The SERENADE project; a step forward in the safe by design process of nanomaterials: The benefits of a diverse and interdisciplinary approach

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Abstract: Developing safe nanomaterials has become a major concern in all the industry sectors using advanced materials. However, there are very few initiatives addressing this issue. The SERENADE project, with its long-term funding scheme, provided a unique opportunity to foster a coordinated, yet diverse approach to investigate the safe-by-design

development of nanomaterials in a variety of application fields, using a targeted set of inter-disciplinary case studies. The originality of the approach was to cover as many multiple technology readiness levels (TRLs) and life cycle stages as possible, combined with shared hazard and end-of-life assessments in an effort towards a (more) comprehensive and resource driven research.

1. The necessity of more comprehensive research activities

Although nanotechnology and its founding principles can be traced back as far as Richard Feynman's speech in 1959, general awareness of the benefits as well as possible associated risks spans only over the past 1½-2 decades. This is best documented by the rapid rise in the number of nano related publications (on average, an annual increase of ca. 15% over the past 20 years) to reach now a rate of one paper every 2.5 minutes (see e.g. [1]). Concerns regarding nanotechnologies triggered the launch of several large research initiatives, such as the US National Nanotechnology Initiative (NNI) or Europe's Nano Safety Cluster (NSC), but also national project such as the French consortium specifically dedicated to examine the Safe by Design (SbD). This project called "Safe(r) Ecodesign Research and Education applied to NAnomaterial DEvelopment", or SERENADE, which started in 2012 for a total duration of 9 years.

Although there are many definitions of SbD, the general underlying concept is to minimize EHS (environment, health and safety) concerns by taking adequate measures early in the development of a product to control exposure and hazard, and thus risk (see e.g.[2]) For the purposes of the present article, SbD refers essentially on its technical aspects, and includes the terms Safe- and Safer- by Design. Recent efforts, e.g. the European projects Gov4Nano, Nanorigo and Riskgone, include the SbD process as a main component in risk governance issues.[3-5] Key governance issues such as stakeholder interactions, ethics, general acceptance and regulation, are highly dependent on the cultural and geographical context; consequently these aspects have not been considered in the present work.

The general structure and strategy of SERENADE has been described in detail previously.[6] Briefly, the research activities centered around environmental- and human exposure reduction, biocompliance, end of life and risk modeling fed into the central safe nanomaterial design objective (Fig 1). In this work, the term biocompliance is used to include applications with targeted toxicity for which "hazard reduction" would be inaccurate. More recent reports dealing with the organization of the SbD process[7] show strong resemblance with the general SERENADE scheme, with the notable difference that risk, its hazard and exposure components, and SbD appear as separate entities feeding into a larger nanosafety loop. The approach addressing technical issues within SERENADE shows also clear similarities with the five "S.A.F.E.R" (S: surface, structure; A: alternate material, F: Functionalization, E: encapsulation; R: reduce quantity) principles proposed earlier.[8]

Since in the initial research efforts within SERENADE, the contribution of the four research fields to the overall SbD objective was unevenly distributed (in particular, a marked predominance of biocompliance related research), a more balanced approach of the SbD process has been implemented in the form of case studies. This strategy was later on also followed by the EU Horizon2020 project Nanoreg 2, focusing on SbD nanomaterials and including this concept to the innovation chain[9, 10]

2. The implementation of a coordinated case study strategy

To adhere to the full concept of SbD, the case studies within our project needed to meet different criteria as closely as possible:

1) addressing the entire life cycle and thus different Technology Readiness Levels (TRLs), i.e. examining processes and mechanisms from the early stages of formulation to the end-of-life/disposal. The link between life cycle and TRL is that, *a priori*, materials examined at the use- and end-of-life phases are at a more advanced development stage than those at the earlier life cycle phases (e.g. formulation).

2) staying close to reality, i.e. the objects chosen for the case studies need to have an actual economic relevance, viz. being (or being included in) products that are on the market or will be on the market in a foreseeable future. This excludes "model" nanomaterials which, although being (or having been) extensively studied, have little or no commercial applications. It can be noted that this market relevance is the only non-technical aspect of the selection criteria.

3) favoring a complete risk assessment, i.e. having a balanced focus on hazard and exposure. In other words, interdisciplinarity was a pressing requirement.

