, non-covalent modifications of carbon nanomaterials do not compromise their physical properties and conserve their desired properties, while improving their solubility quite remarkably.

  The non-covalent bond functionalization of carbon-based materials often results in the formation of a composite material having a specific function by interaction between hydrogen bonds and electrostatic forces between graphene and functional molecules, the greatest advantage of which is maintaining the bulk structure and excellent properties of the material, and also improving its dispersibility and stability. The methods for the functional modification of surface non-covalent bonds mainly include π-π bond interaction, hydrogen bonding, ionic bonding, and electrostatic interaction modification. The non-covalent bond functionalization process is simple with mild conditions, while maintaining the structure and properties of the material. However, the disadvantage of this method is that other components (such as surfactants) are introduced.

  In the case of graphene, due to stacking and van der Waals force, the surface modification of graphene is important because it makes the material hydrophobic by nature and prevents it from being dissolved in both organic and aqueous solutions. To remedy this issue, its solubility in common solvents must be increased. This will prevent stacking between the graphene layers through noncovalent functionalization using various surface-modifying agents such as PNIPAANm or aromatic molecules.

  In the case of CNTs, they are poorly soluble in most organic solvents due to their tendency to become entangled and form 3-D networks through determined van der Waals interactions. Therefore, non-covalent functionalization becomes a more attractive solution for various groups attached onto the CNT surfaces without affecting the conjugated π system and also increasing the solubility in aqueous and organic solvents.

  The functionalization is done by the addition of surfactants or polymers (e.g. pyrene or poly(N-vinyl carbazole) (PVK), among others). Polymers favour CNT dispersion in polar solvent, due to wrapping of polymer or block copolymer in the CNT surface through a hydrophobic part and exposing their polar domain towards the polar solvent.

- **Element doping:** this type of modification usually adopts annealing heat treatment, ion bombardment, arc discharge and other means to incorporate different elements into graphene, thereby resulting in the substitution of defects and vacancy defects in graphene and maintaining the intrinsic two-dimensional structure of graphene. Simultaneously, its surface properties change to give new performances. Element doping adjusts the energy band structure of graphene, but the doping process is difficult to control quantitatively. This approach is often used for electronic applications**.**

Strategies for inorganic nanomaterials (metallic and metal oxide nanoparticles)

- **Encapsulation or coating**

These strategies based on the encapsulation or coating of the nanomaterial could be generally applied either to metallic or metal oxide nanoparticles such as TiO_2, ZnO or CuO, among others. The encapsulation or coating of these materials is an effective way to avoid toxicity due to the slower rate of release posed by the silica or alumina shell. In particular, the researchers suggest that the hazards of ZnO and TiO_2-based-sunscreens for consumers specifically are linked to the generation of reactive oxygen species[31]. Therefore, the hazard may be reduced by silica, alumina, and lignin coatings. However, some limitations could arise related to the photocatalytic characteristic, which can be counteracted if the nanoparticles are coated with silica or aluminum oxide. Experiments show that depending on the completeness of the coating, the photocatalytic activity of TiO_2 and ZnO can be reduced, and the transparency of sunscreens retained[32,33].

  - *Amorphous silica or alumina coating:* A commonly applied safer-by-design strategy aims at reducing the generation of reactive oxygen species (or radicals) on exposure to sunlight by silica or alumina coatings (combined with silicones). It was demonstrated that the SiO_2 coating improves nanoparticle biocompatibility *in vitro* on a variety of nanomaterials including Ag, Y_2O_3, and ZnO nanoparticles and mammalian cell lines. SiO_2 is one of the most studied shell candidates because of its relative ease in preparation, great ecological soundness, and compatibility with other different materials which spurred us to prepare the core/shell structured composite of ZnO and SiO_2 and anticipated that would accomplish novel properties coming about because of the synergic interaction of these two chemical components.
  - *Lignin coating/encapsulation:* This approach has been applied to TiO_2 nanoparticles but it can be extended to the case of other metal oxide nanoparticles such as ZnO. The strategy is based on a nontoxic, biocompatible shell that neutralizes the free radicals by scavenging them with natural antioxidants before they exit the particle. In the case of TiO_2, the new lignin@TiO_2 composites preserve the scattering and absorption properties of TiO2 because the particles retain their nanoscale dimensions as preferred by the cosmetic industry. Although the target properties for photocatalysis and sun-protection applications are the opposite, exactly the same knowledge is required to optimize either one.
  - *Coating with phosphonates:* it has also been suggested as a safer-by-design strategy for metal oxides because such a coating can reduce the dissolution of metal ions and the generation of reactive oxygen species at the nanomaterial surface.

- **Doping**

Several safe(r)-by-design studies have focused on Fe doping of CuO or ZnO nanoparticles. The rationale behind this is that Fe doping should decrease the dissolution of metal ions (of Cu or Zn) that are held to be responsible for cytotoxicity. A decrease of metal ion dissolution by Fe doping of ZnO and CuO nanoparticles in several media was shown in the studies of George et al.[34] , Xia et al. [35], and Naatz et al [36].

3.4. Safe by process design

Process and Material design are two different but complementary approaches to address safety issues in NMs production. Unlike SbMD, Safe-by-Process-Design (SbPD) will evaluate exposure risks for HARNs and MCNMs and will be implemented through risk management measures. However, those are not opposite strategies. SbPD could be implemented on modified nanoparticles after material changes. Indeed, this is a full approach to deal with any potential risk.

We can define process design as the design of new or improved processes to produce chemicals and materials[37]. Process design does not change the intrinsic properties (e.g., hazard properties) of the chemical or material, but it can make the production of the substance safer and more sustainable (e.g., more energy or resource efficient production process, minimizing the use of hazardous substances in the process). The process design includes upstream steps, such as the selection of the feedstock.

A batch of possible applications within SbPD approaches will be proposed to minimize exposure levels. These SbPD strategies and risk management measures will be selected regarding particle exposure levels, according to the information from measure campaigns performed in WP4, and they will be evaluated in terms of performances using Occupational Exposure Models developed in Task 3.2. Occupational exposure model will estimate exposure levels for any person who manipulates nanoparticles in the chemical/material production and processing phase, considering a variety of process conditions and different risk management measures. With the support of this model, the efficacy of each SbPD strategy can be evaluated.

3.4.1. List of SSbD design principles for safer processes

Figure 5 depicts the main principles of Process Design[7]. The two first principles are more related to safety aspects and the last two principles address the sustainability dimension. Therefore, due to this deliverable is focus on Safe-by-Design, only principle 1 and principle 2 will be cover in detail in the following paragraphs. However, sustainability strategies will be also proposed to the companies in the questionnaires (Annex I).

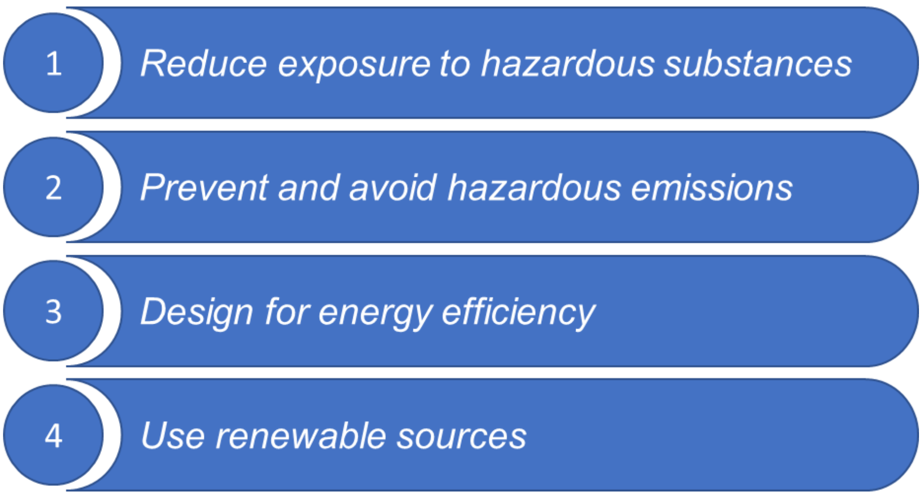

Figure 5 - Principles of Process Design

Principle 1: Prevent and avoid hazardous emissions

It is based on applying technologies to minimize and/or to avoid hazardous emissions or pollutants in the environment[38], selecting processes that:

- Minimize the generation of hazardous waste
- Minimize generation of emissions (e.g., Volatile Organic Compounds, acidifying and eutrophying pollutants, heavy metals etc.)

