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SAbyNA

H2020-NMBP-15-2020

Simple, robust and cost-effective approaches to guide industry in the development of safer nanomaterials and nano-enabled products

Start date of the project: 01/03/2020

Duration 48 months

D4.2 Requirements for improvement of existing strategies for SbD of NFs/ NEPs to be implemented by industry

WP	4	Name of the WP		
Dissemination level[1]	Public		Due delivery date	M22, 31 December 2021
Nature[2]	Report		Actual delivery date	M22, 24 December 2021

Lead beneficiary	ISTEC
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[1] Dissemination level: **PU** = Public, **PP** = Restricted to other programme participants (including the JU), **RE** = Restricted to a group specified by the consortium (including the JU), **CO** = Confidential, only for members of the consortium (including the JU)

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Deliverable abstract

This deliverable reports the work executed in Task 4.2. It evaluates the SbD methods collected in Deliverable 4.1 on the basis of their potential usability in industry. Although important from a conceptual point of view, in fact, the SbD methods described in D4.1 were not all suitable for industrial nano-manufacturing. To extract usable and accessible SbD methods from the whole list, Partners identified the factors that determine usability: clarity, accessibility, scalability, cost/benefits balance, retention of technical functions, number and types of limitations. These factors were evaluated for each SbD methods, and this evaluation provided the basis for their selection. Methods classified as "usable" covered a broad spectrum of practical cases. Partners identified at least on usable SbD method for minimizing risk arising form the physicochemical drivers described in D4.1; notably, the list reported in this deliverable contains also SbD methods that target risk originating from release of nanoparticle due to the properties of the supporting matrix. Selected methods covered most of the hazardous mechanisms that determine the toxicity of NF and NEP, and essentially all SbD approaches described in D4.1 were described in at least one selected resource. For the usable methods, these deliverable reports usability cards that summarize the characteristics of the method, report the target physicochemical property, list potential limitation, and report the link to resource. These usability cards provide a useful tool for finding and accessing SbD resources.

Table of Content

List of Figure and Table

Abbreviations

NF	Nano-form
NEP	Nano-Enabled Product
DoW	Description of Work
ECHA	European Chemical Agency
OECD	Organisation for Economic Co-operation and Development
SbD	Safer by Design, or Safety by Design
WP	Work Package

1. Introduction

This deliverable analyzes the safety-by-design resources collected in the Deliverable 4.1 with the aim of extracting a list of approaches and methods that can be used in a real manufacturing of NFs and NEPs. One of the major hurdles that prevents several SbD approaches to be implemented in current nano-manufacturing is their low accessibility. In view of the establishment of the SAbyNA platform, this task selects methods with a proved potential to be used by industry and improves their accessibility. As such, this deliverable describes the multiple factors that determine the accessibility of these methods, and, on the basis of this analysis, establishes criteria for selecting usable SbD resources.

Task 4.2 was conducted in close collaboration with T5.2 in order to provide a comprehensive and global strategy towards the design of safer NFs, NEPs and associated nanoprocesses as early as possible in the industrial innovation process. Both D4.2 and D5.2 promote the use of usability cards, a schematic summary of each resource that should facilitate their implementation in the SAbyNA guidance platform.

In order to avoid ambiguities in the use of terminology, we recall that, within SAbyNA, the Safe by Design (SbD) concept refers to the minimization of risks arising from NFs and NEP while retaining their technical function. Previous work, described in D4.1, has provided a repository of available SbD methods. The aim of task T4.1 was to identify, map and sort the existing strategies used to reduce or mitigate risks associated with the use of NFs/ NEPs at all life cycle stages. Safe-by-Design strategies were identified among publications in scientific journals, projects' deliverables, and guidelines from international agencies. The selected resources were mapped and sorted according to a set of quality criteria, which enable the identification of information gaps that could be filled during the project. For this purpose, an Excel file was built and used to classify existing resources in several categories (e.g., reviews, publications, reports, and industrial know-how). The literature survey (T4.1) identified 75 documents (2010-2020) with approximately ¾ of these published in the last three years. Among these articles, reviews, concept articles and position papers (35 documents) were separated from research articles (54 SbD approaches). A total of 19 SbD approaches reported from projects (deliverables) were also analyzed.

An important outcome of Task 4.1 has been the identification of links between physicochemical sources of hazard and corresponding SbD approach. These links provided us the basis for grouping SbD methods according to the physicochemical hazard drivers so that, once a driver will be identified, a list of potential SbD methods can be explored quickly.

This deliverable builds on the work of the previous Task 4.1 and expands background knowledge about the SbD methods with information about usability and accessibility. As we discuss in the following sections, criteria of usability will be established that take into account several aspects. Usability cards, summaries of SbD methods for quick consultation, will be presented for methods classified as "usable".

2. Description of task 4.2

From DoW:

Improving usability and accessibility of existing resources for SbD strategies towards safer NF and NEP along their life cycle. [M6 to M22] LEITAT, ISTEC, CEA, IOM

The collection of strategies, frameworks, guidelines or other resources identified in T4.1 will be analysed and structured to improve their usability and facilitate their implementation in some particular cases. The work in this task should be aligned with the work in T5.2 to provide the user with integrated SbD solutions for NFs/NEPs and their processes at all stages of products life cycle. One of the main challenges that has not been overcome yet by the existing approaches on SbD strategies is their low accessibility for the potential users, and this is one of the main objectives of this task in SAbyNA. The first action in the process of improving resources usability will be to compile and place them in one platform (the outputs from D4.1); second will be to provide a clear guidance on their usability, including their limitations (basis for new/tailored SbD strategies proposals) and third will be to identify the possibilities for their implementation in real scenarios. This task will also work closely with WP6, contributing to SAbyNA guidance development by providing the workflows for the module on SbD solution towards safer NFs and NEPs products along their life cycle.

3. Description of the work and main achievements

3.1 Resources information. Newly identified resources and extension of physicochemical descriptors.

Table 1 lists resources about SbD identified during the last year added to the list already provided in D4.1. These resources cover an important section of the risk assessment of NFs and NEP, because they focus, mainly, on assessment of exposure, a risk factor that we deemed to be under-represented in the previous list. In view of these new resources, a thorough description of the physicochemical drivers of risk required an extension of physicochemical specifications of the "key physicochemical properties of interest for risk" and the "mechanism of concern" of our classification scheme. In line with the recommendation of the OECD report "physico-chemical decision framework to inform decisions for risk assessment of manufactured nanomaterials"(ENV/JM/MONO(2019)12), these new specification for mechanism of concern, in addition to hazard, was: "release", when the risk arises from a high probability of releasing a NF from the NEP. In the field "key physicochemical properties of interest for risk", the new specifications were: "Resilience of NEP matrix" to indicate a risk arising from reduced resistance of the matrix to external factors (e.g., aging): the higher the matrix resistance, the lower is the NF release; "Dispersion of NFs in the NEP matrix" to indicate the spatial distribution of the NFs within NEP matrix: a good dispersion means a uniform and homogeneous distribution of NFs within the matrix. Due to several factors, in fact, NFs can aggregate/agglomerate leading to inhomogeneous distribution within the matrix, weakening the interaction with the matrix, thus promoting its release. Another factor influencing the release is the "NFs content", that is, the amount of NM incorporated in the nano-enabled product. Intuitively, a reduction of the NF quantity can ensure the reduction of the NF release. Finally, "Location of NFs in the NEP (coating or embedded)" to indicate the location of the NM within the NEP as a factor determining the probability to get in contact with it. The functional NF could be at the surface, and, as such, able to interact with the external environment, or embedded (e.g., in a polymer composite) and then isolated from the external environment and unable to be releases.

Table 1. List of new resources in addition to those in Deliverable 4.1

Year	Title	Authors	Document Type	Source title	Volume	Issue	Art. No.	Page start-end	DOI
2014	Formulation effects on the release of silica dioxide nanoparticles from paint debris to water	Stefano Zuin, Andrea Massari, Arlen Ferrari, Luana Golanski	Article	Science of the Total Environment	*476-477*			*298-307*	doi.org/10.1016/j.scitotenv.2014.01.029
2021	Towards the development of safer by design TiO2-based photocatalytic paint: impacts and performances	A. Rosset, V. Bartolomei, J. Laisney, N. Shandilya, H. Voisin, J. Morin, I.Michaud-Soret, I.Capron, H.Worthman, G.Brochard, V.Bergé, M.Carriere, F.Dussert, O.Le Bihan, C. Dutouquet, A.Benayad, D.Truffier-Boutry,	Article	Environmental Science: Nano	8			758-772	10.1039/d0en01232g
2021	TiO2 nanoparticles coated with bio-inspired ligands for the Safer-by-Design development of photocatalytic paints	Jérôme Laisney, Aurélie Rosset, Vincent Bartolomei, Daniela Predoi, Delphine Truffier-Boutry, Sébastien Artous, Virginie Bergé, Gregory Brochard and Isabelle Michaud-Soret	Article	Environmental Science: Nano	8	1		297-310	https://doi.org/10.1039/D0EN00947D
2013	Monitoring migration and tranformation of nanomaterials in polymeric composites during accelerated aging	G Vilar, E Fernández-Rosas, V Puntes, V Jamier, L Aubouy, S Vázquez-Campos	Article	Journal of Physics	429		012044		doi:10.1088/1742-6596/429/1/012044
2013	Exploring release and recovery of nanomaterial from commercial polymeric nanocomposites	Martí Busquets-Fité, Elisabet Fernandez, Gemma Janer, Gemma Vilar, Socorro Vázquez-Campos, R Zanasca, C Citterio, L Mercante, Víctor Puntes	Article	Journal of Physics	430		12048		doi:10.1088/1742-6596/429/1/012048
2018	Excellent binding effect of L-methionine for immobilizing silver nanoparticles onot cotton fabrics to improve the antibacterial durability against washing	Jing Zhou, Dongrong Cai, Qingbo Xu, Yanyan Zhang, Feiya Fu, Hongyan Diao, Xiangdong Liu	Article	Royal Society of Chemistry Advances	8			24458-24463	DOI: 10.1039/c8ra04401e
2011	Fate of nanoparticles during life cycle of polymer nanocomposites	T Nguyen, B Pellegrin, C Bernard, X Gu, J M Gorham, P Stutzman, D Stanley, A Shapiro, E Byrd, R Hettenhouser and J Chin	Article	Journal of Physics	304		12060		doi:10.1088/1742-6596/304/1/012060
2012	Improved dispersion of carbon nanotubes in polymer at high concentrations	Chao-Xuan Liu and Jin-Woo Choi	Article	Nanomaterials	2			329-347	doi:10.3390/nano2040329
2016	Quantitative rates of release from weathered nanocomposites are determined across 5 orders of magnitude by the matrix, modulated by the embedded nanomaterial	Wendel Wohlleben, Nicole Neubauer	Article	Nanoimpact	1			39-45	http://dx.doi.org/10.1016/j.impact.2016.01.001
2019	Safer-by-design flame-sprayed silicon dioxide nanoparticles: the role of silanol content on ROS generation, surface activity and cytotoxicity	Laura Rubio, Georgios Pyrgiotakis, Juan Beltran-Huarac, Yipei Zhang, Joshi Gaurav, Glen Deloid, Anastasia Spyrogianni, Kristopher A. Sarosiek, Dhimiter Bello and Philip Demokritou	Article	Particle and Fibre Toxicology	16		40		doi.org/10.1186/s12989-019-0325-1

3.2 Harmonization of data entries

3.2.1 ECHA Technical Function

In the SbD approach, preserving the NFs' function is essential, and the need to use a harmonized technical function terminology is required. We, then, used the descriptor list for the technical function provided by the ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.12: Use descriptors (December 2015). For each SbD resource analyzed, we identified the technical function of the NF specific for its intended use. Unfortunately, not all resources (N=10) reported information about the technical function; in some cases, we could retrieve the technical function from previous papers, or infer it on the basis of the information provided by the resource. Figure 1 displays the number of resources counted for each technical function described in the resources of our repository.

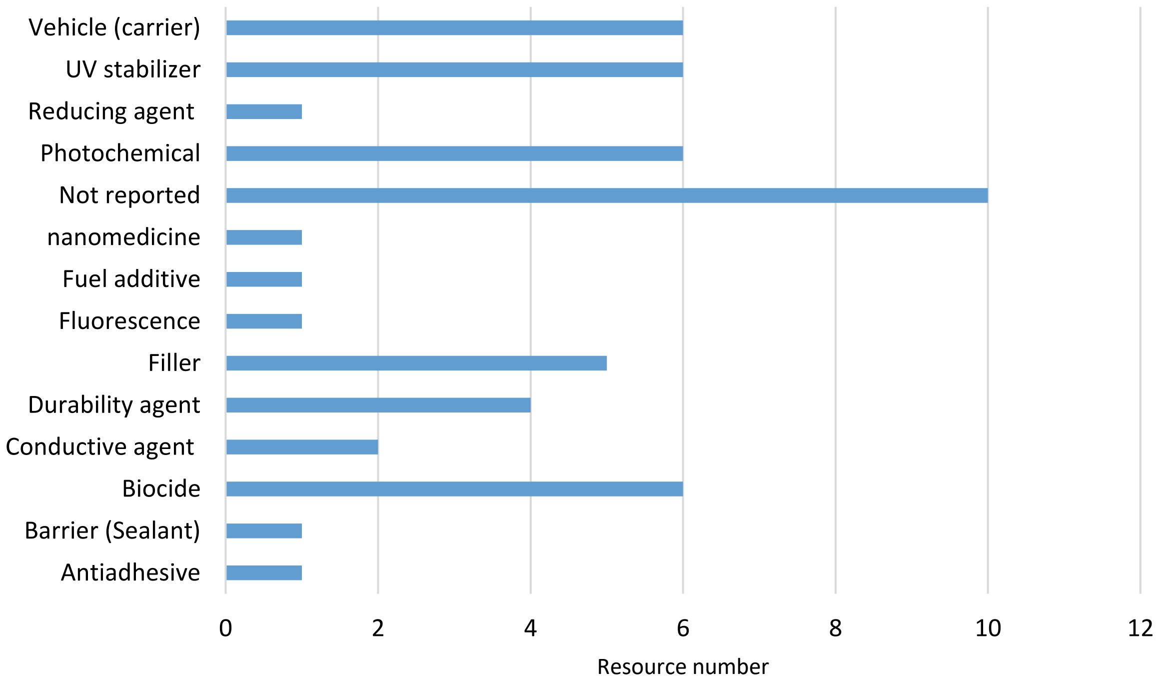


Figure 1. Number of resources per Technical Function present in our list of SbD resources

3.2.2 Harmonization of SbD approches

The SbD strategies described in the resources were initially described by free texts in the 4.1 table. For this deliverable, that information was rationalized into a grouping scheme comprising 13 classes (or, categories) of SbD methods. These classes where, in order of number of resources describing them, coating, doping, matrix composition, support, NFs content, process, aspect ratio, surface chemistry, size, encapsulation; NFs/matrix affinity and substitution.

Table 2 summarizes these different SbD strategy categories. As described in D4.1, similarly to the SbD approaches, the mechanism of concern and the key physico-chemical properties were collected. We observed that the same SbD strategy may target different mechanism of concern and the physico-chemical driver. For example, coating SbD strategy is used to minimize, or even suppress, the following hazardous mechanisms: “affinity to aquatic and terrestrial organisms”, “soluble compound release”, “Surface reactivity”, “Interference with intracellular redox processes” and “NFs release”. A cumbersome example of the use of SbD strategies that results in new risks is the minimization of the release of NF with high aspect ratio: while increasing the NFs aspect ratio reduces the release of the NF from the NEP, essentially because it limits the detachment from the NEP matrix, at the same time, it leads to higher hazards for the NF. In these cases, a balance between old and new risk has to be carefully considered.