4) reflecting the actual variety of nanomaterials. This differs from criterion #2 above in so far as the focus is on addressing the chemical and structural diversity of available materials

rather than market shares. Also, this criterion is not related to typical grouping and/or read-across efforts which obey different rules (see e.g. the EU Horizon 2020 project Gracious, NanoHarmony), which tend to reduce diversity.

From criterion #4, it is evident that no single case study could meet all criteria. The objective became to select/define a set of case studies, which collectively address the four criteria mentioned above. The outcome of this process was the launch of 5 case studies examining paint, cosmetics (sunscreens), food packaging, Ag nanowires and quantum dots (QDs). Figure 2 and Table 1 display their relevance to the 4 selection criteria. The detailed contents will not be presented here since the results are reported elsewhere. [11-27].

The balanced hazard-exposure approach in criterion #3 appears under-represented (Fig 2, Table 1). As a matter of fact, exposure was examined with specific protocols according to the targeted application and the diverse nature of the nanomaterials in the different case studies. For example, while mechanical aging (abrasion, drilling) was a basic exposure assessment for paint,[12, 28] this was of course not an issue for sunscreens.[28] As opposed to exposure assessment, basic hazard assessment was not material- or application dependent. As a consequence, instead of conducting a separate toxicity characterization in each case study, the hazard assessment was handled in an action shared among all other case studies, and only specific biological targets were examined within the individual case studies. The obvious benefit of this process is that the same groups using the same experimental protocols performed the toxicity assessment. The results obtained with this approach are particularly valuable, since they are directly comparable across the set of case studies. To the best of our knowledge, this was the first time that this shared hazard characterization has been applied to a set of case studies examining nanomaterials along the life cycle. The EU H2020 project Nanoreg 2 also launched a series of case studies without however implementing the shared hazard assessment approach developed here.[10]

Following the same strategy, the assessment of the end-of-life stage of the life cycle has also been a shared effort. The approach consisted in examining the behavior of nanomaterials in a wastewater treatment context. Indeed, for many nanomaterials reaching the end of the use phase, the "sink" are the sewer and storm-drainage systems. Ideally, these systems lead to a wastewater treatment plant (WWTP). The nanomaterials entering a WWTP differ greatly in terms of aging/degradation; i.e. short-lived nanomaterials without significant modification (e.g. cosmetics), to compounds exposed to years of weathering (e.g. paint). While the nanomaterials themselves and their degradation stages show a large variety, the waste water treatment technologies do not. Therefore, just as for the base toxicity assessment, the behavior of nanomaterials in a WWTP has been shared with defined equipment and protocols to ensure comparability of the results and to save resources.

The common point of all the case studies was reducing the risk by addressing the hazard and/or the exposure. Unfortunately, none of the case studies in this project could formally address risk modeling. Conventional hazard reduction strategies were tested in the different case studies (Table 1). In our set of case studies, adapting the surface properties was the most popular solution to address the hazard. It is noteworthy that none of the present studies investigated hazard reduction by changing the mineralogy of the material. Similarly, among the usual exposure reduction design strategies, limiting the release, e.g. a more efficient embedding into a matrix, was the preferred approach. Interestingly, reducing the quantity of nanomaterials within a product, which is one of the easiest safety measures to implement from a technical point of view, has formally been addressed only for the paint and cosmetics studies, i.e. for products at a higher TRL.

3. Re-designing the design of safe(r) nanomaterials ?

Clearly, there is no single SbD approach for nanomaterials that supersedes all others. Recently, *in-silico* approaches (e.g. QSAR, machine learning, databases) offer promising alternatives/additions to an experiment based SbD (see e.g.[29, 30] and the projects such as NanoCommons, NanoInformatiX, CEINT-NIKC), but still need further development. The increasingly popular case study strategy used here needs to account for actual technical, practical problems or imperatives during the manufacturing, the use or the disposal of the nanomaterials/product, that are often overlooked in most "regular" academic projects. This solution, which includes market relevance, needs to be handled with some caution. From the above examples, it is evident that "case study" needs to be thought of in the plural. A case study investigating a given product/material can only address a limited number of the typical hazard- and exposure reduction SbD strategies (Table 1). To have an entry for each strategy, it is therefore necessary to conduct a set of case studies since hazard and exposure reduction strategies depend on the material as well as its application. Selecting case studies in order to cover most or all of the general hazard and exposure measures is necessarily a coordinated process. The result is a set of case studies examining a diversity of materials and products. It is important that this diversity lies not only in the nature or texture of the nanomaterial, but also that in the life cycle coverage (Fig. 3) since some concerns/ problems become more pressing as the TRL increases (see e.g. "quantity" in Table 1).