To ensure those conditions, the following criteria should be considered: Critical air mass (%), Critical water mass (%), Biological oxygen demand (g/kg), Chemical oxygen demand (g/kg), Total organic carbon (g//kg), Non-Aqueous Liquid Discharge (m^3 /kg), Wastewater to treatment (m^3 /kg), and Amount of hazardous waste (kg/kg)

Principle 2: Reduce exposure to hazardous substances

The goal is to eliminate exposure to chemical hazards from processes as much as possible. Substances which require a high degree of risk management should not be used and the best technology should be used to avoid exposure along all the life cycle stages. Some actions to be implemented to accomplish this principle are:

- Eliminate or minimize risk through reduction of the use of hazardous substances
- Analyze and avoid as much as possible the use of substances identified as substances of very high concern (SVHC)
- Consider value chain-specific regulations
- Reduction and/or elimination of hazardous substances in manufacturing processes

Commonly, some indicators are used to corroborate the actions proposed before, such us the potential biodegradability of manufactured chemical/material and/or the classification of raw chemicals/materials as SVHC.

3.4.2. Specific safe by process strategies depending on production of the case studies

In contrast to SbMD strategies, evaluation system for processes is not so specific, being a more general classification system regarding occupational safety and health (OSH) aspects. Therefore, case studies will be classified in terms of safety:

- Negligible Risk
- Low Risk
- Medium Risk
- High Risk
- Very High Risk

Therefore, the following strategies will be based on recommendations for RMM concerning different levels of risk, and advice on process design concerning accomplishing the main principles of SbPD.

- **Avoid Hazardous Emissions**

  Design and optimize manufacturing processes to minimize the generation of hazardous waste and emissions. Consider:

  - Process modifications to reduce or eliminate the use of hazardous chemicals and materials, thereby minimizing the generation of hazardous waste.
  - Closed-loop systems to recycle and reuse waste materials within the production process, preventing their release into the environment.

- **Adopt Safer Alternatives and Substitute Hazardous Substances**

  Prioritize the elimination or minimization of risk by reducing the use of hazardous substances in the manufacturing process. This can be achieved by:

  - Identifying and assessing safer alternatives to hazardous chemicals, aiming to substitute them with less toxic or non-toxic materials
  - Minimizing the use of harmful substances while maintaining product efficacy and performance.

3.4.3. Strategies for Risk Management

To ensure workplace safety, it is essential to minimize risks to the lowest feasible level using preventive actions, prioritizing them accordingly. Hence, wherever possible, exposure to harmful particles and liquids, including MCNMs and HARNs, via inhalation, skin contact, or ingestion, should be either completely eradicated or managed to the most practical extent. This approach adheres to the principles of the hierarchy of controls, which offers a systematic method for enhancing workplace safety[39]. It provides a framework for selecting the most efficient control measures aimed at eliminating or reducing risks arising from a company's operations. This hierarchy encompasses several steps, which include:

1. Elimination
2. Substitution
3. Technical measures (Engineering controls)
4. Organizational measures (Administrative controls)
5. Personal Protective Equipment (PPE)

Elimination/Substitution is the most effective control measure. It involves completely removing the nanomaterial from the process or substituting it with a less hazardous alternative which is an approach considered as SbMD and SbPD. If possible, choose to work with non-nanomaterials or less toxic nanomaterials to eliminate or reduce the risks associated with nanotechnology.
If elimination or substitution is not feasible, engineering controls should be implemented. These controls are designed to isolate workers and the environment from nanomaterial hazards. Examples include:

- Containment: Using closed systems or isolators to handle nanomaterials.
- Ventilation: Employing local exhaust ventilation systems to capture and remove airborne nanomaterials.
- Process Automation: Reducing human involvement in processes through automation to minimize exposure.

Regarding Administrative Controls, it involves implementing policies, procedures, and guidelines to manage nanomaterial risks. These controls may include:

- Work Practices: Establishing safe work practices for handling nanomaterials, such as proper storage, labeling, and waste disposal.
- Training: Providing comprehensive training for workers to ensure they are aware of the risks and know how to work safely with nanomaterials.
- Access Control: Limiting access to areas where nanomaterials are used and enforcing entry requirements.
- Emergency Response: Developing emergency plans and procedures for responding to incidents involving nanomaterials.

And finally, if no other measures are efficient, Personal Protective Equipment (PPE) must be implemented. PPE is considered a lower-level control, and it is an important layer of protection for workers. PPE includes items like respirators, gloves, lab coats, and eye protection designed to safeguard individuals from direct contact with nanomaterials.

A well-recognized variation of the general hierarchy of control principle is known as the "STOP principle." This risk management concept focuses on implementing strategic, technical, organizational, and personal measures to address safety concerns. In the STOP principle, the highest priority is given to strategic actions (S), which include elimination and substitution of hazards, followed by technical measures (T), organizational and administrative steps (O), and finally, personal protection (P). Table 2 offers an overview of the measures outlined within the STOP principle.

Table 2 - STOP principle basic measures.

Priority	Measures	Examples
1	S measures (Strategy)	Substitution of processes or substances (SbPD, SbMD) Redesigning / Modifying processes Low-emission forms or processes
2	T measures (Technical)	Enclosing/isolating Exhaustive ventilation Setting/design of operation
3	O measures (Organizational)	Training Work instructions Strategic planning
4	P measures (Personal)	Respiratory protection Dermal protection Eye protection

STOP Principle

The hierarchy of controls and the STOP principle establishes priorities in the following order:
(1) Strategic measures
(2) Technical measures
(3) Organizational measures
(4) Personal measures

Under this principle, if it is not feasible to completely eliminate the risks, the next best approach is to reduce them through substitutions that involve using less hazardous processes or substances. If substitution is not viable, the implementation of technical measures becomes crucial. PPE is considered the last resort in this hierarchy of control.

But, when it comes to materials within the nanometer range, these strategies of risk management must be reevaluated considering certain factors that directly influence the emission potential or dustiness potential of materials such as MCNMs and HARNs. Understanding these factors is crucial for minimizing exposure and ensuring the safe handling of nanomaterials. Some key factors that influence dustiness potential include:

- Particle Size: Nanoparticles, by definition, have sizes on the nanometer scale (typically less than 100 nanometers). Due to their small size, nanoparticles are more prone to becoming airborne when disturbed compared to larger particles. The high surface area-to-volume ratio of nanoparticles contributes to their dustiness.
- Particle Shape: The shape of nanoparticles can affect their dustiness. Nanoparticles with irregular shapes or high aspect ratios (e.g., nanowires or nanotubes) may be more likely to become airborne when agitated or dispersed.
- Surface Chemistry: Surface modifications can affect the agglomeration and dispersion of nanoparticles, impacting their propensity to become airborne.
- Mechanical Processes: Mechanical processes like milling, grinding, or cutting can generate dust and aerosols containing nanomaterials.