Table 2. Definition of Categories of SbD resources

SbD strategy category	Description	Example	Number of SbD resources	References
Surface chemistry	Modification of the NF surface composition	Study of different common solvents to enhance the dispersability of MWCNT in	3	10.1039/c9nr01162e 10.1088/17426596/429/1/012048 10.3390/nano2040329

		PDMS matrix. Functionalization of CNTs by carboxyl groups.		
Support	NP attached to framework of different material The NFs is attached onto a bigger particle.	In the context of cosmetic application, TiO_2 NFs is grafted onto crystal of nanocellulose. The UV filtration is improved, and the nanocomposite shows a new functionality that allow to reduce the surfactant content (ref).	5	10.1007/s41742-020-00252-7 10.1021/acssuschemeng.8b02004 10.1016/j.ceramint.2017.11.028 10.1039/c7ra02506h 10.1039/d0en01232g
Substitution	Substitution of the materials by a safer material with the same technical function	Quantum dot replaced by a Dye doped silica NP.	1	10.1016/j.impact.2020.100267
Size	Modification of NF size	AgNP size variation (30nm to 75nm) by coating.	2	10.1016/j.impact.2020.100267 10.3390/ijerph120808828
Process	Modification of any processes occurring along the NFs life cycle	Integration in the process design of the best available practices to prevent, assess, control, and manage CNT emissions and workers exposures.	4	10.1016/j.impact.2020.100267 10.1088/1742-6596/838/1/012018 10.1088/1742-6596/429/1/012050
NFs/matrix affinity	Enhancement of the NF stability in the product matrix.	Modulation of the NF photo-catalytic properties and improvement of the adhesion to the paint matrix with the addition of bio-inspired ligands.	1	10.1021/acs.est.7b02390
NFs content	Reduction of the NF concentration	Modification of the polymer matrix content to limit NP emissions in drilling operations	4	10.1007/s11095-019-2747-8 10.1016/j.impact.2018.06.003 10.1080/02786826.2017.1330535 10.1039/c8ra03403f
Matrix composition	Change in matrix composition.	Paint matrix modification (styrene-acrylic copolymer instead of acrylic copolymer). Pigments addition (TiO_2) to enhance the matrix stability when it is exposed to UV light.	7	10.1007/s11051-015-2962-0 10.1016/j.scitotenv.2014.01.029 10.1088/1742-6596/304/1/012060 10.3390/nano2040329 10.1016/j.impact.2016.01.001 D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
Encapsulation	NFs is encapsulated in safer materials.	Lowering of side effects of anaesthetic molecule by embedding NP in binary lipid mixtures of citrem and SPC	1	10.1039/c9cp01878f
Doping	Chemical composition of the NF is modified. A substance is added in low amount to tune the NFs properties	Tuning the cytotoxicity of zinc oxide nanoparticle through iron doping.	5	10.1021/acsami.7b06657 10.1016/j.taap.2016.01.002 10.1021/nn1028482 10.1021/nn901503q
Coating	A material is added to cover the NFs surface	Hermetic encapsulation of ZnO nanorods in a biologically inert, nano-thin amorphous SiO_2 coating during their gas-phase synthesis.	18	10.1016/j.colsurfa.2020.124792 10.1002/pssa.201900619 10.1016/j.impact.2020.100267 ISBN: 978-80-87294-89-5 10.1039/C8RA07374K 10.1016/j.jconrel.2016.08.011 10.2147/IJN.S97476 10.1016/j.taap.2015.07.012 10.3390/ijerph120808828

				10.1039/c3en00062a 10.1016/j.biomaterials.2013.12.057 10.3109/17435390.2012.739665 10.1021/nn305719y 10.1088/1742-6596/429/1/012044 D 7.1 – Report on the development of SbyD strategies applied to CuO SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
Bridge	A ligand is added to connect the NFs to each other	Assembly of AgNP bridged together by a bio-inspired molecule covalently bonded to the nanoparticle surface through its three thiol functions.	3	10.1039/c9nh00286c 10.1039/D0EN00947D 10.1039/c8ra04401e
Aspect ratio	The NF length and diameter are modified.	The toxicity is reduced by reducing the length of Ag nanowires.	3	10.1007/s11051-020-04791-0 10.1016/j.impact.2020.100267 10.1039/c8en00890f

3.3 Factors that determine the usability of a SbD method

For a SbD method to be implemented in an industrial scenario, several requirements have to be fulfilled: in the following, the factors, identified by SAbyNA, that will be used to select usable methods from the general repository.

- **Goal/aim**. The recognition of SbD resources conducted in D4.1 revealed a diffuse misuse of the concept of SbD. Some of the resources, for example, described generic chemical transformation of NFs without any focus on design, or, worst, without reporting the specific problem they were trying to solve. In the present Deliverable, we considered "usable" only those resources that described clearly the problem they solved, starting from the identification of the physical-chemical drivers of hazard of the NFs, their modification, and prove of reduced hazard.
- **Clarity**. In the attempt to capture the point of view a potential user of the SAbyNA SbD platform, we assessed the clarity of each resource identified in D4.1. To be usable, SbD resources had to provide a logical description of the method, avoid technical jargon and abuse of acronyms, provide references to additional resources eventually cited.
- **Accessibility**. To be used, a resource should be accessed easily. The criteria of accessibility we have established include 1) the availability of a working web link to the resource, 2) the open-access option, or, alternatively, a clear indication of the price of the resource; in any case, we have given priority to resources publicly available for free.
- **Technical function**. A usable and useful SbD method must reduce risks and preserve functionality of a NF as much as possible. The resources selected on the basis of their usability provide evidence of both these requirements of a working SbD method.
- **Applicability**. Scale and scalability of process. The implementation of SbD procedure at an industrial scale must be compatible with the production of big volumes. Most of the SbD methods described in the available sources, however, are developed at a laboratory scale. We selected SbD methods that can be up-scaled to industrial processes.
- **Cost/benefit balance**. Although the assessment of costs will be part of the final platform of SAbyNA, we attempted an evaluation of possible costs of the selected resources, aware that the evaluation of the balance between costs and benefits is left to individual final users. In any case, we considered the use of expensive materials (e.g., precious metals) or specialized equipment and infrastructures as a limitation to the usability of the method.
- **Regulatory aspects.** Depending on the field of application, NF/NEP night be subject to specific regulation that rules its application in addition to eventual assessment of safety. Information about legal requirement were taken into account when reagents or process of a specific SbD method were subjected

to regulation. For example, the use of dangerous reagents leads to some limitations to the implementation of SbD methods also if the final NF or NEP is absolutely safe.

- **General conclusion.** This field was used to collect general information useful to decide about usability, but not classifiable in one of the previous criteria.

3.4 Analysis of usability of available SbD method

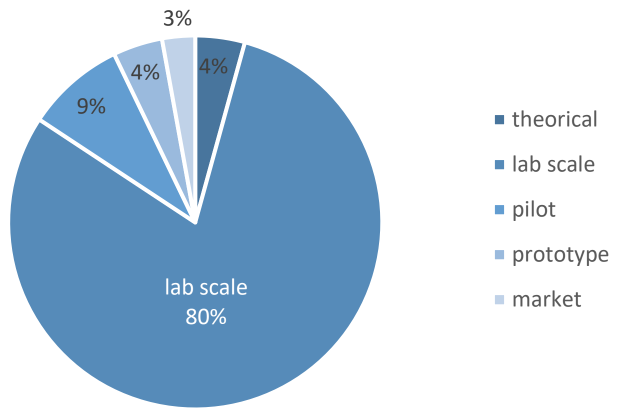
For each SbD method in our repository, we assessed all the requirements/factors of usability by mean of the Excel grid reported in Table 3. Using the grid allowed us to summarize information about usability in a succinct, yet effective way, which enabled the selection of methods.

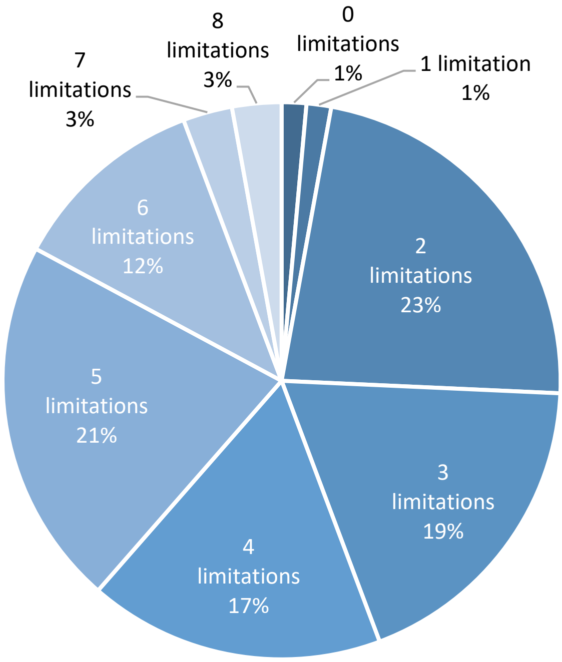
Table 3. Overview of the usability information gathered for all resources

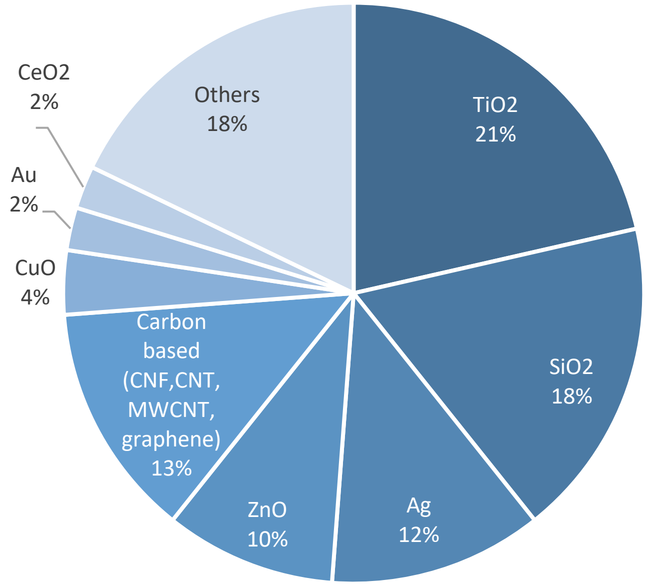
Resource title (example of usability assessment)	**GOAL / AIM**	**CLARITY**	**ACCESSIBILITY**	**TECHNICAL FUNCTIONS**	
	Is the goal/main aim of the SbD strategy clear?	Is the SbD strategy **easy to understand?**	Is the SbD strategy **easy to access** (is it publicly available) And sufficiently high on a search criteria (e.g., "google etc")?	Are the NF technical functions maintained after applying the SbD strategy?	
	Y/N	Y/N	Y/N	Y/N	
	LIMITATION(S)				
	Note: **if no**, we consider it a limitation	Note: **if no**, we consider it a limitation	Note: **if no**, we consider it a limitation	Note: **if no**, we consider it a limitation	
Hierarchical nano ZnO-micro TiO2 composites: High UV protection yield lowering photodegradation in sunscreens	Yes, the author aimed to produce a hierarchical composite of ZnO NPs ancored onto TiO2 microparticles that presents higher UV adsorption and higher SPF value, and a recuced photocatalitic adverse effect	Yes	No - Part of scientific paper not openly available without purchase.	Yes, the NMs was used as UV filter in sunscreens	
MECHANISM(S) OF CONCERNS		**APPLICABILITY**		**SCALE & SCALABILITY OF PROCESS**	
Are the **mechanism(s) of concern of the NF/NEP reduced** after applying the SbD strategy?	Is the SbD "bringing" to **new mechanism(s) of concern**?	Is the SbD strategy **applicable to other NF/NEP**?	**If Y - Specify to which other NF(s) the SbD strategy can be applied**	At which **"scale"** is the SbD strategy applied/implemented?	Is it possible to **scale-up** the SbD strategy?
Y/N	Y/N	Y/N. If Y, please specify in column H.		Real production scale/ Pilot scale/ Lab scale	Y/N
Note: **if no**, we consider it a limitation?	Note: **if Yes**, we consider it a limitation	Note: **if no**, we consider it a limitation		Note: **if at lab scale**, we consider it as a limitation	Note: **if no info**, we consider it a limitation
Yes, the production of ROS and the production of free radicals	No	Y (potentially, not reported in the study)	Potentially to any other NPs that present photocatalytic activity	Lab scale	Yes, potentially
COST / BENEFIT & COST		**REGULATORY ASPECTS**	**CONCLUSION**	**LIMITATION**	**Comment**
Are there any information on cost/benefit of the implemented SbD?	**If Y** - Are the cost a potential limitation for real case application?	Does the SbD comply with current Regulatory Requirements?	**Is the SbD applicable to a real case?**	Which are the main **limitations**?	How to **improve usability**?
Y/N	Y/N	Y/N	Free text. Brief conclusion stating if the SbD is suitable to be applicable in a real case. If not, please try to explain which are the main limitations and if it would be possible to give any suggestion/recommendation to make it applicable (in next column O).	Free text, pointing out which were the limitation. NOTE	Free text, pointing out which aspects can be improved and how.
Note: **if no info**, we consider it a limitation	Note: **if Yes**, we consider it a limitation	*We will decide if we will keep or not this entry field because we may not have enough info to understand the applicable regulation*			
Yes, the study investigate the benefit due to the ZnO amount reduction in sunscreen production	No	Yes, the author is aware of the regulatory aspects	Yes, the results show a reduction in free radicals production, an higher SPF values and a more photostable UV filter with a reduced relese of ZnO NPs	Strategy appliable only to photocatalytic NFs	Add information on NPs release in relavant media, as sea water and synthetic swaet, that can mimic the real exposure conditions

Importantly, rationalizing information in the grid enabled us to execute a statistical analysis of the outcomes, which had the advantage of avoiding subjective judgement. Table 4 reports the results of the usability analysis, from which it emerged that a very high fraction of the resources (79%) can be potentially used in industrial nano-manufacturing. Another important information that emerged from our analysis is that the most common, and most used, NFs are represented, suggesting that a wide range of manufacturers may be potentially interested in some of the resources we have collected.

Table 4. Analysis of usability requirements of SbD resources in the repository

<table>
<tr><td>Clarity</td><td>93% have a clear goal</td></tr>
<tr><td>Accessibility</td><td>37 % of the literature is open access</td></tr>
<tr><td>Technical function</td><td>81% of resources report a technical function
68% maintain the technical function</td></tr>
<tr><td>Mechanism of concern</td><td>90% of resources report technical function
75% reduce the mechanism of concern
13% bring new mechanism of concern</td></tr>
<tr><td>Applicability</td><td>86% are applicable to other NF/NEP</td></tr>
<tr><td>Scale and Scalability of the process</td><td>97% of resources describe a potential scalability

</td></tr>
<tr><td rowspan="2">Cost/Benefit Cost</td><td>29% report cost/benefit</td></tr>
<tr><td>No information about the cost limitation</td></tr>
<tr><td>Regulatory aspects</td><td>Yes, but not expert judgement</td></tr>
<tr><td colspan="2">76% can be potentially implemented in real manufacturing</td></tr>
</table>





3.5 Selection of resources

3.5.1 Criteria of selection

The analysis of usability aims at compiling a list of SbD methods that industry can adopt to produce safe (or, as-safe-as-possible) NFs and NEPs. For the specific objectives of SAbyNA, it is especially important to identify SbD methods for the production of nano-enabled paints and of nano-enabled filaments for 3D printing. Overall, we have established the following criteria for selecting usable methods:

1- **Usability**: the total number of limitations, computed for all factor of usability, was used as major decision factor. Limitations listed in the Excel grid for clarity, aim, and applicability to real cases were considered with high weight. Contrarily, limitations due to cost (i.e. cost not reported) or accessibility (i.e., open access or not) were considered less important. The usability was the main criterion used for the selection.

2- **Sector specific resources**: the fact that the resource was directly linked with the paint or 3D printing, or linked in some way with the SAbyNA case study (e.g., SbD of NF composed of Ag, SiO_2, CNT and TiO_2) was considered a plus for the resource selection.