Even within a given hazard or exposure reduction measure, diversity is important. Indeed, the implementation of these measures can take several forms depending on the material and its intended use. For example, limiting the release is approached differently whether sunscreens or self-cleaning paints and stains are considered: in the case of sunscreens, release *per se* is unavoidable, therefore the strategy to avoid exposure to the potentially harmful TiO_2 nanomaterial is to apply a protective coating with a durability extending far beyond the intended use to protect not only the customer, but also the environmental media these cosmetics are released to. At the opposite, in self-cleaning paint, the same TiO_2 compound is used for its photocatalytic properties. Consequently, applying a coating would be detrimental to the desired property, and exposure reduction then focuses on strong attachment to a weathering- and TiO_2 resistant matrix.

Promoting diversity to cover as many hazard and exposure limiting strategies as possible, might convey a false sense for scattered research efforts. As a matter of fact, to be relevant, diverse cannot be equated with scattered, since this would be incompatible with the need for a coordinated process. The basic toxicity and end-of-life evaluations implemented within the SERENADE case studies initiative demonstrates the strong appeal of shared efforts. Beyond the obvious benefits of sharing human and financial resources, this approach also increases the relevance of the thus generated data. While funding agencies worldwide promote harmonized testing, these efforts essentially rest on Standard Operating Procedures (SOPs) defined within individual projects. Unfortunately, despite the multiplicity of projects dedicated to establishing harmonized methods (and the quasi-unavoidable duplication of efforts), these initiatives have not yet produced a solid set of broadly accepted methods. This is still an important step forward, since formalized CEN or ISO standards or OECD guidelines (which are largely based on the projects mentioned above) are the result of much lengthier processes. Nevertheless, even well-conceived SOPs need to allow for some flexibility (especially regarding required instrumentation) to increase their acceptance. The resulting quasi-unavoidable intra-SOP variability is of course detrimental to intercomparability. The approach developed within the SERENADE project initiated a significant change with its shared base toxicity assessment: since the same operators used the same procedures with the same instrumentation, there is no comparability issue regarding the results. Of course, this approach deserves to be extended beyond the assessment of basic hazard and end-of-life indicators, i.e. any opportunity characterization sharing should be seized to overcome any differences/ in operational procedures.

As indicated above, the research developed in the SERENADE was not meant to support grouping efforts which are mostly based on material characteristics and properties.[31, 32] Nevertheless, by covering several application types (e.g. paints and stains, food packaging…), the results of the SERENADE case studies may open the road for an alternative kind of categorization. Products within a given application will undergo similar or identical exposure and hazard testing. For example, lip-gloss and sunscreens, although different in chemical nature, have the same aging/release mechanisms potentially affecting the same biota, and therefore should be tested with the same experimental protocols. In this context, diversifying the products tested in a given application type is actually an asset, since trends identified with compounds of varied nature could be indicative of risk linked to a specific type of use rather than the type of material. Of course, the findings of the SERENADE case studies do not permit such a generalization on their own but they fit within this type of extrapolation of results.

From the above, it is tempting to advocate in favor of a multiplicity of case studies. Obviously, things are not that straightforward: just as too few case studies may leave important hazard and exposure options unaddressed, too many case studies may also work against efficiency. Intuitively, multiplying case studies bears the risk of duplicating efforts and overloading shared characterizations efforts, likely to eliminate the benefits of the uniqueness of a unified operator-protocol-instrumentation approach. As often, it becomes a matter of compromise: current and future projects dedicated to the SbD of nanomaterials need to focus on a balance between comprehensiveness, i.e. covering a variety of situations, and efficiency, i.e. focusing on key parameters while avoiding duplicating efforts. From a practical point of view, this obviously calls for careful coordination. In this context, the size of the consortium also becomes a factor. Indeed, too few participants might not cover the range of expertise needed to comprehensively cover all aspects of hazard and exposure reduction strategies; an extended consortium comes with tougher coordination issues.