- Temperature and Humidity: Environmental conditions, such as temperature and humidity, can influence the dustiness of nanomaterials. Lower humidity levels may increase dustiness.
- Handling Methods: The way nanomaterials are handled, such as pouring, weighing, or transferring, can affect the release of particles.
- Workspace Size: The size of the area where nanomaterials are manipulated can affect the dispersion and dilution of airborne particles.
- The amount and concentration of nanomaterials being manipulated can influence the potential for emissions. Larger quantities and higher concentrations are generally associated with greater emission potential.

Managing dustiness is crucial to minimize the occupational and environmental risks associated with nanoparticles. Dust control measures, including engineering controls, containment, and proper handling procedures, should be implemented to reduce dustiness and protect workers and the environment from potential nanoparticle exposure. Additionally, risk assessments and exposure monitoring can help evaluate and mitigate the risks associated with nanoparticles and their dustiness in specific workplace settings.

Following the aforementioned factors, a group of selected RMM especially aimed for nanomaterials have been selected, validated within the framework of projects from the European Commission such as NanoReg. Table 3 summarizes the degree of recommendation of different technical measures when dealing with NMs in the workplace.

Table 3 - Recommended technical measures when working with nanomaterials. (HEPA = High-efficiency particulate arrestance; LEV = Local Exhaust Ventilation).

Engineering controls	
Highly recommended (High protection)	Local exhaust enclosure (Glove Box) HEPA filtered down flow booth Custom-fabricated enclosures HEPA filtered down flow room Ventilated Laboratory Hood + built-in water wash down systems (sprays) Negative pressure rooms
Acceptable level of protection (non-hazardous nanomaterials)	Ventilated Laboratory Hood (partial enclosure) Biological safety cabinet (small amounts of nanomaterials) Walk-in hoods Ventilated collar-type exhaust hoods Movable LEV systems with HEPA filter (extendable arms) Receiving hood (hot process) Work processes in furnaces (High cost)
Not recommended	Biological safety cabinet (amounts above 100 g) Ventilation by dilution
Personal Protective Equipment (PPE)	
Highly recommended (High protection)	Self-contained breathing apparatus Filtering full mask with inhalation valves (P3) Filtering half mask with inhalation valves (P3) Nitrile gloves – Double glove for large exposure periods Full body protective coverall (EN type 4-6) made of PE laminated with built-in hood Tight-fitting dustproof (i.e. non-vented) safety goggles Boot covers Safety shoes
Acceptable level of protection (non-	Half-Face particulate mask (P3) Neoprene gloves/Butyl gloves

hazardous nanomaterials)	Full body protective coverall (EN type 4-6) made of polypropylene with or without built-in hood Laboratory coats (Non-woven) Safety glasses
Not recommended	Filtering Facepiece (FFP3) Latex/Cotton/PVC gloves Laboratory coats (cotton/spunbonded polypropylene) Safety glasses

4. SbD strategies proposed for the case study materials

In this section we provide a deeper and more detailed analysis of the SbMD strategies that can be apply a specific type of nanomaterials, in particular the types of material that have been developed during DIAGONAL project, these are high aspect ratio nanomaterials (HARNs) and multicomponent nanomaterials (MCNMs). Furthermore, not only specific SbMD strategies were proposed to companies, but a general batch of Safe by Process and Risk Management were proposed as well to complete the whole vision of SSbD.

Among the first group we have: (i) carbon-based nanomaterials (carbon nanotubes and graphene) and (ii) silver nanorods, whereas within the second group we found: (i) metal oxide nanoparticles (ZnO), CuPdRh and titanium carbide (TiC). These strategies are mostly based in the above explained 5 principles with additional consideration of the material type and the final application. More in detail, the project will study:

• Silver nanowires for conductive tracks (printed electronics) – DTI

• Ni-P metal matrixes reinforced with graphene for nanocomposite coatings (automotive, oil and gas) – Creative Nano

• TiC NPs as reinforcement for metal matrix composites as lightweight alloys (automotive/aerospace) - IRIS

• ZnO nanoparticles (NPs) for UVA/B filters in sunscreens (cosmetics) and for bioimaging (health) – Phornano

• Graphene mixtures applied into smart fabrics (textile) – GXT

• Metallic oxide nanoparticles (Cu, Pd, Rh) over ceramic substrates of CeO_2/ZrO2 used in automotive catalytic converters - Monolithos

• Carbon nanotubes (CNTs) matrixes for industrial floor coatings - OCSIAL

4.1. Case study 1: Metallic HARNs for printed electronics - DTI

4.1.1. Case study overview

During the execution of DIAGONAL project DTI is developing silver nanowires (AgNW) to be used in conductive tracks for printed electronics. The nanomaterial consists of silver nanowires feature high electrical conductivity with better flexibility and optical transparency.

Production process: AgNWs form through a reduction reaction of $AgNO_3$ using ethylene glycol (EG) and are capped by polyvinylpyrrolidone (PVP). The final product from the process is a paste with 26% of Ag nanowires that will be used for ink formulations. The functionality of Ag nanowires for this demonstrator is to improve the electrical conductivity of the ink. The manufactured AgNWs (HARN) are on average 15 µm long and 0,18 µm wide.

The toxicity results reveal a moderate-low toxicity for DTI materials (lung and immune cells models) whereas the materials did not exhibit toxicity when they were tested using skin and gastrointestinal exposure models.

Additional information about the description of this case study and the toxicity results can be found in D5.2 and D4.5, respectively.

4.1.2. Safe by material strategies

Based on the toxicity results and in the scientific studies found in the literature the following strategies were proposed for this case study:

- *SbD strategy that allows to prepare silver nanowires with controlled dimensions*.

  The relationship between the nanowires' dimensions and their toxicity is still insufficiently studied. However, some studies reported that the AgNWs-induced cytotoxicity depends on their length and diameter, increasing gradually as the length increases[40]. According to studies reported in literature, a SbD approach might be to **promote the use of short AgNWs**. The strategy will be based in the addition of **halide salts as co-nucleants** (KBr, NaBr, KCl, NaCl, and KF). As a result, the diameter and the length of nanowires could be modulated (independently) in a wide range, allowing us to fabricate size standards.

- *Surface modification of silver nanowires using capping agents*

  Synthesis of AgNP needs a reducing agent and requires and capping agent to prevent aggregation of AgNP. Due to specific functional groups from capping agents, they can be attached to the surface of synthesized AgNP, thus, reducing surface energy and preventing grain growth and particle agglomeration. Capping agents sometimes provide electrostatic and steric stabilization effects for the dispersion of AgNP suspensions.

Polyvinyl pyrrolidone (PVP) is the most used for the synthesis of silver nanowires. The effect of varying the molecular weight (MW) on the shape of the nanoparticles has also drawn attention. It was found that PVP with molecular weight (Mw) 1.300.000 has the best efficiency, yield, and reproducibility on the synthesis of silver nanowires that using this capping agent[41].

DTI is currently using PVP in their process, however they use a low molecular weight PVP (Mw = 40 kDa). It was suggested to **use the high Mw PVP** since, according to the literature, it might result in a general improvement of the synthesis process and also on the materials properties.

- *Strategy to enhance the functionality of the material*

  PVP could remain in the nanowire surface after washing with several solutions containing water. If so, the PVP residue on the surface of the silver nanowire acts as a large resistance by interfering with the movement of the electric currents, and the manufactured electrode that is adapted with residual PVP applied on conductive materials surface is inevitably has poor electrical property. To improve electrodes electrical property, a specific alkaline solution was used for striving to disconnect the binding relationship with high surface bonding energy between silver and residual PVP.