3- **Repetitions and redundancies discarded.** Our analysis revealed that many resources reported the same SbD method, but used for different NFs. In these cases, we retained only the most comprehensive resource which provided the link between a physico-chemical drivers of risk and the strategies to minimize it.

4- Resources focused on processes discarded. WP5 will identify the most effective processes to implement a specific SbD strategy.

5- Resources focused on the performance of nanomedicines rather than on their safety where discarded because not relevant for the final SAbyNA platform.

For the sake of completeness, we report in this deliverable both selected (Table 5) and discarded (Table 6) resources, although grouped in different lists. Due to their different nature, selection on the usability of reports and deliverables from other projects about SbD are listed in table 7. Only for the selected one, we compiled usability cards, which report a synthetic description of the SbD, area of application, link to the original resource.

3.5.2 List of selected resources

Table 5. List of selected resources from publications, with, in orange the resources developing SbD approach for hazard, and, in blue, SbD approaches for minimizing release. For each resource, the NF chemistry, the selection justification, the mechanism of concern, the key physico-chemical property for risk and the SbD approach are listed.

Risk= release or Hazard or both	NFs Chemistry	Selection	Justification	Mechanism of concern	Key physicochemical properties identified for risk characterization	Harmonizations Implemented SbD modifications	Resource title
Hazard	TiO2	YES	Good usability, paly with the NFs dispersion in Matrix	Affinity to aquatic and terrestrial organisms	Surface chemistry	Coating	Optimizing the dispersion of nanoparticulate TiO2-based UV filters in a non-polar medium used in sunscreen formulations – The roles of surfactants and particle coatings
Release	TiO2	YES	Good usability, using NFs on support decrease the NFs dustiness and have been show (elsewhere) to preserve the NFs function	Reactive oxygen species generation	Dustiness potential	Support	Exposure Assessment During the Industrial Formulation and Application of Photocatalytic Mortars Based on Safer n-TiO2 Additives
Hazard	TiO2 and ZnO	YES	Good usability, improve functionality and reduce risk	Surface reactivity	Surface reactivity	NFs content	Nano-engineering safer-by-design nanoparticle based moth-eye mimetic bactericidal and cytocompatible polymer surfaces
Hazard	TiO2 and ZnO	YES	The use of support as SbD reduce the NFs toxicity	Surface reactivity	Surface reactivity	Support	Hierarchical nano ZnO-micro TiO2 composites: High UV protection yield lowering photodegradation in sunscreens
Hazard	TiO2	YES	Good usability and effective SbD strategy to reduce risk. The method have been proved to be effiscient in actual product	Surface chemistry	Surface chemistry	Coating	Silica modification of titania nanoparticles enhances photocatalytic production of reactive oxygen species without increasing toxicity potential in vitro

Hazard	**TiO2**	**YES**	**Bad usability, but paint sector specific**	Photocatalytic activity	Surface reactivity		Characterization of photocatalytic paints: A relationship between the photocatalytic properties-release of nanoparticles and volatile organic compounds
Hazard	**TiO2**	**YES**	**Good usability of SbD support that can be apply to the targeted industrial sectors**	Reactive oxygen species generation	Surface reactivity	Support	Safer-by-design hybrid nanostructures: an alternative to conventional titanium dioxide UV filters in skin care products
Release	**TiO2**	**YES**	**Good usability, provide SbD strategy to the paint sector**	Release	NFs content	Support	Towards the development of safer by design TiO2-based photocatalytic paint: impacts and performances
Release	**TiO2**	**YES**	**Good usability, provide SbD strategy to the paint sector**	Release	NFs content	Bridge	TiO2 nanoparticles coated with bio-inspired ligands for the Safer-by-Design development of photocatalytic paints
Hazard	**Ag**	**YES**	**Good usability , SbD bridging to reduce NFs dissolution**	Soluble compound release	Dissolution rate	Bridge	Safer-by-design biocides made of tri-thiol bridged silver nanoparticle assemblies
	Ag	**YES**	**Good usability , play with NFs Size to reduce the dissolution**	Soluble compound release	Length, diameter - size	size	Safe by Design implementation in the nanotechnology industry
Hazard	**Ag**	**YES**	**Good usability**	Fiber-like toxicity	Aspect ratio - shape	Aspect ratio	A toxicology-informed, safer by design approach for the fabrication of transparent electrodes based on silver nanowires
Release	**Ag**	**YES**	**Good usability, provide SbD strategy limiting the NFs release**	Release	Aspect ratio - shape	Bridge	Safe by Design implementation in the nanotechnology industry

Hazard	**SiO2**	**YES**	**Good usability and the substitution SbD strategy is well applied**		Chemical composition	Substitution	Safe by Design implementation in the nanotechnology industry
Release	**SiO2**	**YES**	**Good usability , SbD coating to reduce worker exposure**	Surface reactivity	Dustiness potential	Coating	Safe by Design implementation in the nanotechnology industry
Hazard	**SiO2**	**YES**	**Good usability , SbD coating to reduce NFs dissolution, Paint sector releated**	Surface reactivity	Surface chemistry	Coating	Cytotoxicity of nanomaterials applicable in restoration and conservation
Hazard	**SiO2**	**YES**	**Good usability and relevant for paint industrial sector**	Affinity to aquatic and terrestrial organisms		Matrix composition	Influence of paints formulations on nanoparticles release during their life cycle
Release	**SiO2 NP and MWCNTs**	**YES**	**Good usability, provide SbD strategy to the plastic sector**	Release	Aspect ratio - shape	Coating	Monitoring migration and tranformation of nanomaterials in polymeric composites during accelerated aging
Release	**SiO2 NP and MWCNTs**	**YES**	**Good usability, provide SbD strategy to the plastic sector**	Release	Aspect ratio - shape	Matrix composition	Fate of nanoparticles during life cycle of polymer nanocomposites
Hazard	**SiO2 NPs**	**YES**	**Good usability, provide insigh on SAbyNA case study**	Surface reactivity	Surface chemistry	Doping	Safer-by-design flame-sprayed silicon dioxide nanoparticles: the role of silanol content on ROS generation, surface activity and cytotoxicity
Release	**Amorphous SiO2**	**YES**	**Good usability, provide SbD strategy to the paint sector**	Release	Resilience of the NEP matrix	Matrix composition	Formulation effects on the release of silica dioxide nanoparticles from paint debris to water
Release	**MWCNTs**	**YES**	**Good usability, provide NFs**	Release	Dispersion of NFs in the NEP matrix	Matrix composition and surface chemistry	Improved dispersion of carbon nanotubes in polymer at high concentrations

Release	**CuO & ZnO**	YES	**Reduction of release**	Release	Aspect ratio - shape, Surface chemistry	NFs/matrix affinity	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach
Hazard	**ZnO**	YES	**Good usability and relevant for paint industrial sector**	Surface reactivity	Surface reactivity	Coating	Influence of paints formulations on nanoparticles release during their life cycle
Hazard	**ZnO**	YES	**Yes, a SbD doping, therory and experimental testing**	Reactive oxygen species generation	Dissolution rate	Doping	Decreased dissolution of ZnO by iron doping yields nanoparticles with reduced toxicity in the rodent lung and zebrafish embryos
Hazard	**Au**	YES	**Good usabiility and test a framework**			Coating	Targeted polyethylene glycol gold nanoparticles for the treatment of pancreatic cancer: From synthesis to proof-of-concept in vitro studies
Release	**Multiple**	YES	**Good usability, provide SbD strategy to the plastic sector**	Release	NFs/NEP matrix affinity	Coating	Exploring release and recovery of nanomaterial from commercial polymeric nanocomposites
Release	**Multiple**	YES	**Good usability, provide insight on matrix degradability**	Release	NFs/NEP matrix affinity	Matrix composition	Quantitative rates of release from weathered nanocomposites are determined across 5 orders of magnitude by the matrix, modulated by the embedded nanomaterial

Table 6. List of discarded (i.e., not usable) resources, with in orange the resources focusing on SbD for minimizing hazard, and, in blue SbD, approaches for minimization of release.

Risk= release or Hazard or both	NFs Chemistry	Selection	Justification	Mechanism of concern	Key physicochemical properties identified for risk characterization	Harmonizations Implemented SbD modifications	Resource title
Hazard	**TiO2**	**NO**	**Average usability, aspect ratio for photocatalytics toxicity not a relevant SbD strategy**	Reactive oxygen species generation	Aspect ratio - shape	Aspect ratio	The shape of titanium dioxide nanomaterials modulates their protection efficacy against ultraviolet light in human skin cells
Hazard	**TiO2**	**NO**	**Bad usability,**	Photocatalytic activity	Surface reactivity	Surface chemistry	A chemoinformatics approach for the characterization of hybrid nanomaterials: Safer and efficient design perspective
Hazard	**TiO2 and ZnO**	**NOT for now**	**Review need to be detaiiled**	Affinity to aquatic and terrestrial organisms		NFs content	Assessing Sunscreen Lifecycle to Minimize Environmental Risk Posed by Nanoparticulate UV-Filters – A Review for Safer-by-Design Products
Hazard	**Ag**	**NO**	**Bad usability, coating SbD is presented in other resources**	Soluble compound release	Chemical composition	Coating	The 3D Design of Multifunctional Silver Nanoparticle Assemblies Embedded in Dielectrics
Hazard	**Ag**	**NO**	**NO, process related**	Affinity to aquatic and terrestrial organisms	Chemical composition	process	Safe by Design implementation in the nanotechnology industry

Hazard	**SiO_2**	**NO**	**Bad usability,**	Trojan horse phenomena	Length, diameter - size	NFs content	Formation of Protein Corona on Nanoparticle Affects Different Complement Activation Pathways Mediated by C1q
Release	**SiO_2 & Al_2O_3**	**NO**	**Bad usability,**	Release		Content	The effect of nanosilica (SiO_2) and nanoalumina (Al_2O_3) reinforced polyester nanocomposites on aerosol nanoparticle emissions into the environment during automated drilling
Release	**CNTs**	**NO**	**Process related**	Fiber-like toxicity		process	Towards large scale aligned carbon nanotube composites: An industrial safe-by-design and sustainable approach
Hazard	**CNTs & GO**	**NO**	**Bad usability,**	Fiber-like toxicity	Chemical composition	Doping	Enzymatic oxidative biodegradation of nanoparticles: Mechanisms, significance and applications
Release	**CNTs**	**NO**	**Process related**	Fiber-like toxicity	Dustiness potential	process	Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products

Hazard	**ZnO**	**No**	**SbD coating with same materials already describe**	Reactive oxygen species generation	Dissolution rate	doping	Towards large scale aligned carbon nanotube composites: An industrial safe-by-design and sustainable approach
Hazard	**ZnO**	**NO**	**Bad usability,**	Fiber-like toxicity	Aspect ratio - shape	size and coating	Do nanoparticle physico-chemical properties and developmental exposure window influence nano ZnO embryotoxicity in Xenopus laevis?
Hazard	**Graphene**	**NO**	**NO, process related**		Length, diameter - size	process	Safe by Design implementation in the nanotechnology industry
Hazard	**CNF**	**NO**	**NO, process related**	Fiber-like toxicity	Length, diameter - size	aspect ratio	Safe by Design implementation in the nanotechnology industry
Hazard	**local anesthetic agent bupivacaine (BUP)**	**NO**	**Relevant for nanomedecine**	Soluble compound release	Dissolution rate	Encapsulation	Citrem-phosphatidylcholine nano-self-assemblies: Solubilization of bupivacaine and its role in triggering a colloidal transition from vesicles to cubosomes and hexosomes
Hazard	**Graphene Oxyde Iron nanohybrid**	**NO**	**SbD do not reduce the risk**	Reducing agent	Surface reactivity	support	In Vitro Pulmonary Toxicity of Reduced Graphene Oxide-Nano Zero Valent Iron Nanohybrids and Comparison with Parent Nanomaterial Attributes
Hazard	**Nanoclays**	**NO**	**Bad usability,**	Surface chemistry	Surface chemistry	doping	Early Assessment and Correlations of Nanoclay's Toxicity to Their Physical and Chemical Properties

	binary mixture of citrem and soy phosphatidylcholine	**NO**	**Focus on nanomedecine**			coating	A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies
	Au	**No**	**Nanomedecine**			Coating	A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells
Hazard	**Iron oxide**	**NO**	**Bad usability,**	Soluble compound release	Dissolution rate	Coating	Biodegradation of iron oxide nanocubes: High-resolution in situ monitoring
Hazard	**CuO**	**NO**	**SbD already describe**	Soluble compound release	Dissolution rate	doping	Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu-O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos
Hazard	**CeO2**	**No**	**SbD coating with same materials already describe**	Surface reactivity	Surface chemistry	coating	Effects of amorphous silica coating on cerium oxide nanoparticles induced pulmonary responses
Hazard	**CeO2**	**No**	**SbD coating with same materials already describe**	Surface reactivity	Surface chemistry	Coating	An in vivo and in vitro toxicological characterization of realistic nanoscale CeO2 inhalation exposures

Table 7. Selection report for reports of other projects.

Chemistry	Selection	Justification	Mechanism of concern	Key physicochemical properties identified for risk characterization	Harmonizations Implemented SbD modifications	Resource title
CuO	**No**	**Other toxicity studies are needed**	Surface reactivity	zeta potential	Coating	D 7.1 – Report on the development of SbyD strategies applied to CuO
SiO2	**Yes**	**Average Usability, relevant sector of activity and NFs used.**	NFs release	Dustiness potential	Agglomeration	D8.8 - Report on the implementation and effectiveness of safe-by-design approaches
SiO2	**Yes**	**Average Usability, relevant sector of activity and NFs used.**	NFs release	Dustiness potential	Agglomeration	D8.8 - Report on the implementation and effectiveness of safe-by-design approaches
TiO2	**No**	**Good usability, but extremly specific SbD**	NFs release	Matrix resilience	Matrix composition	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
TiO2	**No**	**Usability can be improve, SbD effisciency inexistant, howver very relevant SbD for targetted industrial sectors**	NFs release	Matrix resilience	Matrix composition	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
Ag	**Yes**	**Good usability and relevant SbD strategy**	NFs release	NFs/matrix affinity	Binding	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
Ag	**Yes**	**Good usability and relevant SbD strategy**	NFs release	NFs/matrix affinity	Shape	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
Ag	**Maybe**	**Good usability and relevant SbD strategy but similar to previous one**	NFs release	NFs/matrix affinity	Shape	D3.4: REPORT on the evaluation (and prediction) of the impact of safer-by-design strategies on the release of NM throughout the life cycle of a NM-enabled products
	No	**Process related**		Chemical stability		SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
	No	**Process related**		Dustiness potential		SAFETY BY DESIGN: PRODUCTION OF ENGINEERING

						SURFACE MODIFIED NANOMATERIALS
	No	Process related		Length, diameter - size		SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
	Yes		NFs release	Dustiness potential	Coating	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
	No	Process related				SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
	No	Applicability is limited				SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
TiO2	Yes	Good applicability, and relevant to industral sector	Reactive oxygen species generation	Surface chemistry	Coating	SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
	No	Process related				SAFETY BY DESIGN: PRODUCTION OF ENGINEERING SURFACE MODIFIED NANOMATERIALS
Graphene	Yes	Usability ok, SbD strategy relevant for the industrial sector	NFs release	Dustiness potential	liquid/moisture	D2.3 Final comparative risk assessment and life Cycle assessment for candidate materials after SbD implementation in "hot spots" along the life cycle
	No	Good usability, but already describe in the article resources	Chemical composition	Substitution	Safe by Design implementation in the nanotechnology industry	D2.3 Final comparative risk assessment and life Cycle assessment for candidate materials after SbD implementation in "hot spots" along the life cycle

3.5.3 Overview of the selection

Figure 2 summarizes the outcome of the selection of usable resources. For each SbD strategy, we reported the total number of resources and, next to it, the number of the selected/usable one (dark blue columns). Importantly, we could select at least one resource describing for each of the SbD methods identified, with the only exception of those focusing on encapsulation and size variation because they did not fulfil the requirements for selection; in addition, we removed those focusing on processes, because not relevant to WP4 objectives (red columns). The analysis revealed that the most developed SbD methods are those targeting coating and matrix composition. These SbD methods, in fact, are very flexible to be adapted to a variety of different NFs.