4.1.3. Company feedback

DTI is interested in the implementation of **Safe by Material Design strategies**. According to the company, the changes proposed in terms of material production are easy to implement and they might improve the product quality with a negligible investment cost. 2. Within the SbMD strategies that have been proposed, the company is interested in: (1) modification of the molecular weight of the capping agent PVP to improve the process efficiency, (2) use of co-nucleants agents to prepare silver nanowires with controlled dimensions (i.e. shorter and thinner).In addition to these, two additional strategies that are more related to the process design but also affects the material are foreseen for their implementation, these are: (1) increase the temperature during the nanowires synthesis to produce thinner wires and (2) use of an alkaline solution to remove the residual PVP from the surface of the nanowires.

DTI have selected these strategies because they are easy to implement and might yield improvements in product quality. However, the suggested alternatives to capping agents will require an extensive study are likely to yield inferior product quality. This is why this strategy is not foreseen. Overall, the company expectations would include improvements in product quality and a better environmental and toxicological profile for the nanomaterials.

About the workplan, DTI expect to implement the first SbMD strategy before December 2023, and subsequently test each suggested strategy afterwards (1 strategy/month).

Regarding the proposed **Safe by Process strategies**, more detailed process strategies are needed before implementation. A safer alternative to acetone is preferred. Also, co-solvents might help reduce the use of acetone, but none has been identified. In addition, the current system already recycles acetone from waste via distillation on rotavapor. This will improve work safety, but needs more investigation before implementation – e.g., alternative chemicals and improved recycling methods compared with current.

Furthermore, other Risk Management Measures will be implemented such as Engineering controls (Ventilated Laboratory Hood -partial enclosure-, General ventilation -25/35 m^3/hour per person in the lab-) and PPE (Nitrile gloves – Double glove for large exposure periods, Boot covers, Neoprene gloves/Butyl gloves or Safety glasses). In fact, lab coats, safety googles, neoprene gloves/Butyl gloves and fume hoods have been already implemented and next month Boot covers, and Nitrile gloves are planned to be implemented.

Finally, considering the **sustainability** dimension, material efficiency will be improved for the silver nanowires synthesis with design options to maximize the yield of the reaction between silver nitrate, ethylene glycol and sodium chloride which should be investigated. The potential recovery of valuable substances from the generated waste could both reduce the amount of waste (and thus also cleaning-related impacts) and the amount of raw materials used. The sourcing of the materials will also be optimized, procuring reagents from more local sources (at least within EU). Silver nitrate ink printing process will be optimized as well through the optimization of using of printing equipment and associated electricity consumption. Upscaling effects can enable this by amortizing more easily equipment costs and improving energy efficiency.

DTI expect to implement the first SusbD strategies between November 2023 – January 2024 following the next work plan:

a. Surfactant replacement (SbMD 1) was also expected to improve product quality (SusbD 1): November 2023
b. Procuring reagents from more local sources (at least within EU): November 2023
c. Test printing to improve reproducibility: December 2023
d. Test recycling after printing to recover silver – testing leaching reagents and processes (sonication & shredding): January 2024

4.2. Case study 2: Graphene reinforced metallic coatings - CNano

4.2.1. Case study overview

Creative Nano (CNano) produces nanocomposite coating composed of a nickel (Ni) metal matrix and commercially available graphene nanoplatelets (GNPs) with applications in industrial sectors such as automotive, and oil and gas thanks to its anti-corrosion properties. The addition of small amounts of graphene can significantly enhance the corrosion resistance of the coatings thanks to the chemical stability and non-permeability of graphene. As a result, Ni/graphene coatings are currently being explored as substitutes for hard chromium in machinery and automotive applications. The graphene used in the project is commercially available graphene nanoplatelets (av-PLAT-7; Avanzare). The incorporation of GNPs is expected to increase wear resistance and reduce friction for the application of coatings in machinery (tools, gear) and automotive (pistons) to replace hard chromium coatings.

The toxicity results reveal a moderate-low toxicity for CNano materials (lung and immune cells models), it depends on the models and concentration used. For skin exposure, the toxicity is due to the nickel matrix. Whereas the materials did not exhibit toxicity when they were tested using gastrointestinal exposure models. More details can be found in D4.5.

Based on the toxicity results and in the scientific studies found in the literature the following strategies were proposed for this case study.

4.2.2. Safe by material strategies

The toxicity results revealed some issues regarding the toxicity of the material tested. However, they are mostly related to the metal matrix (nickel) rather than to the nanomaterial itself. From the point of view of material design, strategies attempted to reduce agglomeration of the graphene powders can be proposed. These are summarized as follows:

- *Surface modification of graphene via covalent functionalization*
    - Covalent Attachment of Organic Functionalities to Pristine Graphene: the main purpose is the **dispersibility of graphene** in common solvents that is a crucial move toward the formation of nanocomposite materials with graphene. Most attractive organic species: free radicals and dienophiles[42].
    - Covalent Attachment of small biomolecules (e.g., glycine, glucose) to partially oxidize graphene.

The disadvantage of applying a covalent functionalization is that the structure of graphene could be disrupted, affecting the functionality of the NMs. In addition to this, However, these strategies are often more complex to implement.

- *Surface modification of graphene via covalent functionalization*

The methods for the functional modification of surface non-covalent bonds mainly include π-π bond interaction, hydrogen bonding, ionic bonding, and electrostatic interaction modification. The non-covalent bond functionalization process is simple with mild conditions, while maintaining the structure and properties of graphene. However, the disadvantage of this method is that other components (such as surfactants) are introduced. In addition to surfactants, the functionalization could be done through **aromatic compounds, biomolecules or polymers**.

Non-covalent modifications of carbon nanomaterials do not compromise their physical properties and conserve their desired properties, while improving their solubility quite remarkably. Therefore, a feasible strategy (at lab scale) could be **surface non-covalent modification of graphene by using surfactants** (i.e., pluronic) or others (i.e., oleic acid).

- *Element doping*

4.2.3. Company feedback

CNano has highlighted its interest in implementing safe by design strategies. One of the main goals of the company is to develop new materials following Safe and Sustainable by materials and/or process design strategies in order to (i) improve health and safety of the personnel, (ii) reduce generation of hazardous waste (particularly nanoparticles) during production of nanocomposite coatings and (iii) provide new metal coatings with similar or better properties compared with Hard Chromium (HC) that is produced by Cr^{6+}-containing plating baths, a highly toxic and carcinogenic compound.

In the specific case of **Safe by Material design**, strategies based on the surface modifications of GNPs were proposed with the aim of improve the dispersibility of this nanomaterial. Among these SbMD strategies, the surface modification of graphene via non-covalent functionalization (by using surfactants) and the element doping were selected by the company for their implementation.

The selected modifications will most likely improve the dispersion of graphene in the electrolytic bath which will be relayed to the electrodeposited nanocomposite coating, to increase its wear and corrosion resistance properties to match or surpass those of HC. Replacing HC coatings is of paramount importance for the safety of the personnel in plating shops as well as for the protection of the environment. Cr(VI) species like CrO_3 and chromic acid are currently included in the REACH authorization list (Annex XIV of Reach, entries 16-22). The expectations of CNano after implementing these SbMD strategies are the production of Ni/Graphene nanocomposite coatings with low coefficient of friction and high corrosion resistance capable of replacing HC. The company is testing currently different surfactants at lab scale, expected to finish by February 2024. The best surfactant will be then upscaled to pilot scale (10-20 L baths).

In the case of **Safe by Process strategies**, CNano are developing a safe by process design approach in the context of DIAGONAL, where they have redesigned the electroplating platform to reduce the amount of graphene nanoparticles ending up in wastewater and to increase the quality of the final products (the latter is related to sustainability) as process modifications to reduce or eliminate the use of hazardous chemicals and materials. In summary, the new platform enables the use of ultrasonication in parallel with the electroplating process, something that was not previously possible. This both improves the quality of the final nanocomposite coatings and reduces the amount of graphene nanoplatelets ending up in wastewater.

Nanoparticle hood, ventilated laboratory hood (partial enclosure) and general ventilation (25-35 m^3/hour per person in the lab) are implemented as engineering controls and nitrile gloves – double glove for large exposure periods, half-face particulate mask (P3) and laboratory coats (non-woven) as PPE. All of them are already implemented in the laboratories apart from the nanoparticle fume hood (currently investigating options to install a new smaller one, dedicated to handling nanoparticles, closer to the plating lines).

An *ad-hoc* **sustainable strategy** has been selected as well for CNano. Specifically, improving material efficiency for the nickel-plating bath (high environmental, social and economic benefits): Design options to improve is the incorporation and the dispersion of graphene into the nickel-based coatings (taking place at the cathode). The potential recovery of nickel from the generated bathing waste could both reduce the amount of waste (and thus also cleaning-related impacts) and the amount of raw materials used. This strongly depends on the incorporation of graphene into the nickel-based coating (to which our new platform will likely contribute). The new design also reduces the release of nickel and graphene into the wastewater. CNano will produce a significant amount of sustainable results by April 2024.

4.3. Case study 3: Metal Matrix Composites (MMC) with nano-size reinforcement for Ti and Al based composites - IRIS

4.3.1. Case study overview

IRIS material consisted of a metal matrix composite of Ti-6Al-4V with nano-size reinforcement of titanium carbide (TiC) nanoparticles. It will be used in DIAGONAL project for manufacturing lightweight alloys for aerospace and automotive applications.

At the beginning of the project, three different industrial case studies were carried out with the same material (Ti-6Al-4V + 1%TiC nanopowder): (i) Coupon for the mechanical test, (ii) Gearbox (in whole or in part) and (iii) Actuator support. Currently only the first is considered.

Therefore, the nanomaterial used in DIAGONAL project a MCNM made by metallic and cermet powders (Ti-6Al-4V with nano-size reinforcement of titanium carbide (TiC) nanoparticles).

4.3.2. Safe by material strategies

Since there were not relevant issues regarding the toxicity of the material tested, the proposed strategies are not aimed at reducing toxicity. However, some strategies could be applied that might improve the material properties.

- *Surface modification of titanium carbide (TiC) particles*

TiC particles could be surface modified by coupling agent isopropyl trioleic titanate (NDZ105) to reduce the agglomeration of TiC particles in the matrix[43].

- *Use of alternatives reinforcements*

A selection of candidates for TMC reinforcements could be investigated including SiC, Si_3N_4, Al_2O_3, TiN, and TiB[44].

- *Network-Strengthened Ti-6Al-4V/(TiC+TiB) Composites*

Hybrid (TiC+TiB) network could be investigated for improvement of composite strength. Hybrid (TiC+TiB) network-strengthened Ti-6Al-4V—based composites can be fabricated via an integrated low-energy ball-milling and reaction hot-pressing-sintering technique[45].

4.3.3. Company feedback

The interest of IRIS in implementing the proposed strategies was expressed in the questionnaires that were used to collect the company feedback and commitment.

IRIS highlighted that the company is very careful in terms of safety, and they are concerned about the implementation of SSbD for improving both: workplace safety and worker safety. In fact, IRIS is aware of the lack of guidelines related to the use of metal powders in the additive manufacturing field and, therefore, IRIS has proposed itself as end user within the Diagonal project to pursue this purpose.

Regarding the proposed **Safe by Material Design strategies**, the company would be interested in exploring and implemented all the strategies proposed, being their first interest the surface modification of TiC by using a coupling agent (e.g.isopropyl trioleic titanate - NDZ105) to reduce the agglomeration. In addition to this they would be interested in the combination of Ti+TiB to increase the strength of the composites and, in the last place they would be interested in the use of alternative reinforcements (SiC, Si_3N_4, Al_2O_3, TiN and TiB).

The reasons why IRIS would be interested in applying the proposed strategies rely on the fact that the TiC particles are in the nanometric range. Therefore, dealing with this type of material may not make the working environment safe once inhaled even while wearing PPE. The company claimed that if it were possible to reduce the nanomaterials agglomeration during the deposition process, they should remain more anchored to the 3D printed object than in air. As regards the other modifications, they could give the object built in 3D superior mechanical properties, but a mechanical characterization must always be carried out.

Despite their interest in implementing these strategies, IRIS is not a nanomaterial manufacturer company and, for this reason, the implementation of such a SbM strategy would not depend on them. In other words, IRIS does not produce the nanopowders so the company cannot ensure whether these changes could be applied to the powders during their production. The implementation of these strategies would be in the nanopowder suppliers' hands. Therefore, it would not be feasible to implement any of these strategies under the scope of this project.

Regarding the proposed **Safe by Process strategies,** IRIS will introduce some slight changes to the production process through two possible solutions: the first is to create an inert gas recirculation system that is used during the deposition process in such a way as to reuse the gas and at the same time filter and capture the powder released into the atmosphere inside a specific work area; the second is to purchase a totally closed system for filling the powder feeder tanks. In fact, the second solution has already been implemented by IRIS for about a month.

4.4. Case study 4: Metallic NPs (ZnO_x) for applications in cosmetics and biomedical industries - Phornano

4.4.1. Case study overview

Phornano is involved in DIAGONAL project developing and manufacturing zinc oxide (ZnO) nanoparticles applied into two different types of nano-enabled products: sunscreens and bioimaging probes. In particular:

• Case 1: ZnO nanoparticles will be applied in formulations to develop skin sun protectors, thanks to the strong absorbance over the UVA/B range.

• Case 2: Manganese doped Zinc Oxide Nanoparticles (Mn@ZnO) to be used as fluorescent nanoprobes for biomedical imaging (fluorescence probe) as substitute of the less safe Cd-based quantum dots (QDs). ZnO composition is zinc oxide while Mn@ZnO composition is 95% (wt%) Zinc Oxide 5% Manganese (wt%).

4.4.2. Safe by material strategies

The toxicity results (lung, gastrointestinal tract and primary immune cells response) suggested that there are some concerns regarding the toxicity of some samples. Some strategies could be applied that might improve the toxicological profile of these ZnO Nps.

- *Encapsulation or coating*

Hazards of ZnO based sunscreens for consumers specifically are linked to the generation of reactive oxygen species. A commonly applied safer-by-design strategy aims at reducing the generation of reactive oxygen species (or radicals) on exposure to sunlight by silica or alumina coatings (combined with silicones).

- Amorphous silica or alumina coating

- Lignin coating or encapsulation

- Coating with phosphonates

Despite the advantages of nanoencapsulation, the adverse health effects of inorganic and synthetic organic UV filters cannot be completely eliminated, and their environmental impact remains a concern.

- *Fe doping of ZnO and ZnO-Mn nanoparticles*

The rationale behind this strategy is that Fe doping should decrease the dissolution of metal ions (of Cu or Zn) that are held to be responsible for cytotoxicity.

- *Use of alternative materials*[46]

This strategy would rely on the use of potentially safer substitutes for these materials. This would be transparent nanoparticles composed of ethyl cellulose and zein (a corn derivative consisting mainly of protein) with for example encapsulated quercetin, rutin, or retinol.

Thus, the replacement of synthetic UV filters with eco-friendly, natural, biobased photoprotectants- which are potentially safer – and encapsulation into biocompatible eco-friendly nanoparticles has the potential to satisfy both environmental and health concerns whilst providing effective photoprotection.

There are many known biobased photoprotectants, such as flavonoids (i.e., quercetin and rutin), lignin (i.e., p-coumaric acid), and carotenoids (i.e., b-carotene, lutein, lycopene, retinol). Quercetin and rutin are the most extensively studied biobased photoprotectants, and both have even been individually incorporated into solid-lipid nanoparticles (SLNs) for sunscreen applications.