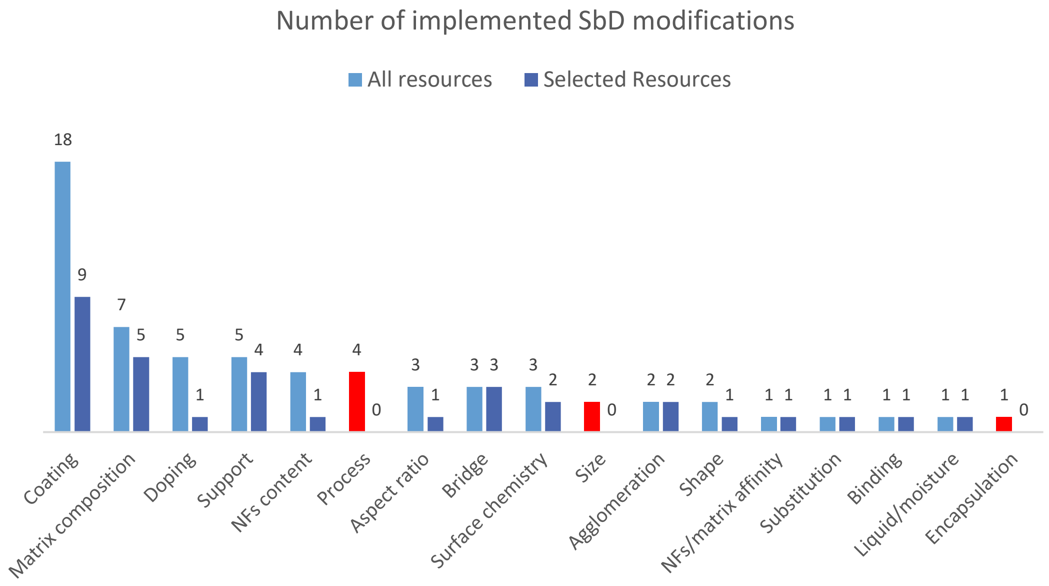


Figure 2. Total number of resources identified (light blue) and number of resources judged usable (dark blue) for each SbD method previously identified. Red columns indicate methods for which no usable resource was selected.

Figure 3 displays the comparison of the histograms for the total number (light blue) and of the usable resources grouped per key physical chemical property of concern. We observe that only for "zeta potential", "chemical stability" and the "length/diameter/size" we could not select any usable resource. We notice, however, that, when length/diameter/size are the source of risks, a practicable solution is to change the dimensions of the NFs, for example, by tuning the synthesis protocol, or by modifying the aspect ratio, for which as many as 5 usable resources were selected. For "Trojan horse phenomena" and the "reducing agent", two examples of physicochemical sources of hazard listed in the OECD guideline, we could not identify any resource.

In any case, he most represented physicochemical property of concern for risk were "NFs/NEP matrix affinity" and "dustiness potential" described in 9, and 8, resources respectively.

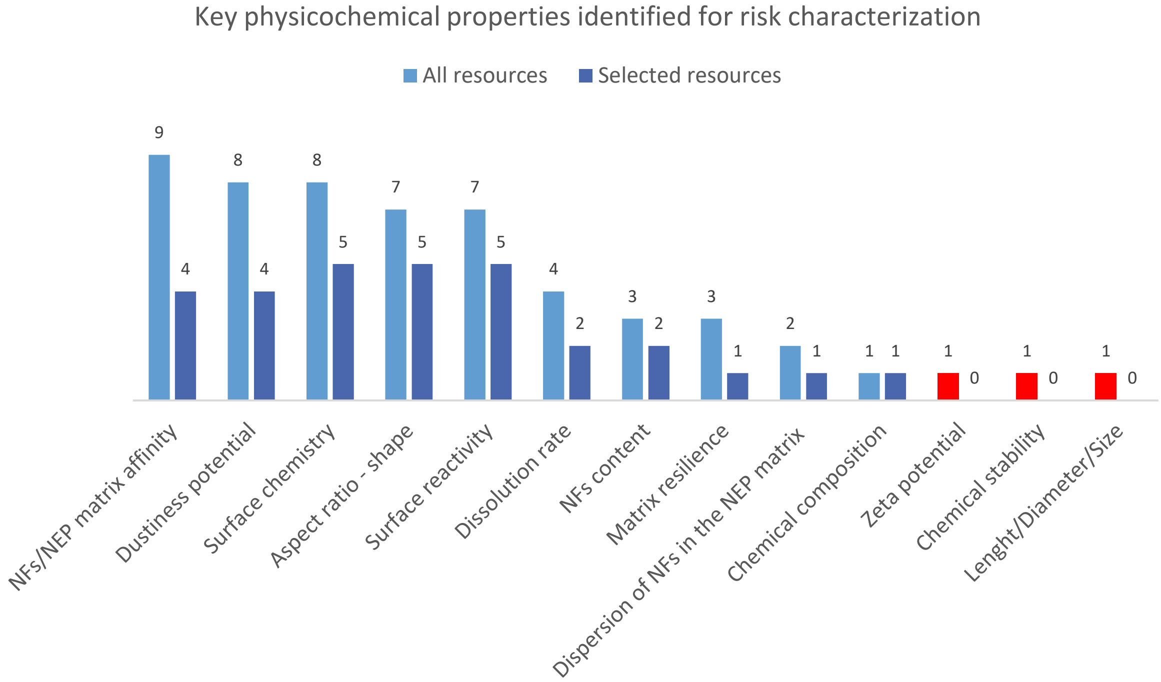


Figure 3. Total number of resources identified (light blue) and number of resources judged usable (dark blue). Red columns indicate the physicochemical properties for which no usable resource was selected.

When looking to the panel of mechanisms of concern (Figure 4), “release” was by far the most represented one. SbD methods aimed at reducing release represented about 35 % of the total number of all resources selected. This high number of resources may arise from the very general character of this mechanism that can be initiated by a variety of phenomena. By contrast, other mechanisms (i.e., surface reactivity, ROS generation, affinity to terrestrial and aquatic organisms) are more specific and require specific SbD strategies. We do not exclude that in the future, specific mechanisms of release may be extracted from the general group in which we have grouped all resources relative to this mechanism.

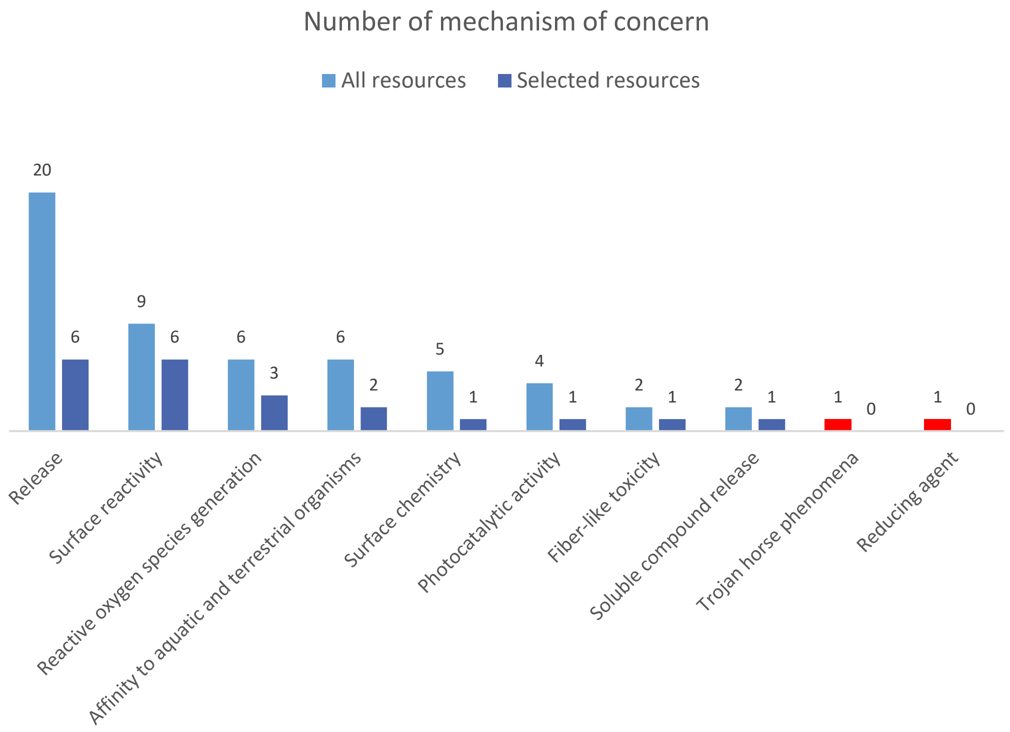


Figure 4. Total number of resources (light blue) and usable (dark blue) resources grouped according to the mechanism of concern.

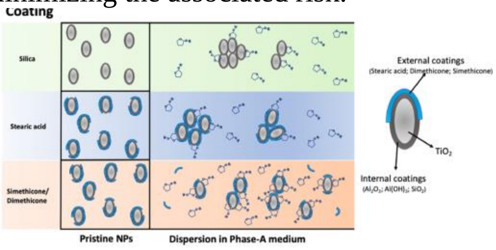
3.6 Usability Cards

For a rapid access to the selected SbD resources, we envisaged usability cards that provide all useful information about a method at glance (goal, physicochemical information, resource type, link to the full text). This information is organized according to the template below. Usability cards for all selected resources are available as annexes of this deliverable.

<table>
<tr><td colspan="2">SAbyNA RPSbDxxx</td><td colspan="3">Title</td></tr>
<tr><td colspan="5">Scope / abstract:</td></tr>
<tr><td>NFs chemistry:</td><td>Mechanism of concern:</td><td>Key physico-chemical property for risk:</td><td colspan="2">Safe by design strategy apply:</td></tr>
<tr><td colspan="5">Main content:</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type</td></tr>
<tr><td colspan="3">Source :</td><td colspan="2">Owner of the resource</td></tr>
</table>

4. Annex

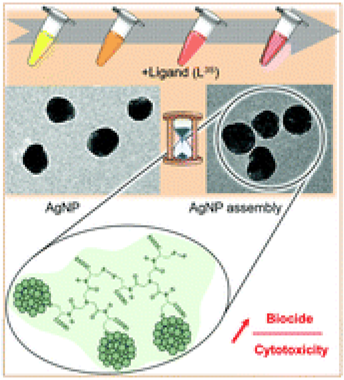
USABILITY CARDS FOR SELECTED RESOURCES

<table>
<tr><td colspan="3">RNF/NEPSbD 1</td><td colspan="3">Optimizing the dispersion of nanoparticulate TiO2-based UV filters in a nonpolar medium used in sunscreen formulations – The roles of surfactants and particle coatings</td></tr>
<tr><td colspan="6">Scope / abstract: Manufactured TiO2 NFs are widely used in cosmetics as UV blockers. The environmental risk associated with these NFs strongly depends on their concentration, aggregation state, and surface chemistry. Controlling these parameters in the sunscreen formulation is crucial in order to optimize the NFs content and better understand their fate, transport, and toxicity at the product's end-of-life. In the present work, the dispersion in sunscreen oil phase of four nanoparticulate UV filters having different coating characteristics was studied as a function of the oil composition. All the UV filters had a nano-TiO2 core. Three of them were coated with a primary layer of aluminum (hydro)oxide and a secondary external layer of different polymers giving a hydrophobic character. The fourth UV-filter was coated with SiO2 only, giving a hydrophilic character. The oil phase was composed of emollient oils and an emulsifying agent containing two surfactant molecules: Octyldodecyl xyloside (ODX) and PEG30 dipolyhydroxystearate (DHS). The NFs were dispersed in the oil in the presence or absence of the emulsifying agent. Their aggregates size was evaluated, together with the speciation of the surface chemistry before and after the dispersion in oil.</td></tr>
<tr><td>NFs chemistry: TiO_2</td><td>Mechanism of concern: Affinity to aquatic and terrestrial organisms</td><td colspan="2">Key physico-chemical property for risk: Surface chemistry</td><td colspan="2">Safe by design strategy apply: Coating</td></tr>
<tr><td colspan="6">Main content: In this work, surfactants normally used to stabilize W/O emulsions were highlighted to be also fundamental in stabilizing the nanoparticulate UV filters dispersions. A compromise needs to be considered between the stability of the mineral UV filter's external coating and its capability to let the surfactant molecules diffuse into the inner spheres of the nanoparticle. In this light, T-dim ENMs showed the best performance, given that the external PDMS coating was stable and not significantly degraded during the dispersion procedure but permeable enough to allow the diffusion of the ODX surfactant through the surface, leading to a finer ENMs dispersion and to an enhancement of the UV absorbance almost by a factor 2. This work brings light on the necessary step to optimize the use of nanomaterials in sunscreen product. Decreasing the amount of nanoparticulate UV filters in a sunscreen. formulation and better predicting their environmental fate and toxicity are key levers in the approach of minimizing the associated risk.


Drawback: Toxicity of the better dispersed system should be evaluated, the performance in a real cream formulation can be tested, an estimation of the reduction of release can be done by modeling to see the overall impact of the reduced amount on the environment.</td></tr>
<tr><td colspan="4">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="4">Source : 10.1016/j.colsurfa.2020.124792</td><td colspan="2">Colloids and Surface A</td></tr>
</table>

<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 6</td><td colspan="3">Exposure Assessment During the Industrial Formulation and Application of Photocatalytic Mortars Based on Safer n-TiO2 Additives</td></tr>
<tr><td colspan="5">Scope / abstract: Titanium dioxide nanoparticles (n-TiO2) are added to photocatalytic mortars to improve urban air quality. Their activity can be increased by dispersing and binding them on natural sepiolite surface. Workers handling photocatalytic additives can be exposed to n-TiO2. However, the release of nanoparticles to the workplace can be different if the material used is raw n-TiO2 powders or if the nanoparticles are supported on sepiolite. In this work, we compare occupational exposure to n-TiO2 for raw n-TiO2 and a hybrid additive n-TiO2/sepiolite obtained by a proprietary process.</td></tr>
<tr><td>NFs chemistry: TiO2</td><td>Mechanism of concern: Reactive oxygen species generation</td><td colspan="2">Key physico-chemical property for risk: Dustiness potential</td><td>Safe by design strategy apply: Support</td></tr>
<tr><td colspan="5">Main content: In summary, inhalation exposure to nano-titanium dioxide has been proved to be lower when formulating and applying mortars flled with n-TiO2/sepiolite hybrid photocatalytic additive compared to raw n-TiO2 Data showed that the number of particles released was lower when the n-TiO2/sepiolite hybrid was added compared to the raw n-TiO2. The dispersion and immobilization of the TiO2 nanoparticles on the surface of a natural silicate could constitute a safe-by-design approach. Overall, the n-TiO2/sepiolite hybrid additive improves the mortars’ photocatalytic activity and can be used as a safer material.</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="3">Source : 10.1007/s41742-020-00252-7</td><td colspan="2">International Journal of Environmental Research</td></tr>
</table>

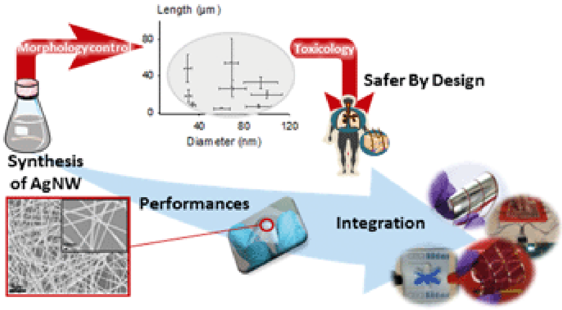
<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 74</td><td colspan="3">Safer-by-design biocides made of tri-thiol bridged silver nanoparticle assemblies</td></tr>
<tr><td colspan="5">Scope / abstract: Silver nanoparticles (AgNPs) are efficient biocides increasingly used in consumer products and medical devices. Their activity is due to their capacity to release bioavailable Ag(I) ions making them long-lasting biocides but AgNPs themselves are usually easily released from the product. Besides, AgNPs are highly sensitive to various chemical environments that triggers their transformation, decreasing their activity. Altogether, widespread use of AgNPs leads to bacterial resistance and safety concerns for humans and the environment. There is thus a crucial need for improvement. Herein, a proof of concept for a novel biocide based on AgNP assemblies bridged together by a tri-thiol bioinspired ligand is presented. The final nanomaterial is stable and less sensitive to chemical environments with AgNPs completely covered by organic molecules tightly bound via their thiol functions.</td></tr>
<tr><td>NFs chemistry: Ag</td><td>Mechanism of concern: Soluble compound release</td><td colspan="2">Key physico-chemical property for risk: Dissolution rate</td><td>Safe by design strategy apply: Bridge</td></tr>
<tr><td colspan="5">Main content: we described an assembly mechanism of AgNPs bridged together by a bio-inspired tri-thiol molecule. This process, driven by thiol binding to surface Ag(I), results in the formation of a scaffold that protects the NPs from massive transformations induced by various environmental conditions normally responsible for their fast dissolution, sulfidation or agglomeration.