4.4.3. Company feedback

The interest of Phornano in implementing the proposed strategies was collected in the questionnaires that were provided to the partner.

As the company highlighted, they are aware of the importance of implemented SSbD strategies in their developments. In particular, they mentioned that they have been involved in several initiatives related to the construction of SSbD toolbox. According to their response, Phornano clearly understands the need for safety and sustainability during each step of the production chain is of high importance and requires the involvement of every sector of human activities.

For the specific case of **Safe by Material Design strategies**, Phornano expressed their interest in the implementation of some of these strategies. The interest of the company would be motivated by the fact that such strategies could represent an advance in SSbD tools and would require constant interdisciplinary knowledge exchanges.

Among the SbMD strategies that were proposed to Phornano, they would be interested in the ZnO doping with iron with the aim of reducing the release of metallic ions and, in this manner, reduce the toxicity of the material. In addition to this, Phornano has proposed a second SbMD strategy that would be based on the functionalization of ZnO nanoparticles' surface with active biocomponents, such as flavonoids, malic acid, and/or other natural component in the production of cosmeceutics (cosmetics with therapeutic properties).

Phornano selected these strategies since they are aligned with their aims of producing nanomaterials via safe, sustainable and circular processes. They expect the promotion of responsible production and conscious consumption by implementing these strategies.

Lastly, the company pointed out to be able to deliver the modified materials (ZnO-Fe NPs, ZnO-Malic acid NPs) by the second week of December 2023.

Regarding the **Safe by Process strategies**, 4Nano will reduce the use of hazardous chemicals and materials through the substitution of synthetic chelating agent ethylene-glycol by whey, and further, substitution of whey by starch chelating gel; and they will implement closed-loop systems to recycle and reuse waste materials within the production process with a new closed-loop system to use the gaseous species generated during the synthesis. The gases are boiled in water and produce acid precursors, which when in contact with metallic powder (obtained by recycling electronics waste, such as batteries), produce the metallic salts needed for the synthesis of the nanoparticles.

4.5. Case study 5: Graphene applied in fabrics and metal coatings - GXT

4.5.1. Case study overview

Within DIAGONAL project, GXT will focus on the development of graphene-based conductive patterns able to bring thermal and electrical properties on textiles for fashion or industrial applications. GXT will use a graphene nanoplatelets mixture from several suppliers (M15 (XG Science), C500 (XG Science) and G7 (Nanesa) to produce textiles with electrical and thermal properties, as well as into paints, to develop reinforced coating formulations.

4.5.2. Safe by material strategies

In general, the toxicity results reveal that GXT materials are quite safe. Toxicity was detected for the sample consisting of small flakes at the highest concentration (lung model) and for the polymer matrix when testing them using the gastrointestinal model.

Therefore, it seems that there are some issues regarding the toxicity of the material tested, however the results depend on the model used and concentration, and they are more related to the polymer matrix. These would be addressed by implementing safe by process strategies.

Graphene flakes are already chemically functionalized to improve the composite application, looking to optimize the nanomaterials and the nano enabled products. In addition to this, surface modification strategies can be suggested to reduce the agglomeration of the graphene nanoplatelets and improve the functional properties:

- *Surface modification of graphene via covalent functionalization*
    - Covalent Attachment of Organic Functionalities to Pristine Graphene

The main purpose is the dispersibility of graphene in common organic solvents that is a crucial move toward the formation of nanocomposite materials with graphene. Most attractive organic species: free radicals and dienophiles[42].

    - Covalent Attachment of small biomolecules (e.g., glycine, glucose) to partially oxidize graphene.
- *Surface modification of graphene via non-covalent functionalization*

The non-covalent bond functionalization process is simple with mild conditions, while maintaining the structure and properties of graphene. However, the disadvantage of this method is that other components (such as surfactants) are introduced.

Non-covalent functionalization could be achieved through aromatic compounds, surfactants, biomolecules and polymers.

4.5.3. Company feedback

As samples GXT-1 and GXT-6 resulted toxic in some models, a suggested strategy could be the **substitution of the polymer** matrix by a less toxic one.

Another possible strategy could be to **reduce the amount** of small flakes (GXT-2) in the formulation. A **combination of small and large flakes** in the formulation is suggested. In this way, the toxicity related to these small flakes could be minimized while **maintaining the properties** of the material (electrical conductivity).

None of the proposed strategies to GXT will be applied by the company because, according to them, modifying the powder graphene will mean changing the properties and they already have a water-based graphene to avoid dealing with powder nanoforms. The results of the toxicity study were mainly due to polymer toxicity, and they already have from a supplier a non-toxic polymer. They could reduce the small flakes amount as this is mainly for fashion purposes and will not affect the properties of the final product.

Therefore, two different strategies for process design will be applied. First, a safer alternative to hazardous chemicals, through the substitution of the polymer matrix by a less toxic one; and second, minimizing the use of harmful substances reducing the amount of small flakes (GXT-2) in the formulation.

GXT selected a new polymer that, based on supplier information, is not toxic. This was the easiest way without having an impact on the final product. Screen printing ink are widely available polymer which gives the flexibility to choose a safer one. According to the company, no problems are expected related to the implementation of this strategy. As a result, GXT expect to produce a safer material.

In addition, some RMM will be applied such as HEPA filtered down flow room and PPEs (Filtering half mask with inhalation valves (P3), Nitrile gloves – Double glove for large exposure periods and Half-Face particulate mask (P3)) to deal with exposure issues. Anyway, GXT have already applied some engineering control in the past and the other action can be implemented right away while the HEPA filtered down flow room will take few months to be installed.

Finally, from the **sustainability** perspective, GXT already do many of the SusbD strategies implemented before the DIAGONAL project, such as decreasing energy consumption or utilize renewable feedstocks and energy sources.

4.6. Case study 6: Nanocatalytic powders (Cu, Pd, Rh) as coating in automotive industry - Monolithos

4.6.1. Case study overview

Monolithos applies metallic oxide nanoparticles (Cu, Pd, Rh) over ceramic substrates of CeO_2/ZrO2 used in automotive catalytic converters. The nanomaterials used in this industrial case are CuPdRh polymetallic nanoparticles. This novel catalyst's innovation lies in the substitution of up to 85% of the platinum group metals (PGMs) with Cu nanoparticles non-critical, cheaper, and relatively abundant transition metal.

Its high catalytic efficiency and durability comes from the fact that transition metal nanoparticles, such as Cu particles, do not agglomerate during their deposition on the monolith and during the catalytic process. As a result, without agglomeration, the catalytically active area of the particles is maximized, which in turn increases the overall catalytic ability of the converter. Moreover, the importance of nanoparticle formation during the autocatalyst synthesis can be observed by the effect of thermal ageing of the catalyst during its operating life, which results in the increase of metal particle size (metal sintering) finally leading to reduced catalytic activity.

4.6.2. Safe by material strategies

Monolithos case study is already optimized from the point of view of safe by material design. Monolithos has a commercial product based on these materials (Prometheus catalyst) that allows the same functionality with 85% less use of PGMs in comparison to commercial catalysts. This catalyst is manufactured by **using recycled materials**, in particular those obtained from Spent automotive catalysts which are the richest PGM, as stated in Yakoumis et al.[47].

Despite the process and the product seem to be optimized from a SbD point of view (also for sustainability), we can suggest a strategy aimed at reducing the aging effect of the catalyst and the hazards during the use stage. In addition to this, whether the reduction or complete substitution of Pd in the catalyst formulation.