Moreover, these architectures do not prevent Ag(I) release but only slow it down, providing a nanomaterial that can be regarded as a novel promising safer-by-design biocide. Its tunable and controlled ion release and low sensitivity to the surrounding medium make it a long-lasting biocide with drastically reduced hazard for humans and the environment with respect to currently employed technologies. The mixed sp^3–sp hybridization of L-thiols bound to surface Ag is likely to be responsible for the particular behavior of AgNPs involved in assemblies. The two hybridizations could mirror ligand binding on two different chemisorption sites, as hollow and on-top sites that favor stabilization of the assembly and dissolution into ions, respectively</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="3">Source : 10.1039/c9nh00286c</td><td colspan="2">Nanoscale Horizons</td></tr>
</table>

<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 82</td><td colspan="2">Formulation effects on the release of silica dioxide nanoparticles from paint debris to water</td></tr>
<tr><td colspan="4">Scope / abstract: In this work, paint formulations containing the same amount of silicon dioxide (SiO_2) nanoparticles but differing in the pigment volume concentration (PVC) and in amount and type of binder and pigment, were studied through leaching test to investigate the influence of these parameters on release of Si from paint. The results indicate greater release of Si, about 1.7 wt.% of the SiO_2 nanoparticles in the paint, for paint formulated with higher PVC value (63%), suggesting that the PVC is a crucial factor for release of SiO_2 nanoparticles from paints. A paint sample with the higher amount of binder and less calcite filler exhibited a lower release of Si among the paints with a low PVC value (35%), and no SiO_2 particles were detected in leachates collected from this paint. This could be due to the fact that a high portion of binder forms a suitable matrix to hold the SiO_2 ENPs in paint. The paint sample in which the amount of calcite was partially substituted with TiO_2 pigment did not show an important reduction on Si release. This work suggests that paint debris containing SiO_2 nanoparticles may release a limited amount of Si into the environment, and that by adjusting the properties of the binder in combination with common pigments it is possible to reduce the release of SiO_2 nanoparticles.</td></tr>
<tr><td>NFs chemistry: SiO_2</td><td>Mechanism of concern: Release</td><td>Key physico-chemical property for risk: Resilience of the NEP matrix</td><td>Safe by design strategy apply: Matrix composition</td></tr>
<tr><td colspan="4">Main content: Four paints with the same content of SiO_2 ENPs but with different PVC value, pigment and binder were used. Results suggested that volume fraction of the pigment phase could be a crucial factor for the release of SiO_2 ENPs from paints. In addition, high portion of binder forms a suitable matrix to hold the SiO_2 ENPs in paint. Silanized silica ENPs have an increased compatibility with acrylate binder, giving an increased incorporation of the silica particles in the polymer matrix. Regarding the solid paint debris obtained for the scope, it is well recognized that the smaller the residue size, the larger the surface area of the residue that is in contact with water, producing higher leachability of the substance from the solid material.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="2">Source : 10.1016/j.scitotenv.2014.01.029</td><td colspan="2">Science of the Total Environment</td></tr>
</table>

<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 62</td><td colspan="2">A toxicology-informed, safer by design approach for the fabrication of transparent electrodes based on silver nanowires</td></tr>
<tr><td colspan="4">Scope / abstract: Fabrication of silver nanowires (AgNWs) with fine and independent control of both the diameter (from 30 to 120 nm) and length (from 5 to 120 µm) by concomitant addition of co-nucleants and temperature control is demonstrated, and used for the preparation of size standards. Percolating random networks were fabricated using these standards and their optoelectronic properties were measured and compared with regard to the nanowire dimensions. The transparent electrodes appear suitable for various applications besides, in vitro toxicological studies carried out on murine macrophages with the same size standards revealed that AgNWs are weakly toxic. The global knowledge dealing with the combination of nanowire dimensions associated with optoelectronic performances and related toxicity should encourage the rational use of AgNWs, and guide the choice of the most adequate AgNW dimensions in an integrated approach.</td></tr>
<tr><td>NFs chemistry: Ag</td><td>Mechanism of concern: Fiber-like toxicity</td><td>Key physico-chemical property for risk: Aspect ratio - shape</td><td>Safe by design strategy apply: Aspect ratio</td></tr>
<tr><td colspan="4">Main content: The article perform a screening of Ag nanowire functionality and toxicity of different length to encourage the rational use of AgNWs in a “safer by design” approach.



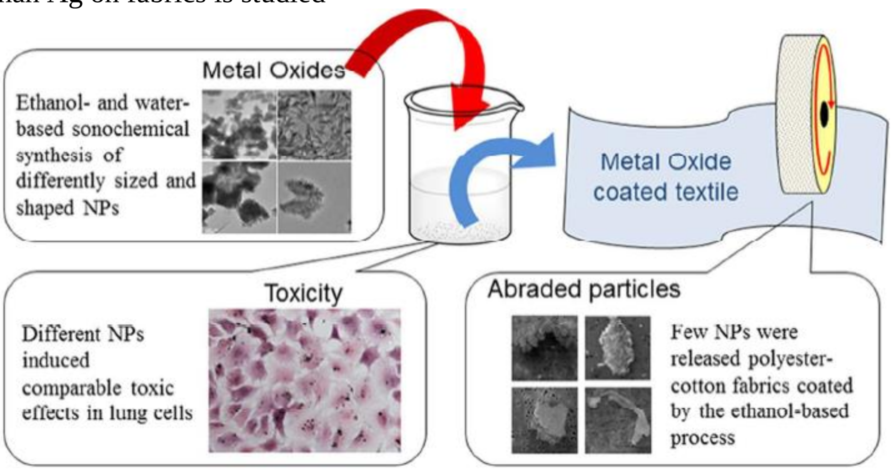
By careful modifications of the polyol process, in particular, precisely defined halide ion concentrations and temperature setting, independent fine tuning of the diameter and length of AgNWs has been successfully demonstrated. Size standards were prepared accordingly, and used for the fabrication of transparent electrodes. The AgNWs were found to be weakly toxic for macrophages and showed a length-dependent toxicity, with the toxicity decreasing with length.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="2">Source : 10.1039/c8en00890f</td><td colspan="2">Environmental Science Nano</td></tr>
</table>

SAbyNA RNF/NEPSbD 30	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach

Scope / abstract: Nano metal oxides have been proposed as alternatives to silver (Ag) nanoparticles (NPs) for antibacterial coatings. Here, cotton and polyester–cotton fabrics were sonochemically coated with zinc oxide (ZnO) and copper oxide (CuO) NPs. To understand the potential respiratory impact of the NPs, the coated textiles were subjected to the abrasion tests, and the released airborne particles were measured. A very small amount of the studied metal oxides NPs was released from abrasion of the textiles coated by the ethanol-based sonochemical process. Lung and immune cells viability decreased after 24 h of exposure only at the highest studied NPs concentration (100 µg/mL). Calculations revealed that the exposures of the NPs to human lung due to the abrasion of the textiles were lower or comparable to the minimum doses in the cell viability tests (0.1 µg/mL), at which acute cytotoxicity was not observed. The results alleviate the concerns regarding the potential risk of these metal oxide NPs in their applications for the textile coating and provide insight for the safe-by-design approach.

NFs chemistry: ***Cu** and **Zn***	*Mechanism of concern:* ***Fiber-like toxicity***	*Key physico-chemical property for risk:* ***Surface chemistry***	*Safe by design strategy apply:* ***Coating** and **NFs/matrix affinity***

Main content: The resource test different parameters that could modify the NFs toxicity (NFs chemistry, size and shape) and NFs exposure (texile matrix, NFs attachment method), application of safer anti-bacterial NF of Zn and Cu rather than Ag on fabrics is studied



The sonochemical technology provides a new way to efficiently coat textiles with NPs and the product safety need to be assessed by holistic approaches. The coating process, rather than the NP physical and chemical properties, is shown to be the main factor in modulating the NP release. The ethanol-based process led to less release than the water-based process. However, water-based process is safer for the manufacturing phase. This study provides data for the safe-by-design approach and balance of the risks during the manufacturing and product usage phases, with the eventual goal of applying the nano-enabled antibacterial textiles in the local and global mitigation strategies against the spread of infectious diseases.

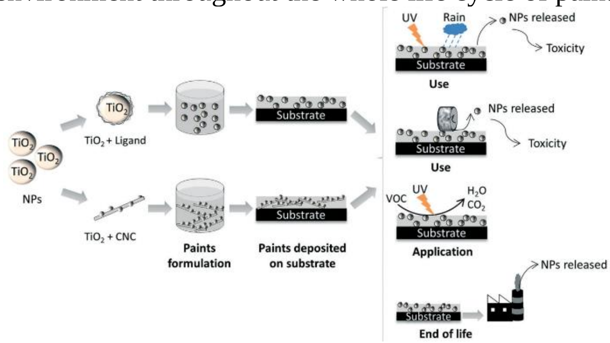
Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : 10.1021/acs.est.7b02390	Environmental Science and Technology

RNF/NEPSbD 83	**Towards the development of safer by design TiO2-based photocatalytic paint: impacts and performances**

Scope / abstract: Addition of titanium dioxide (TiO_2) (nano)particles into photocatalytic paints represents a promising alternative aiming to mineralize gaseous pollutants, such as volatile organic compounds (VOCs) into innocuous species (H_2O and CO_2). To mitigate potential risks associated with the use of these nano-objects, we report a safer by design strategy to develop a photocatalytic paint containing TiO_2 nanoparticles (NPs) taking into consideration the safety aspects over its life cycle. Specific innovative types of TiO_2 NPs were synthesized. These nanoparticles were then incorporated into an organic matrix-based paint. These paints were applied on standard substrates and underwent artificial weathering in an accelerated weathering chamber with controlled parameters. Photocatalytic efficiency towards airborne VOCs was measured for all the paints. Mechanical solicitation through abrasion and incineration tests were performed to assess the potential emission of airborne particles that could lead to human or environmental exposure. Using this safer by design strategy, we succeeded in decreasing the negative impact of TiO_2 on the paint matrix while keeping a good photocatalytic efficiency and reducing the NP release. Specifically developed TiO_2 NPs exhibit similar photocatalytic properties and enhanced physical properties as compared to paints containing the reference TiO_2 NPs, while reducing their potential hazards.

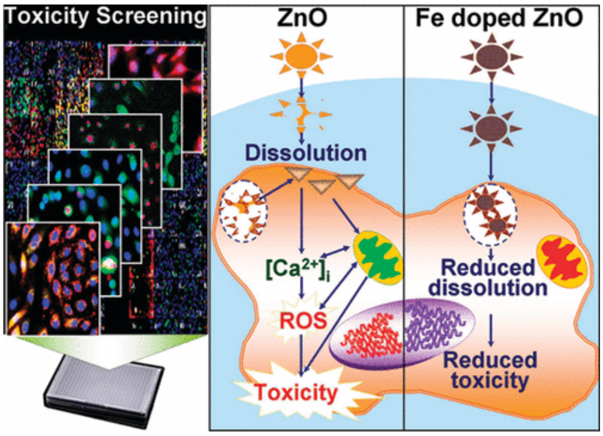
NFs chemistry: ***TiO_2***	*Mechanism of concern:* ***Release***	*Key physico-chemical property for risk:* ***NFs content***	*Safe by design strategy apply:* ***Support***

Main content: The strategy of this study involves a reduction of the amount of TiO_2 NPs incorporated in the paints and/or the incorporation of self-protecting TiO_2 NPs for given photocatalytic properties and thus, a lower release of TiO_2 NPs into the environment throughout the whole life cycle of paints.

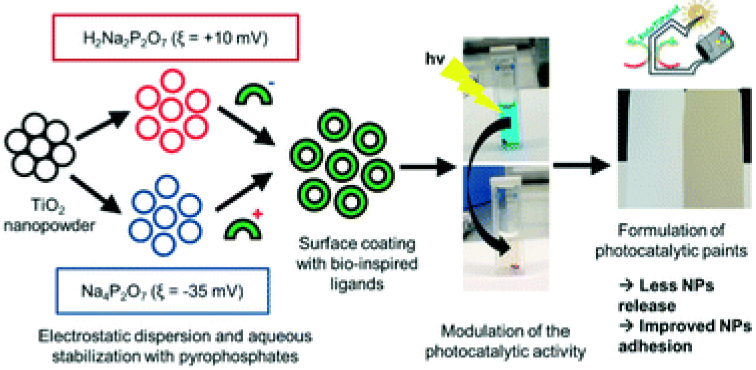


By taking into account the reduction of TiO_2 concentration inside the paint and the NPs released while keeping a good photocatalytic efficiency, commercial paint with TiO_2 NPs + PEG3350 (polyethylene glycol) with [PEG3350]/[Ti] ratio = 1/1 and TiO2 + 0.5%wt CNC appear to be the most promising candidates. These results confirm the potential of adding TiO_2 NPs into paints for air purification but require a fine-tuning of several parameters of the paint formulation such as the matrix.

Recommendations for use: (e.g. link to other resources) *J. Nanopart. Res.*, 2015, **17** , 149 *Environ. Sci.: Nano*, 2017, **4** , 1998 —2009 *Environ. Sci.: Nano*, 2021, **8** , 297 —310	*Resource type* *Nano-specificity*
Source : **https://doi.org/10.1039/D0EN01232G**	**Environmental Science: Nano**

RNF/NEPSbD 75	**Use of a Rapid Cytotoxicity Screening Approach To Engineer a Safer Zinc Oxide Nanoparticle through Iron Doping**		
Scope / abstract: We demonstrate the use of a multiparameter cytotoxicity assay that evaluates toxic oxidative stress to compare the effects of titanium dioxide (TiO2), cerium oxide (CeO2), and zinc oxide (ZnO) nanoparticles in bronchial epithelial and macrophage cell lines. The nanoparticles were chosen on the basis of their volume of production and likelihood of spread to the environment. Among the materials, dissolution of ZnO nanoparticles and Zn2+ release were capable of ROS generation and activation of an integrated cytotoxic pathway that includes intracellular calcium flux, mitochondrial depolarization, and plasma membrane leakage. Purposeful reduction of ZnO cytotoxicity was achieved by iron doping, which changed the material matrix to slow Zn2+ release.			
NFs chemistry: ***Zn***	*Mechanism of concern:* ***Soluble compound release***	*Key physico-chemical property for risk:* ***Dissolution rate***	*Safe by design strategy apply:* ***Doping***
Main content: ZnO was comparatively more toxic than TiO2 and CeO2 nanoparticles based on the principle of particle dissolution and shedding of toxic Zn2. This toxicity could be reduced by iron doping which leads to a stabilization of material crystal structure. In ZnO containing sunscreens, for instance, subtle changes in crystal structure may not compromise their protection against sunlight although it may affect the electrical and magnetic properties of this material. 			
Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*		
Source : 10.1021/nn901503q	ACS nano		

RNF/NEPSbD 84	**TiO_2 nanoparticles coated with bio-inspired ligands for the Safer-by-Design development of photocatalytic paints**		
Scope / abstract: It is reported the electrostatic stabilization in aqueous media with pyrophosphate buffers of different pH range followed by the coating with bio-inspired molecules (lysine, deferoxamine, dopamine) and polymers (poly-acrylic acid, polyethylene glycol, poly-dopamine) of 4-5 nm spherical photocatalytic TiO_2 NPs for the development of safer-by-design photocatalytic paint. Photocatalytic activity of the TiO_2 nanocomposites was investigated by following the degradation of methylene blue (MB) under irradiation. Results showed a modulation of the photocatalytic activity (decrease or increase of the MB degradation rate) as function of the nature/binding strength of the bio-inspired coating on the oxide surface.			
NFs chemistry: ***TiO_2***	*Mechanism of concern:* ***Release***	*Key physico-chemical property for risk:* ***NFs content***	*Safe by design strategy apply:* ***Bridge***



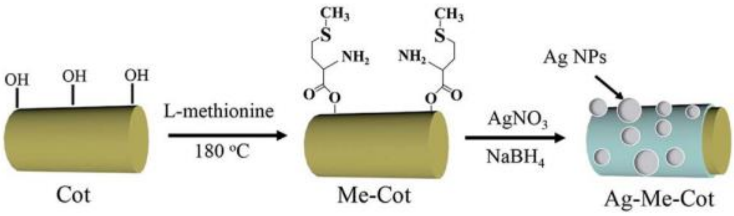
Main content: The nanocomposites exhibit variable photocatalytic activities based on the degradation of MB under UV-vis irradiation, meeting the initial objective toward the safer-by-design development of a self-cleaning paint. As most of the ligands decreased more or less strongly the photocatalytic activity of the TiO_2 NPs, fewer particles in number would be necessary in the paint formulation for observing the same self-cleaning effect, and concomitantly, a lower amount of NPs would be released by mechanical stress, use or ageing over the paint life cycle.

Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : https://doi.org/10.1039/D0EN00947D	**Environmental Science: Nano**

<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 85</td><td colspan="2">Monitoring migration and transformation of nanomaterials in polymeric composites during accelerated aging</td></tr>
<tr><td colspan="4">Scope / abstract: The work described here is focused on the evaluation of the migration and transformation of NM included in polymer nanocomposites (NC) during accelerated climatic ageing. To this aim, it was generated polyamide 6 (PA6) NC with different degree of compatibility between the NM and the polymeric matrix. These NC were submitted to accelerated aging conditions to simulate outdoor conditions (simulation of the use phase of the polymeric NC). The NC contain as nanofillers MWCNT and SiO2 NP with different surface properties to influence the compatibility with the polymeric matrix. The dispersion of SiO2 NP in the NC depended on their compatibility with the matrix. However, SiO2 NP were aggregated at the end of the accelerated aging process. Oppositely, compatibilized MWCNT (MWCNTMB) decreased the degradation of the polymer. Nevertheless, the nanomaterial migrated likewise to the surface during the ageing process. In order to evaluate the possible changes in the structure of nanomaterials due to the aging process, NM were extracted from the polymer by calcination. SiO2 hydrophilic nanoparticles were not affected by the aging process. However, both types of MWCNT were affected by the aging of the NC.</td></tr>
<tr><td>NFs chemistry:
MWCNT and SiO_2</td><td>Mechanism of concern:
Release</td><td>Key physico-chemical property for risk:
Aspect ratio - shape</td><td>Safe by design strategy apply:
Coating</td></tr>
<tr><td colspan="4">Main content: Analysis of NC properties before and after ageing demonstrated that release of NM from polymer NC depends mainly on polymer degradation. The process of polymer degradation in NC materials under climatic conditions can be reduced by the inclusion of well-dispersed MWCNT. However, in the case of SiO2 NP degradation of the polymer is not dependent on the dispersibility of the nanofiller in the matrix. Therefore, the size, shape, and chemical composition of the nanofiller was shown to influence the release of NM to the environment.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="2">Source : 10.1088/1742-6596/429/1/012044</td><td colspan="2">Journal of Physics: Conference Series</td></tr>
</table>

<table>
<tr><td colspan="2">SAbyNA
RNF/NEPSbD 86</td><td colspan="3">Exploring release and recovery of nanomaterial from commercial polymeric nanocomposites</td></tr>
<tr><td colspan="5">Scope /abstract: Few studies have been done in order to understand degradation of polymeric nanocomposites containing nanomaterials and the fate of these nanomaterials, which may occur in suffering many processes such as migration, release and physicochemical modifications. Studies on the migration, release and alteration of mechanical properties of commercial nanocomposites due to ageing and weathering have been performed along with studies on the feasibility of recovery and recycling of the nanomaterials. The project includes the use as model nanocomposites of Polyamide-6 (PA), Polypropylene (PP) and Ethyl Vinyl Acetate (EVA) as polymeric matrix filled with a 3% in mass of a set of selected broadly used nanomaterials; from inorganic metal oxides nanoparticles (SiO2, TiO2 and ZnO) to multi-walled carbon nanotubes (MWCNT) and Nanoclays. These model nanocomposites were then treated under accelerated ageing conditions in climatic chamber. Additionally, recovery of the nanomaterials from the polymeric matrix was addressed, being successfully achieved for PA and PP based nanocomposites.</td></tr>
<tr><td>NFs chemistry:
SiO_2, TiO_2 and ZnO</td><td>Mechanism of concern:
Release</td><td>Key physico-chemical property for risk:
NFs/NEP matrix affinity</td><td colspan="2">Safe by design strategy apply:
Coating</td></tr>
<tr><td colspan="5">Main content:
Regarding release of material due to accelerated aging, release of material has been found for all the tested composites, but exposure, and so potential risk, only would have to be addressed for the ones were nanomaterial rather than only polymer has been found. Good functionalization of nanomaterials surface to make them compatible with the polarity of the polymeric host is a key factor to determine the degree of degradation upon aging of the resulting composite. Regarding extraction and recovery methods, calcination of PP nanocomposites gave higher yields of recovery (≈100%) than PA dissolution (40-60%), though the morphology and distribution of the organic core remains almost the same in both cases.</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="3">Source : 10.1088/1742-6596/429/1/012048</td><td colspan="2">Journal of Physics: Conference Series</td></tr>
</table>

<table>
<tr><td colspan="2">RNF/NEPSbD 87</td><td colspan="2">Excellent binding effect of L-methionine for immobilizing silver nanoparticles onto cotton fabrics to improve the antibacterial durability against washing</td></tr>
<tr><td colspan="4">Scope / abstract: To improve adhesion of the Ag NPs, various strategies have been tried, but achieving long-term antibacterial effectiveness still remains challenging. Here, L-methionine is proposed as a binder reagent because it has low toxicity towards mammalian cells and has a methyl group to enhance its coordination ability. The antibacterial cotton fabric was fabricated via a very simple pad-dry-cure process: after dipping a cotton fabric in an L-methionine solution followed with heating for esterification, Ag NPs are formed via the reaction of silver nitrate with sodium borohydride. The resulting cotton fabric exhibits an excellent antibacterial property and laundering durability. Its bacterial reduction rates (BR) against both S. aureus and E. coli remained over 97% even after 90 consecutive laundering cycles. Moreover, the modification causes insignificant damage to cotton's characteristics, such as tensile breaking strength, water absorptivity, and vapor permeability.</td></tr>
<tr><td>NFs chemistry:
MWCNT and SiO₂</td><td>Mechanism of concern:
Release</td><td>Key physico-chemical property for risk:
Aspect ratio - shape</td><td>Safe by design strategy apply:
Bridge</td></tr>
<tr><td colspan="4">Main content: L-Methionine can improve adhesive force of Ag NPs onto fiber surface of cotton. The binding effect of L-methionine gives cotton fabrics with a remarkable antibacterial durability that can keep the BR rate more than 97% even after 90 stringent laundering cycles. The high washing durability is contributable to the coordination bonds between Ag NPs and the L-methionine moieties that grafted on the cotton fiber surface.



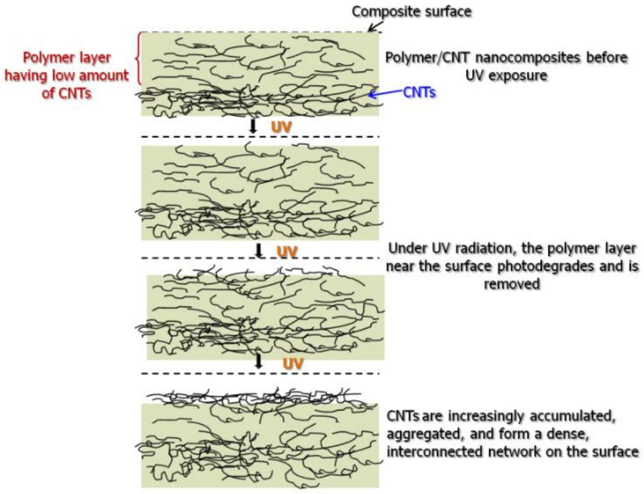
Importantly, the finishing method does not significantly damage cotton natures such as tensile breaking strength, water absorptivity, and vapor permeability. It is believed that the finishing method has great potential for practical applications in biomedical textiles.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="2">Source : 10.1039/c8ra04401e</td><td colspan="2">RSC Advances</td></tr>
</table>

RNF/NEPSbD 88	**Fate of nanoparticles during life cycle of polymer nanocomposites**

Scope / abstract: The fate of nanoparticles in polymer nanocomposites during their exposure to UV environment has been investigated. Epoxy polymer containing multi-walled carbon nanotubes (MWCNTs) and silica nanoparticles were studied. Specially-designed cells containing nanocomposite specimens were irradiated with UV radiation between 295 nm and 400 nm. Epoxy containing MWCNTs exposed to UV radiation degraded at a much slower rate than the unfilled epoxy or the epoxy/nanosilica composite. Photodegradation of the matrix resulted in substantial accumulation of nanoparticles on the composite surfaces. Silica nanoparticles were found to release into the environment, but MWCNTs formed a dense network on the composite surface, with no evidence of release even after prolonged exposure.

NFs chemistry:	*Mechanism of concern:*	*Key physico-chemical property for risk:*	*Safe by design strategy apply:*
MWCNT** and **SiO_2	***Release***	***Aspect ratio – shape***	***Matrix composition***

Main content: Amine-cured epoxy matrix in the nanocomposite underwent photodegradation during exposure to 295 nm to 400 nm UV radiation, resulting in substantial mass loss and marked increase in nanoparticle concentration on nanocomposite surfaces. The rate of mass loss and chemical degradation of MWCNT/epoxy composite was lower than that observed in unfilled epoxy or epoxy/nanosilica composite, suggesting that MWCNTs decrease the photodegradation of the amine-cured epoxy. MWCNTs formed a dense, entangled network on the nanocomposite surface, with no evidence of release even after prolonged exposure to UV radiation. This was responsible for essentially eliminating the release of CNTs to the environment during exposure to UV radiation.



Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : 10.1088/1742-6596/304/1/012060	Journal of Physics: Conference Series

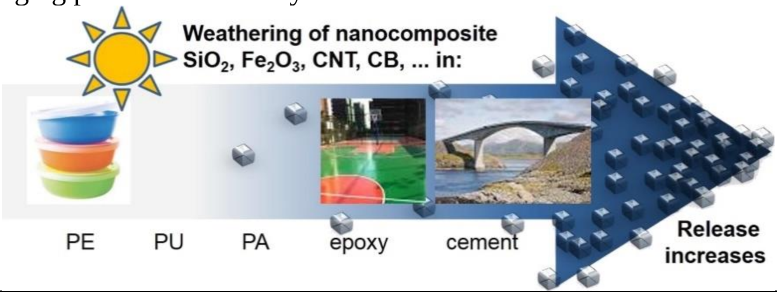
RNF/NEPSbD 89	**Improved dispersion of carbon nanotubes in polymer at high concentrations**

Scope / abstract: The polymer nanocomposite used in this work comprises elastomer poly(dimethylsiloxane) (PDMS) as a polymer matrix and multi-walled carbon nanotubes (MWCNTs) as a conductive nanofiller. To achieve uniform distribution of carbon nanotubes within the polymer, an optimized dispersion process was developed, featuring a strong organic solvent—chloroform, which dissolved PDMS base polymer easily and allowed high quality dispersion of MWCNTs. At concentrations as high as 9 wt.%, MWCNTs were dispersed uniformly through the polymer matrix, which presented a major improvement over prior techniques.

NFs chemistry:	*Mechanism of concern:*	*Key physico-chemical property for risk:*	*Safe by design strategy apply:*
CNT	***Release***	***Dispersion of NFs in the NEP matrix***	***Composition** and **surface chemistry***

Main content: Based on its high solubility for PDMS and MWCNTs respectively, and its ability to retain dispersed state of MWCNTs in presence of PDMS, chloroform was found to be an optimal choice as a common solvent. Also, the surface functionalization of CNTs by carboxyl groups was found to be beneficial for further improvement of dispersion quality. A combinatory approach was developed in which mechanical stirring was used to facilitate the initial dissolution of PDMS inside common solvent, and mild sonication used to as a main tool to disperse MWCNTs within PDMS. Evaporation process was facilitated and expedited by use of vacuum pump and accurate control of elevated temperatures. Solution drying time was significantly shortened.

Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : 10.3390/nano2040329	Nanomaterials

<table>
<tr><td colspan="2">RNF/NEPSbD 90</td><td colspan="3">Quantitative rates of release from weathered nanocomposites are determined across 5 orders of magnitude by the matrix, modulated by the embedded nanomaterial</td></tr>
<tr><td colspan="5">Scope / abstract: Major uses of nanomaterials are as functional fillers embedded in a solid matrix, such as plastics, tires, and coatings. Degradation of the solid matrix during the use phase can lead to a release of the nanomaterial and of fragments which might further degrade and release nanomaterials or smaller fragments in secondary processes. Here we focus on release induced by weathering, and specifically on quantitative rates of the mass of fragments released in the size range between 2 nm and 10 µm. The protocol specifies ISO4892 conditions of UV aging, optionally with rain, then immersed sonication, then size-selective quantification. All of these are elements of the protocol that was developed and pre-validated in a pilot international interlab comparison by the NanoRelease initiative. We rescaled releases for UV dose and immersion volumes, and find that the resulting release rates in units of mg release per MJ photons are determined across 5 orders of magnitude by the matrix (PE, PU, PA, POM, epoxy, cement)</td></tr>
<tr><td>NFs chemistry:
CNT</td><td>Mechanism of concern:
Release</td><td colspan="2">Key physico-chemical property for risk:
Chemical composition</td><td>Safe by design strategy apply:
matrix composition and surface chemistry</td></tr>
<tr><td colspan="5">Main content: The release rates in units of mg release per MJ photons rank primarily by the matrix (PE, PU, PA, POM, epoxy, cement). The key role of the matrix was previously obscured by the design of measurement campaigns that aimed at elucidating the nano-specific effects, by comparing different nanomaterials in the same matrix. We confirm that embedded metal-oxide, carbonaceous, or organic nanomaterials can modulate the release rate up or down, but the overwhelming factor is the matrix. Variations of the aging and sampling conditions or a restriction of quantification to the size range from 2 nm to 150 nm do not affect this conclusion. It is plausible to extrapolate this hierarchy: If the susceptibility of the matrix is more important than any property of the embedded nanomaterial, then the aging process should be yet more decisive

</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="3">Source : 10.1016/j.impact.2016.01.001</td><td colspan="2">NanoImpact</td></tr>
</table>