- *Doping with cationic elements for reducing the aging effect*[48]

The effects of foreign cation doping, at relatively low concentrations (0.5±10 mol%), on the thermal stability of CeO_2 has been extensively investigated: Th^{4+}, Zr^{4+}, Si^{4+}, La^{3+}, Y^{3+}, Sc^{3+}, Al^{3+}, Ca^{2+}, and Mg^{2+}), those with ionic radii smaller than that of Ce^{4+} effectively stabilized the CeO_2 against sintering.

4.6.3. Company feedback

The company is really interested in the implementation of SbD strategies. Indeed, Monolithos is continuously focused on the safety and sustainability aspects of its developed processes aiming at providing sustainable and responsible industrial solutions to face the rising concerns about the use of critical/strategical raw materials for a wide range of applications. To that end, as pointed out during our recent bilateral meeting in the context of T5.3, Monolithos's case study in this project (Transition (or Cu-) based catalytic converter for the abatement of toxic gas emissions of vehicles) has already been optimized from a SSbD point of view.

The application of the nanomaterials (polymetallic nanoparticles of CuPdRh) that Monolithos are producing is catalytic converters for vehicles. The main advantage of their products is the partial substitution of an amount of PGM of conventional catalytic converters by metallic oxide nanoparticles (Cu, Pd, Rh) supported on ceramic substrates of CeO_2/ZrO_2, without compromising the activity and durability. This novel catalyst's innovation lies on the substitution of up to 85% of the PGMs with Cu nanoparticles, since Cu is a non-critical, cheaper, and relatively abundant transition metal. As a result, the cost of current converters can be reduced at half, enhancing the market uptake of more environmentally friendly NEPs with positive implications to the EU dependency on critical raw materials. Thus, the assurance that SSbD strategies are followed during the whole fabrication process of our materials is directly linked with the company's policy.

Among the **Safe by Material design strategies** that were suggested, the company has shown specific interest for (i) minimizing the aging effect of the catalyst by doping with cationic elements and (ii) reduction or compete substitutions of Pd in the catalyst formulation. The reasons because the company has selected these two strategies are explained as follow:

Regarding the first strategy, minimizing the aging effect of the catalyst by doping with cationic elements, the company highlighted that this is the main identified strategy that could be implemented to address and reduce the toxicity of the catalyst (mainly the MON-1 sample – Prometheus catalytic washcoat which was found to be irritant for the skin). The doping of the surface of the catalyst could facilitate the deposition of the active metals while preventing the encapsulation of the metals which takes place during ageing, eventually leading to reduced catalytic activity.

Regarding the second strategy, reduction or compete substitutions of Pd in the catalyst formulation the modification of metal content and especially the suggested partial reduction of Pd could reduce the toxicity of the nanomaterial while the variation of the metal nanoparticles composition could further improve the performance of the catalyst for the abatement of toxic gases found in vehicle's exhausts.

From the company perspective, any potential improvement achieved by implementing the above-mentioned SbMD strategies can result in the fine tuning of our production process, potentially providing both economic benefits as well as competitive advantages for our innovative products based on nanomaterials.

Based on the suggestions provided during the recent interaction with partners in the context of Subtask 5.3.1, further literature review has been conducted to identify the potential $CeZrO_4$ carrier modifications that could be tested aiming at the improvement of the thermal stability during catalyst ageing. Carriers of the following general formula have already been supplied and can be used for the deposition of CuPdRh nanoparticles: $Ce_XZr_YLaYbO_2$. These syntheses are expected to be performed by mid-November 2023 and the catalytic performance will be tested following the well-established testing methods used in Monolithos for evaluating new catalyst formulations under simulated engine exhaust conditions. The tests are expected to be conducted before the end of November 2023. Based on the results obtained, the new catalyst samples (modified) can be supplied to experimentalist partners for physicochemical characterization and toxicity assessment studies. In addition to this, catalytic samples with modified metal ratios (decreased Pd content) are already available and have been found to perform comparably (or better) than the corresponding samples already tested during the project. Thus, these samples could be dispatched to partners for further physicochemical characterization and toxicity assessment studies.

In the case of the **Safe by Process strategies**, the company selected the implementation of closed-loop systems to recycle and reuse waste materials within the production process. Ammonium hydroxide is used for the adjustment of the pH of the solution containing the metal precursors, during the preparation of the catalyst. A subsequent step of the synthesis protocol involves the removal of liquids by evaporation (using a rotary evaporator). The main liquids removed are NH_4OH and H_2O. The use of the rotary evaporator where the solvent vapor is cooled by a serpentine condenser which is used with a chiller to obtain high condensation efficiency allows its recycling into a collection bottle. Then, ammonia can be separated from the water by distillation, and is used again for the next syntheses.

The company remarked that the implementation of the above-mentioned strategies can lead to the minimization of waste production during the synthesis process. In addition to this, barriers were not identified for the implementation of these strategies.

It should be noted that since the on-site exposure campaign performed last November, Monolithos has expanded their production facilities in a new building, which is equipped with ventilated laboratory hoods and walk-in hoods, both proposed as engineering controls. Moreover, for the whole duration of the process, all workers use the following PPE, based on the specific step of the process: Filtering half-masks with inhalation valves (P3), Nitrile gloves – double glove for large exposure periods, tight-fitting dustproof safety goggles, half-face particulate mask (P3), laboratory coats and safety glasses.

All these safe by process strategies and RMM are already implemented by the company.

Lastly, regarding **Sustainability strategies,** Monolithos´ orientation is the sustainability of its processes closing the loop and achieving circularity. Especially for the automotive catalytic convertors´fabrication, recycled metals coming from Spent Automotive catalysts which are the richest in PGM, have already been tested for their utilization in the production of new catalytic converters. Among the proposed SSbD strategies, the company is interested in: (i) study possible outcomes of up-scaling the production line, namely the advantage of higher economies of scale in optimizing the whole system from the energy / materials / emissions-waste perspective and (ii) optimization of the final product use (reparability, durability) and its end of life (EoL) (reuse, recycling). The implementation of these strategies can lead to a significant improvement of the cost as well as the environmental and social sustainability of the current product, also providing a lead time compared to competition in the market. In particular, for the use of recycled PGMs, it can reduce the cost of engine emissions after-treatment systems, and this will help decreasing the final cost of the vehicles.

For EoL catalyst recycling – PGMs recover Monolithos has already developed and patented a low acidity and temperature hydrometallurgical process that allows them to obtain PGMs from spent catalysts fine powder. The PGMs are recovered from spent catalysts in HCl(aq) solution (at recovery rates of 100% for Pt, 92% for Pd and 61% for Rh). The proposed leaching system was a HCl–H2O_2–NaCl medium under mild conditions (70 °C, 2 h), while the high solid per liquid ratio (S/L 70%), provides very promising ground for upscaling in industrial conditions. The recycled PGM containing solutions have already been utilized by Monolithos for the fabrication of new catalytic converters.

The above-mentioned strategies, according to the company feedback (see ANNEXES), are expected to be implemented by December 2023.

4.7. Case study 7: Graphene applied in fabrics and coatings - OCSiAl Europe Sarl

4.7.1. Case study overview

OCSiAl Europe Sarl produces high-purity graphene nanotubes under the TUBALL™ brand name. Its patented process manufactures SWCNTs that are applied in the nanoformulation TUBALL Matrix, for several applications. TUBALL™MATRIX is a highly concentrated mixture of TUBALL™ with various non-volatile or a mixture of compounds with good wetting ability of the TUBALL™ carbon nanomaterial. TUBALL MATRIX 207 is made by 90% Oxirane, mono(C12-14-alkyloxy) methylderivs (as carrier) and 10% of TUBALL™ powder (SWCNTs). In DIAGONAL project, SWCNTs are used as ingredient in an epoxy floor coating additive containing oxirane, mono(C12-14-alkyloxy) methylderivs for industrial floor coatings (TUBALL MATRIX ™207). The aim is to improve the antistatic properties of the coating.