RNF/NEPSbD 66 - 71	**Safe(r) by design implementation in the nanotechnology industry**		
Scope / abstract: The implementation of Safe(r) by Design (SbD) in industrial innovations requires an integrated approach where the human, environmental and economic impact of the SbD measures is evaluated across and throughout the nanomaterial (NM) life cycle. SbD was implemented in six industrial companies where SbD measures were applied to NMs, nano-enabled products (NEPs) and NM/NEP manufacturing processes. The approach considers human and environmental risks, functionality of the NM/NEP and costs as early as possible in the innovation process, continuing throughout the innovation progresses. Based on the results of the evaluation, a decision has to be made on whether to continue, stop or re-design the NM/NEP/process or to carry out further tests/obtain further data in cases where the uncertainty of the human and environmental risks is too large. However, SbD can also be implemented at later stages when there is already a prototype product or process available, as demonstrated in some of the cases. The SbD measures implemented in some of the case studies did not result in a viable solution. For example the coating of silicon nanoparticles with amorphous carbon increased the conductivity, the stability and reduced the dustiness of the particles and therefore the risk of explosion and the exposure to workers. However the socioeconomic assessment for their use in lithium-ion batteries for cars, when compared to the use of graphite, showed that the increase in performance did not overcome the higher production costs. This work illustrates the complexities of selecting the most appropriate SbD measures and highlights that SbD cannot be solely based on a hazard and exposure assessment but must include other impacts that any SbD measures may have on sustainability including energy consumption and waste generation as well as all associated monetary costs.			
NFs chemistry: **Graphene, CNF, SiO2, Ag nanowires, Ag NPs and Si NPs**	*Mechanism of concern:* ***Fibre like toxicity, Surface reactivity, Affinity to aquatic/terrestrial organisms, soluble compound release and photocatalytic activity***	*Key physico-chemical property for risk:* ***Length, diamter (size), chemical composition and dustiness potential***	*Safe by design strategy apply:* ***Process, aspect ratio, substitution, size and coating***

Main content: This study has showed the complexities and barriers of the practical implementation of the NanoReg2 SbD concept as well as the benefits of reducing risk uncertainties along the innovation process instead of doing it at the end. SbD, or similar concepts are implemented in other sectors. Whilst different contexts bring different challenges it is important to collate the shared experiences and knowledge to encourage and facilitate the application of the concept to all industrial sectors. Overall the nanotechnology companies that participated in this study found value on the application of SbD. Avanzare shifted to zero liquid waste and almost eliminated employee handling of graphene in powder form. Group Antolin reduced workers exposure and was able to select the most efficient method for the production of CNFs (the method used for GATam CNFs). HIQ-nano was able to compare the toxicity of both materials and think of new solutions. NanoGap reduced in 50% the silver waste. Nanomakers reduced the risk of explosion, workers exposure and was able to assess the financial viability of the SbD measures. The implementation of SbD in the nanotechnology sector requires expertise in material science, chemical engineering, toxicity, exposure and risk and considerable amounts of data. To streamline the implementation and make it affordable for companies data on physicochemical properties, hazard and exposure should be shared through robust and reliable databases. Training on how to use the databases and risk assessment tools should be provided. This would facilitate the SbD implementation and will further progress the development of sustainable NEPs.

Summary of the companies involved, NMs considered, their application, innovation stage and the SbD measures and results.

NM/Company Country	Market Sector Stage Gate	SbD Pillar	Before SbD	SbD Measure	SbD Result	Conclusions/Benefits
Graphene AVANZARE (Spain)	Electric coatings & paints (Stage 2 Concept)	Safer process (minimal waste, upscale production)	No previous prototype for comparison	SbD principles applied: - wet synthesis in water - recycle of waste into new batches Semi-automatic	Lower exposure as graphene is commercialized in wet form. Reduced handling of dry graphene No liquid waste & very low solid waste	Significant improvement in product sustainability compared to other synthesis

				packing for dry product with LEV		
CNF GRUPO ANTOLIN (Spain)	Automoltive (Stage 5 Market entry)	Safer NM (lower toxicity) Safer process (upscale production)	Exposure risk in production & surface treatment stages High hazard potential due to HARN. Impact driven by high energy resources in production. Emission of greenhouse gases	Three candidate CNFs with different degree of impurities & crystallinity (GAtam, GANF, GANFg) Automated pneumatic transport Improve production process	Workers exposure reduced. Toxicity comparable for the 3 NMs ≠ CNT Environmental Impact reduced due to reduced emissions.	GATam toxicity comparable to GANF. GAtam production more efficient than GANF. Significant energy savings. Healthier working environment
Fluorescent NMs HIQ-NANO (Italy)	Biosensors (Stage 3 Prototype)	Safer NM (lower toxicity)	QD doped SiO2 High ecotoxicity due to the presence of Cd	Substitution of QD for a dye doped SiO2	Lower toxicity. Slightly higher exposure Similar process for both NMs. Changes driven by composition (elimination of Cd).	Similar risk. Reduction in all environmental Impact categories: 5% (Ecotoxicity) to 75% (Ozone Depletion) lower impact per kg of material.
Ag nanowires NANOGAP (Spain)	Photovoltaic panels (Stage 5 Market entry)	Sustainable process	High Ag waste Impact driven by energy demand per Kg AgNF & generated waste Risk of exposure	Change synthesis parameters Automated filtration	Higher process efficiency: contribution to impact categories decrease up to 90%. Reduced exposure but high risk due to the HARN nature of the NM.	Significant improvement in process sustainability
Ag NPs nanoComposix (Czech Republic)	Antibacterial coatings (Stage 3 Prototype)	Safer product (minimum release during use)	Potential consumer exposure to Ag ions	Design solution that limits release of Ag + during use preserving functionality for longer. Selection of low exposure coating method Selection of purification method with low waste Carbon Coating	Low release of Ag + from trolley coating Low exposure: dip coating method High energy consumption	Safer product as release of Ag + during use is insignificant Sustainable product in terms of releases to the environment. Impact due to high electricity consumption & waste generation
Si based NMs NANOMAKERS (France)	Batteries for electric vehicles (Stage 3 Prototype)	Safer NM (lower flammability)	High dustiness High flammability Moderate toxicity	Increase particle size Si@40 nm, Si@C40nm & Si@C75nm	Reduced dustiness Reduced flammability Si@C40nm slightly more toxic Comparable environmental	Considerable lower risk of ATEX for coated NMs. Comparable impact for the three NMs. Higher impact compared to using graphite (without NMs) but better

					impact SEA: High uncertainty in these results due to lack of data	performance A 10% increase in battery capacity did not compensate the extra cost.

CNT: Carbon Nanotubes; CNFs: Carbon Nanofibers; GANF, GAtam, GANFg: Group Antolin CNFs with graphitization degrees of 60, 70 and 90% respectively; HARN: High Aspect Ratio Nanomaterials; NPs: nanoparticles; NMs: nanomaterials; ATEX: Explosive Atmosphere.

Recommendations for use: (eg link to other resources)	*Resource type - Article* *Nano-specificity*
Source : https://doi.org/10.1016/j.impact.2020.100267	**NanoImpact**

SAbyNA RNF/NEPSbD 24	**Silica modification of titania nanoparticles enhances photocatalytic production of reactive oxygen species without increasing toxicity potential in vitro**

Scope / abstract: Titania (TiO_2) nanoparticles were surface modified using silica and citrate to implement a ‘safe-by-design’ approach for managing potential toxicity of titania nanoparticles by controlling surface redox reactivity. DLS and zeta-potential analyses confirmed the surface modification, and electron microscopy and surface area measurements demonstrated nanoscale dimensions of the particles. Electron paramagnetic resonance (EPR) was used to determine the exogenous generation of reactive oxygen species (ROS). All the produced spray dried nanotitania lowered levels of ROS when compared to the corresponding dispersed nanotitania, suggesting that the spray drying process is an appropriate design strategy for the control of nano TiO_2 ROS reactivity. The modification of nanotitania with silica and with citrate resulted in increased levels of ROS generation in exogenous measurements, including photoexcitation for 60 minutes. The dichlorodihydrofluorescein (DCFH) assay of dose-dependent production of oxidative stress, generated by pristine and modified nanotitania in macrophages and alveolar epithelial cells, found no significant change in toxicity originating from the generation of reactive oxygen species. Our findings show that there is no direct correlation between the photocatalytic activity of nanotitania and its oxidative stress-mediated potential toxicity, and it is possible to improve the former, for example adding silica as a modifying agent, without altering the cell redox equilibrium.

NFs chemistry: **TiO_2**	*Mechanism of concern:* ***Surface reactivity***	*Key physico-chemical property for risk:* ***Surface chemistry***	*Safe by design strategy apply:* ***Coating***

Main content: The introduction of silica as coating on TiO_2 enhances the photocatalytic ROS production and decreases oxidative stress. But further confirmations of the data are needed given that the mechanisms are not clear. The SiO_2 coated TiO_2 NPs could be incorporated in final products as paints, coatings, cements, etc.

Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : 10.1039/C8RA07374K	**RSC Advances** – Paper Open access

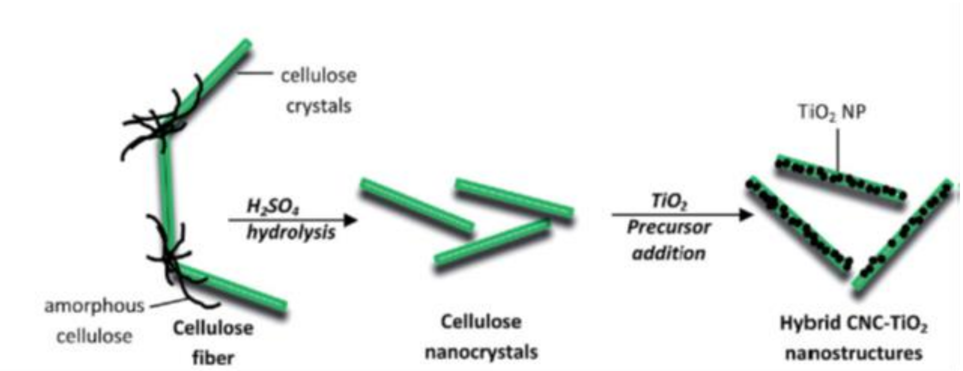
<table>
<tr><td colspan="2">RNF/NEPSbD 39</td><td colspan="2">Characterization of photocatalytic paints: A relationship between the photocatalytic properties-release of nanoparticles and volatile organic compounds</td></tr>
<tr><td colspan="4">Scope / abstract: In the present study, characterization of two paints for indoor and outdoor applications, one containing micro-sized titanium dioxide (TiO_2) particles and the other based on nano-TiO_2, is undertaken in order to understand their environmental impact during the use phase. The photocatalytic efficiency of the paints is determined before and after climatic ageing. The degradation of the paints induced by their ageing is characterized in parallel. Powders, dispersions and paints applied on a substrate are investigated to characterize the state of the nanoparticles (NPs) as a function of their surrounding media. The abrasion of the photocatalytic materials indicates that the presence of TiO_2 (NPs) enhances the organic matrix degradation of the paints due to a greater photocatalytic effect. The online and continuous measurements by PTR-ToF-MS indicate that the degradation of the organic matrix leads to release of organic compounds (formaldehyde, methanol, acetaldehyde and formic acid) into the air which suggests that monitoring only the removal of VOCs (in this case xylene) is not enough to make a proper evaluation of the effectiveness of photocatalytic paints towards VOC elimination. These VOCs emerge exclusively from the degradation of the organic matrix as much lower VOC emissions were measured in the case of the aged paint which exhibits a lower amount of organic components in the matrix. This study links the morphological observations, chemical determination, structural parameters and photocatalytic properties of the paints for future optimization of safer-by-design photocatalytic paints.</td></tr>
<tr><td>NFs chemistry: TiO_2</td><td>Mechanism of concern: Photocatalytic activity</td><td>Key physico-chemical property for risk: Surface reactivity</td><td>Safe by design strategy apply: Modification of organic matrix</td></tr>
<tr><td colspan="4">Main content: The authors declare the possibility of formulating safer-by-design paints, in the future, i.e. less NPs and VOCs releasing paints with the same photocatalytic efficiency. Therefore, the SbD strategy was not applied but only proposed. The suggested SbD strategy, to apply in photocatalytic paint field, could lead to an improvement of safety in terms of exposure but not in term of toxicity.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type
Nano-specificity</td></tr>
<tr><td colspan="2">Source : doi.org/10.1039/C7EN00467B</td><td colspan="2">Environmental Science: Nano</td></tr>
</table>

RNF/NEPSbD 59	**Safer-by-design hybrid nanostructures: an alternative to conventional titanium dioxide UV filters in skin care products**

Scope / abstract: For sustainable development of nanotechnology, nanomaterials should follow a safer-by-design approach so that the associated exposure and hazard risks throughout their entire life cycle can be minimized without compromising their functioning efficiency. In this context, organic–inorganic hybrid nanostructures composed of titanium dioxide (TiO_2) nanoparticles grafted onto cellulose nanocrystals (CNC), using a sol–gel process, were present. After grafting optimization, we show that the overall efficiency of these hybrid nanostructures to filter UV rays can be higher than their conventional counterparts. At the same time, these hybrid nanostructures are proven to stabilize Pickering emulsions, replacing surfactant in formulation. Hence, they may serve as an ideal alternative to the conventionally used inorganic filters and stabilizers in various applications such as skin care products.

NFs chemistry: **TiO_2**	*Mechanism of concern:* ***Reactive oxygen species generation***	*Key physico-chemical property for risk:* ***Surface reactivity***	*Safe by design strategy apply:* ***Support***

Main content: The hybrid nanostructure composed by TiO_2 NPs grafted onto CNC (see Figure) is an alternative to conventional TiO_2 UV filters, reducing the amount of TiO_2 thus reducing the potential toxicity concerns. The hybrid nanostructures showed improved UV absorbance than conventional UV filter and good Pickering emulsion stability, but no toxicological test to evaluate inflammatory responses are reported.



Recommendations for use: (eg link to other resources)	*Resource type* *Nano-specificity*
Source : 10.1039/c7ra02506h	**RSC Advances** – Paper Open access

RNF/NEPSbD New J	**Safer-by-design flame-sprayed silicon dioxide nanoparticles: the role of silanol content on ROS generation, surface activity and cytotoxicity**

<table>
<tr><td colspan="4">Scope / abstract: Surface chemistry, more specifically the surface silanol content, has been identified as an important toxicity modulator for SiO_2 NPs. Here, quantitative relationships between the silanol content on SiO2 NPs, free radical generation and toxicity have been identified, with the purpose of synthesizing safer-by-design fumed silica nanoparticles. The goal is to study the quantitative relationship between the silanol content on SiO2, free radical generation and toxicity.</td></tr>
<tr><td>NFs chemistry: SiO_2</td><td>Mechanism of concern: Surface reactivity</td><td>Key physico-chemical property for risk: Surface chemistry</td><td>Safe by design strategy apply: Surface chemistry</td></tr>
<tr><td colspan="4">Main content: Increasing the silanol content on SiO_2, a lower toxicity was found. The authors demonstrated that it is possible to produce much less toxic SiO_2 NPs by modulating the synthesis conditions influencing the silanol content. However, apart from silanol contents, other factor may also affect SiO_2 toxicity. The usability could be improved through the incorporation in products, in real case use.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Resource type

Nano-specificity</td></tr>
<tr><td colspan="2">Source : doi.org/10.1186/s12989-019-0325-1</td><td colspan="2">Particle and Fibre Toxicology – Paper Open access</td></tr>
</table>

<table>
<tr><td>RNF/NEPSbD 12</td><td>Cytotoxicity of nanomaterials applicable in restoration and conservation</td></tr>
<tr><td colspan="2">Scope / abstract: In this pilot study, we compared the toxic potential of representatives of three of the most common oxide materials applicable in restoration: TiO_2 (standard and purified P25, a mixture of prevailing anatase with rutile crystalline modifications), SiO_2 (bare A200, and R805, R9200 as coated forms of A200), and ZnO. Using two in vitro cytotoxicity assays, WST-1 and LDH, evaluating metabolic activity and cell</td></tr>
</table>

membrane integrity, respectively, we preliminary ranked the tested substances according to their cytotoxic potential, which may be used for their prioritization for further testing and applications. After 24h exposure, a dose-dependent decrease in cell viability was only detected in ZnO NPs and uncoated silica (A200). Hydrophobic coated silicas (R805 and R9200) and TiO_2 NPs (purified and unpurified P25) did not exhibit cytotoxic effects up to the highest tested concentration of 250 µg/mL. Toxicological data related to the physico-chemical characteristics will be applicable in developing both more efficient and safer nano-based products for restoration and conservation.