4.7.2. Safe by material strategies

It seems that there are no important issues regarding the toxicity of the material tested. Despite this fact, surface functionalization strategies of SWCNT can be done to prevent agglomeration and enhance the stability of the nanomaterials suspension.

- *Surface modification of SWCNTs via covalent functionalization*

- Covalent attachment of small biomolecules (e.g. glycine, glucose) to oxidized CNTs.
- *Functionalization of SWCNTs using click chemistry:*
  - Polystyrene-functionalized SWCNTs[49]: improved solubility in organic solvents
  - Polyurethane-grafted SWCNTs[50]
- *Functionalization of SWCNTs using dendritic polymers (to improve solubility)*
  - Carboxylic acid-terminated hyperbranched poly(ether-ketone) (HPEKs) were successfully grafted[51]
  - Well-dispersed epoxy/SWCNT composites were prepared by oxidization and functionalization of the SWCNT surfaces using polyamidoamine generation-0 dendrimer[52].

- *Surface modification of SWCNTs via non-covalent functionalization[53]*

The functionalization is done by the addition of surfactants or polymers. Polymers favor CNT dispersion in polar solvent whereas anionic, cationic, and nonionic surfactants favor the dispersion of CNTs in water. Among the most used surfactants for the functionalization of SWCNTs are:

- Anionic surfactants: sodium dodecylsulfate (SDS) and sodium dodecylbenzene
- Surfactants such as NaDDBS and Triton-X100 have far better interaction than SDS due to benzene ring with CNTs.

4.7.3. Company feedback

OcSiAl Europe Sarl (OCSiAl) is aware of the needs of developing safer and most sustainable nanomaterials and nano enabled products. Indeed, the company has an ongoing policy of initiating its own as well as external independent testing and research, and it has already gathered relevant information on this regards base on the morphology of TUBALL™ nanotubes, and on their safe handling and use in the workplace. In addition to this, TUBALL™ is compliant with all the relevant international, national, and regional requirements of the world's key markets, including the EU and the USA.

Regarding the proposed **SbMD strategies**, the company is interested in the surface modification of SWCNTs via non-covalent functionalization (by using surfactants). In addition, OCSiAl is applying other SbMD strategies. For every Tuball-additive (including TM207 mixture) they have specific process guidelines created and available to support their nano-additive users for processing and handling it effectively, efficient, safe and sustainable. OCSiAl has already implemented some of the strategies successfully. In fact, their nanoform TUBALL has already been commercialized since 2014, their nano-additive since 2017 and their process is constantly under development and improvement internally monitored by their experts. According to the company, every TUBALL additive development and its production follows the principles of our integrated management system (IMS), and SSbD is considered a standard. Any improvement request is managed by their change request process. Therefore, materials modifications of OCSiAl SWCNTs are not foreseen under the framework of DIAGONAL project.

In the case of **Safe by Process Design strategies**, closed-loop systems to recycle and reuse waste materials within the production process are only applicable or necessary for a limited number of processes such as their main raw nano material TUBALL™, for their synthesis process of TUBALL™ and solvent used as the main component of the nano suspension production for the cathode - LIB industry. With that, OcSiAl accomplishes National - & regional requirements occupational safety and limit potential environmental impact.

Regarding the **sustainability dimension**, OcSiAl have switched to 100% green energy sources, they make sure that some important chemical waste will be reused by our partners and improves their packaging materials with recycled component (both plastic and cardboard).

5. Conclusions

In this deliverable, the work conducted under task 5.3.1 (Safe by material Design strategies) and 5.3.2 (Safe by process design strategies) has been collected and described in detail.

First, we have described the general principles for the design of safer MCNM and HARNS, both for SbM and SbP design and then we have emphasized, in the case of SbM design strategies, for specific groups of materials based on their chemical composition (namely carbon-based NMs and inorganic NMs). As a result of the intensive literature research, we came out with a library of well-balanced safe by material design strategies that can be generally applied to these NMs. Among these strategies, we include surface engineering approaches such as covalent or non-covalent functionalization, encapsulation, coating, or element doping. In the case of SbPD strategies, we have provided a library of strategies that can be generally applied to the different processes involved in the NMs manufacture. In addition to this, a list of risk management measures has been also provided in this report.

Second, for the NMs developed in each case study, a preliminary set of materials modifications was recommended to either improve the toxicological profile of the original materials or their functionality. After these preliminary recommendations, an open discussion with the cases study owner was conducted to identify the most feasible and relevant strategies to be implemented.

In many cases, the materials did not exhibit any toxicity, and this is the reason why we did not consider the implementation of Safe by Material strategies for all the case studies including in DIAGONAL project (see Table 4). The companies will start the modification of their materials according to the proposed strategies and, according to the work plan, it is expected to have synthesized the first batches of these modified materials at the end of December 2023 or beginning of January 2024. After that, they would be distributed to WP4 partners for conducting toxicological tests.

Complete feedback from the industrial partners regarding the proposed SbD strategies (including material, process, and sustainability) has been collected in the SSbD questionnaires (see ANNEXES). These questionnaires have helped us to understand the interest commitment of the companies to implementing the recommended strategies. In Table 4, we provided a summary of the strategies that have been selected by each industrial partner for their implementation:

Table 4 – Summary of the SbD strategies to be implemented in each case study.

Company	Case Study	SbMD Strategies to be implemented	SbPD / SusbD Design Strategies to be Implemented
DTI	Metallic HARNs for printed electronics	• PVP with different M_W • Use of co-nucleants agents • Synthesis at higher T • Use of an alkaline solution to remove PVP	**Process**: Surfactant replacement (safer alternative to acetone is preferred) **Sustainability**: Procuring reagents from more local sources (at least within EU) **Sustainability**: Improving energy efficiency. (Silver nitrate ink printing process will be optimized as well through the optimization of using of printing equipment and associated electricity consumption) **Sustainability**: Recycling after printing to recover silver

CNANO	Graphene reinforced metallic coatings	• Non-covalent functionalization of GNPs (by using surfactants) • Element doping	**Sustainability**: Improving material efficiency (Design options to improve is the incorporation and the dispersion of graphene into the nickel-based coatings)
IRIS	Metal Matrix Composites (MMC) with nano-size reinforcement for Ti and Al based composites	-	**Process**: Reduce the use of hazardous chemicals and materials (totally closed system for filling the powder feeder tanks (already implemented)) **Process**: Closed-loop systems to recycle and reuse (inert gas recirculation system that is used during the deposition process)
4NANO	Metallic NPs (ZnO_x) for applications in cosmetics and biomedical industries	• Fe doping of ZnO NPs • Functionalization of ZnO NPs with active biocomponents	**Process**: Reduce the use of hazardous chemicals and materials (substitution of synthetic chelating agent) **Process**: Closed-loop systems to recycle and reuse (use the gaseous species generated during the synthesis)
GXT	Graphene applied in fabrics and metal coatings	-	**Process:** Safer alternative to hazardous chemicals, (substitution of the polymer matrix) **Process**: Minimize the use of harmful substances (reducing the amount of small flakes (GXT-2) in the formulation)
Monolithos	Nanocatalytic powders (Cu, Pd, Rh) as coating in automotive industry	• Cationic element doping of the catalyst surface • Reduction/complete substitution of Pd	**Process**: avoid hazardous emissions - closed-loop systems to recycle and reuse (ammonium) **Sustainability**: circular process: use of recycled metals coming from Spent Automotive catalysts which are the richest in PGM (already implemented)
OcSiAl	Graphene applied in fabrics and coatings	• Non-covalent functionalization of SWCNTs (already implemented)	**Process**: Closed-loop systems to recycle and reuse (solvent used as the main component of the nano suspension production for the cathode) **Sustainability**: 100% green energy sources

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