NFs chemistry: **SiO_2**	*Mechanism of concern:* **Surface reactivity**	*Key physico-chemical property for risk:* **Surface chemistry**	*Safe by design strategy apply:* **Coating**

Main content: In this document the authors work on silica NPs, trying to reduce cytotoxicity of silica NMs. In fact, silanol groups on the surface of bare silica are involved in ROS generation and can cause cytoxicity. The results showed that hydrophobic coating, as $-CH_3(CH_2)_7$ and $-CH_3$, prevents cytoxicity of silica NPs, which may be related to decreased abundance of surface silanol group and reactivity. The main limitation can be associated to the final functional property and application.

Recommendations for use: (eg link to other resources)	*Conference Paper (free)*
Source : ISBN 978-80-87294-89-5	**Nanocon 2018 - Proceedings 10th International Conference on Nanomaterials - Research & Application**

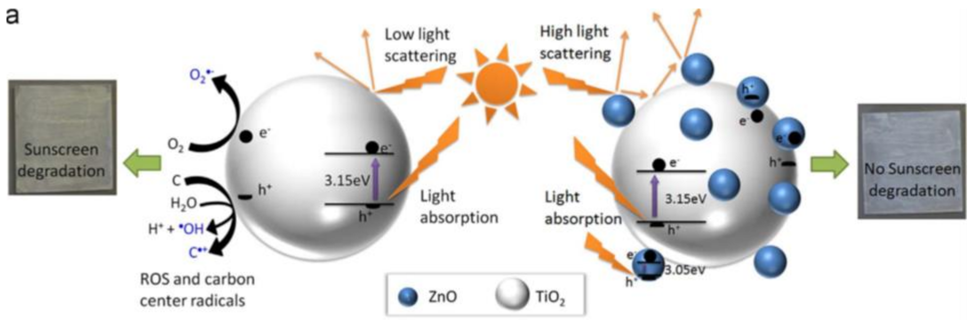
<table>
<tr><td colspan="2">RNF/NEPSbD 22</td><td colspan="2">Nano-engineering safer-by-design nanoparticle based moth-eye mimetic bactericidal and cyto-compatible polymer surfaces</td></tr>
<tr><td colspan="4">Scope / abstract: Nanotechnology provides a new design paradigm for alternative antibacterial strategies in the fight against drug-resistant bacteria. In this paper, the enhanced bactericidal action of moth-eye nanocomposite surfaces with a collaborative nanoparticle functional and topography structural mode of action is reported. The moth-eye nanocomposite surfaces are fabricated in combined processing steps of nanoparticle coating and surface nanoimprinting enabling the production of safer-by-design nanoparticle based antibacterial materials whereby the nanoparticle load is minimized whilst bactericidal efficiency is improved. The broad antibacterial activity of the nanocomposite moth-eye topographies is demonstrated against Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli and Pseudomonas aeruginosa as model bacteria. The antibacterial performance of the moth-eye nanocomposite topographies is notably improved over that of the neat moth-eye surfaces with bacteria inhibition efficiencies up to 90%. Concurrently, the moth-eye nanocomposite topographies show a noncytotoxic behaviour allowing for the normal attachment and proliferation of human keratinocytes.</td></tr>
<tr><td>NFs chemistry: TiO_2 and ZnO</td><td>Mechanism of concern: Reactive oxygen species generation</td><td>Key physico-chemical property for risk: Surface reactivity</td><td>Safe by design strategy apply: NFs content</td></tr>
<tr><td colspan="4">Main content: The authors in this work described the nanoimprinting method to fabricate moth-eye mimetic antibacterial nanocomposite. The author described the remarkable bactericidal activity against Gram-positive and Gram-negative of nanocomposites with TiO_2 and ZnO NPs, obtained reducing the amount of NPs by nanoimprinting, and underlined the good cytocompatibility of these nanoenabled products. Using PMMA as support the author reduced the NPs amount needed to have antibacterial activity and producing no cytotoxic products. Lack of information regarding the mechanical properties of this new products and real cases of application. More accurate test in other relevant media are required.</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Article (no open access)</td></tr>
<tr><td colspan="2">Source : 10.1039/c8ra03403f</td><td colspan="2">RSC Advances</td></tr>
</table>

RNF/NEPSbD 23	Hierarchical nano ZnO-micro TiO_2 composites: High UV protection yield lowering photodegradation in sunscreens

Scope / abstract: TiO_2 is a commonly used semiconductor photocatalyst but, as a paradox, it is also widely used as UV filter in sunscreens. Moreover, its capacity to form free radicals under UV irradiation generates reactive free radicals that provoke sunscreens degradation. In this work a hierarchical composite made of ZnO nanoparticles anchored onto TiO_2 microparticles is developed in a safe-by-design way by using the sol-gel method. The aim of this composite is to gain the advantages of inorganic nanoparticles avoiding their potential drawbacks. The hierarchical composite presents higher UV absorption than the pure TiO_2 or ZnO counterparts. The functional stability study on standard sunscreen reveals a 50% high Solar Protection Factor (SPF) values over time for the hierarchical composite lowering the photodegradation of the formulation. Under authors' knowledge, it is the first time that the combination of these oxides increases the UV attenuation as inhibits the negative effects of free radicals. The high UV absorption without degradation opens a new orientation for the effective use of UV-absorbers without the photocatalyst adverse effects. The results in sunscreens generate a proposed mechanism of functionality that explains the observed differences on the efficiency of photocatalytic activity of these materials for other application fields.

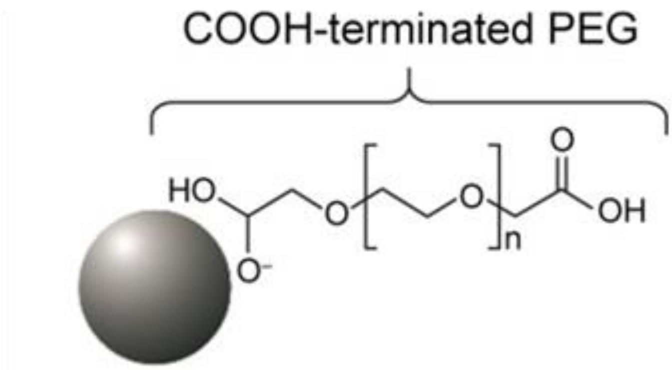
NFs chemistry: **TiO_2 and ZnO**	*Mechanism of concern:* **Reactive oxygen species generation**	*Key physico-chemical property for risk:* **Surface reactivity**	*Safe by design strategy apply:* **Support**

Main content: In this document the authors developed a hierarchical composite made of ZnO nanoparticles anchored onto TiO_2 microparticles. The composite presented higher UV adsorption and higher SPF value, and a reduced photocatalytic adverse effect. The results showed a reduction in free radicals' production, a higher SPF values and a more photostable UV filter with a reduced release of ZnO NPs. However, the strategy can be applicable only to photocatalytic NFs. Limited information about NPs release in relevant media, as sea water and synthetic sweat, that mimic the real exposure conditions.



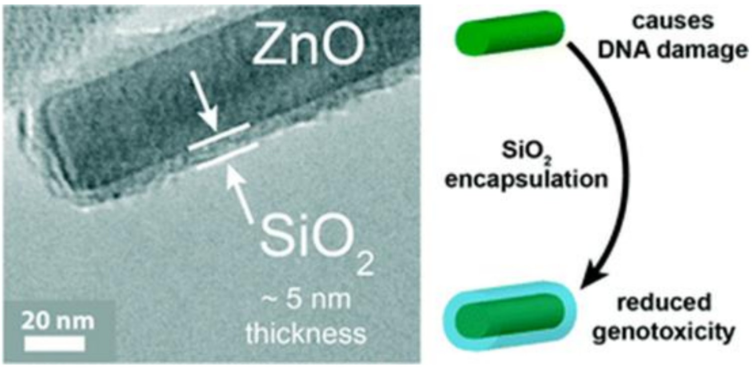
Recommendations for use: (eg link to other resources)	*Article (no open access)*
Source : 10.1016/j.ceramint.2017.11.028	**Ceramics International**

<table>
<tr><td colspan="2">RNF/NEPSbD 44</td><td colspan="2">Targeted polyethylene glycol gold nanoparticles for the treatment of pancreatic cancer: From synthesis to proof-of-concept in vitro studies</td></tr>
<tr><td colspan="4">Scope / abstract: The main objective of this study was to optimize and characterize a drug delivery carrier for doxorubicin, intended to be intravenously administered, capable of improving the therapeutic index of the chemotherapeutic agent itself, and aimed at the treatment of pancreatic cancer. In light of this goal, we report a robust one-step method for the synthesis of dicarboxylic acid-terminated polyethylene glycol (PEG)-gold nanoparticles (AuNPs) and doxorubicin-loaded PEG-AuNPs, and their further antibody targeting (anti-Kv11.1 polyclonal antibody [pAb]). In in vitro proof-of-concept studies, we evaluated the influence of the nanocarrier and of the active targeting functionality on the anti-tumor efficacy of doxorubicin, with respect to its half-maximal effective concentration (EC50) and drug-triggered changes in the cell cycle. Our results demonstrated that the therapeutic efficacy of doxorubicin was positively influenced not only by the active targeting exploited through anti-Kv11.1-pAb but also by the drug coupling with a nanometer-sized delivery system, which indeed resulted in a 30-fold decrease of doxorubicin EC50, cell cycle blockage, and drug localization in the cell nuclei. The cell internalization pathway was strongly influenced by the active targeting of the Kv11.1 subunit of the human Ether-à-go-go related gene 1 (hERG1) channel aberrantly expressed on the membrane of pancreatic cancer cells. Targeted PEG-AuNPs were translocated into the lysosomes and were associated to an increased lysosomal function in PANC-1 cells. Additionally, doxorubicin release into an aqueous environment was almost negligible after 7 days, suggesting that drug release from PEG-AuNPs was triggered by enzymatic activity. Although preliminary, data gathered from this study have considerable potential in the application of safe-by-design nano-enabled drug-delivery systems (ie, nanomedicines) for the treatment of pancreatic cancer, a disease with a poor prognosis and one of the main current burdens of today's health care bill of industrialized countries.</td></tr>
<tr><td>NFs chemistry: Au</td><td>Mechanism of concern:</td><td>Key physico-chemical property for risk:</td><td>Safe by design strategy apply: Coating</td></tr>
<tr><td colspan="4">Main content: The study shows the applicability of a developed framework of nano-carrier of anti-cancer drugs. The method is developed for Au, but it can be extended-PEG coating minimize toxicity, in addition the use of a PEG coaing is cheap. Not clear the long-term stability of PEG coating-OK for short times (<1 2 days).



AuPEG 1</td></tr>
<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Article (open access)</td></tr>
<tr><td colspan="2">Source : 10.2147/IJN.S97476</td><td colspan="2">International Journal of Nanomedicine</td></tr>
</table>

<table>
<tr><td colspan="2">RNF/NEPSbD 64</td><td colspan="3">Influence of paints formulations on nanoparticles release during their life cycle</td></tr>
<tr><td colspan="5">Scope / abstract: The purpose of this study was to identify the parameters of the paint formulation containing SiO_2 NPs of 19-nm diameter that could have an impact on the release induced by aging and abrasion. In order to simulate outdoor aging during the life cycle of the product, painted panels were exposed to accelerated weathering experiments in accordance with the norm EN ISO 16474-3:2013. The surface modification of these paints was characterized by scanning electron microscope coupled with energy dispersive spectrometry (SEM-EDS). These analyses showed that the acrylic copolymer binder has undergone a more significant chemical degradation compared with the styrene-acrylic copolymer. To simulate a mechanical aging, abrasion tests were conducted using a Taber Abraser, simulating critical scenarios of the abrasion standard. The particle size distributions and particle concentrations of the abraded particles were measured using an electric low-pressure impactor. After accelerated aging and abrasion tests, we observed a link between the paint degradations occurring with the release of pristine NPs and the embedded pristine NPs. Surface degradation of acrylic copolymer paints was more significant than that of the styrene-acrylic copolymer paints, and this induced a release of NPs 2.7 times higher. Other parameters like TiO_2 addition as pigments induced a strong stability of paint against light and water, decreasing the total number of NPs released from paints from 30,000 to 1200 particles/cm^3. These results revealed that formulations can be tuned to decrease the number of free NPs released and get a “safe-by-design” product.</td></tr>
<tr><td>NFs chemistry: SiO_2</td><td>Mechanism of concern:
Affinity to aquatic and terrestrial organisms</td><td colspan="2">Key physico-chemical property for risk:</td><td>Safe by design strategy apply: Matrix composition</td></tr>
<tr><td colspan="5">Main content: In this study the authors improved water repellence and scratch resistance of paints containing silica NPs. Using this SbD method, the authors minimized the exposure to paint and paint’s residuals. Safer paints formulations on nanoparticles helps to study the release during the paint life cycle. The paint matrix was modified using styrene-acrylic copolymer instead of acrylic copolymer. The pigments addition of TiO_2 was applied to improve matrix stability when exposed to UV light. The results shows that the SbD method limits the paint degradation and subsequent NPs release.</td></tr>
<tr><td colspan="3">Recommendations for use: (eg link to other resources)</td><td colspan="2">Article (open access)</td></tr>
<tr><td colspan="3">Source : 10.1007/s11051-015-2962-0</td><td colspan="2">J. Nanoparticle Res.</td></tr>
</table>

<table>
<tr><td colspan="2">RNF/NEPSbD 49</td><td colspan="2">Engineering safer-by-design silica-coated ZnO nanorods with reduced DNA damage potential</td></tr>
<tr><td colspan="4">Scope / abstract: Zinc oxide (ZnO) nanoparticles absorb UV light efficiently while remaining transparent in the visible light spectrum rendering them attractive in cosmetics and polymer films. Their broad use, however, raises concerns regarding potential environmental health risks and it has been shown that ZnO nanoparticles can induce significant DNA damage and cytotoxicity. Even though research on ZnO nanoparticle synthesis has made great progress, efforts on developing safer ZnO nanoparticles that can maintain their inherent optoelectronic properties while exhibiting minimal toxicity are limited. Here, a safer-by-design concept was pursued by hermetically encapsulating ZnO nanorods in a biologically inert, nanothin amorphous SiO_2 coating during their gas-phase synthesis. It is demonstrated that the SiO_2 nanothin layer hermetically encapsulates the core ZnO nanorods without altering their optoelectronic properties. Furthermore, the effect of SiO_2 on the toxicological profile of the core ZnO nanorods was assessed using the Nano-Cometchip assay by monitoring DNA damage at a cellular level using human lymphoblastoid cells (TK6). Results indicate significantly lower DNA damage (>3 times) for the SiO_2-coated ZnO nanorods compared to uncoated ones. Such an industry-relevant, scalable, safer-by-design formulation of nanostructured materials can liberate their employment in nano-enabled products and minimize risks to the environment and human health.</td></tr>
<tr><td>NFs chemistry: ZnO</td><td>Mechanism of concern:
Surface reactivity</td><td>Key physico-chemical property for risk: Surface reactivity</td><td>Safe by design strategy apply: Coating</td></tr>
<tr><td colspan="4">Main content: The method is well described and the reduction of toxicity, due to SiO_2-coated ZnO nanorods, is well documented. The process (flame spray pyrolisis) is already used for mass production of NF, therefore the process could be up-scaled.

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<tr><td colspan="2">Recommendations for use: (eg link to other resources)</td><td colspan="2">Article (no open access)</td></tr>
<tr><td colspan="2">Source : 10.1039/c3en00062a</td><td colspan="2">Environmental Science: Nano</td></tr>
</table>