Finally, the benefits of our approach extended beyond the strictly scientific and technical aspect of the SbD process. Indeed, the presence of academia in the consortium resulted in a strong involvement of graduate and postgraduate students in the case studies. Beyond acquiring new skills, the dynamics created by coordinated SbD actions promoted interdisciplinary interactions between students across the entire set of case studies of the

SERENADE project. This momentum was translated to a more formal educational initiative in the form of an annual workshop integrated in a pre-existing graduate curriculum. This workshop addressed four key issues: i) the concept of SbD itself and its implications in an interdisciplinary context for developing safe(r) nanomaterials, ii) the risk assessment, i.e. properly addressing hazard and exposure issues, and how this evolves during the life cycle, iii) the implementation of an SbD approach, i.e. analytical/technical challenges and solutions in an interdisciplinary space, iv) an introduction to the societal and economical aspects i.e. acceptance of nanotechnologies by the general public in different cultural and geographical contexts, and the challenges faced by the corporate sector to engage into the development of nanomaterials in an ill-defined regulatory context.

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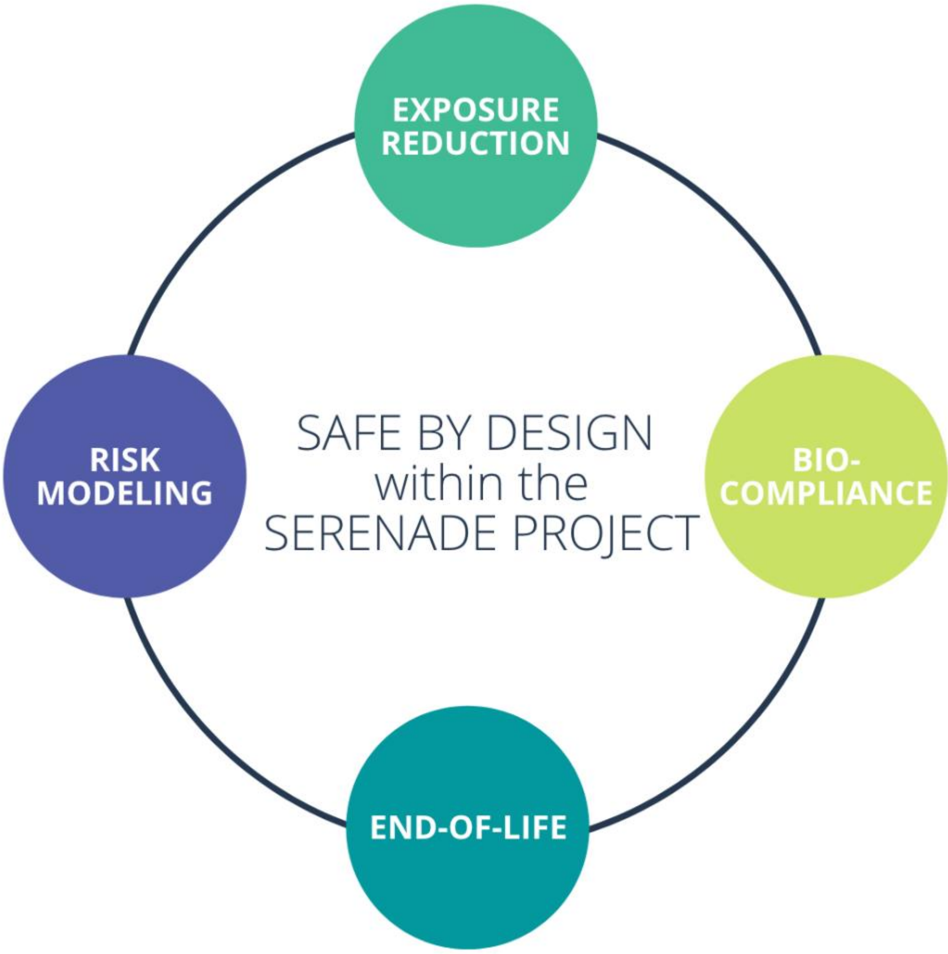

Fig 1: Overall organization of the SERENADE project

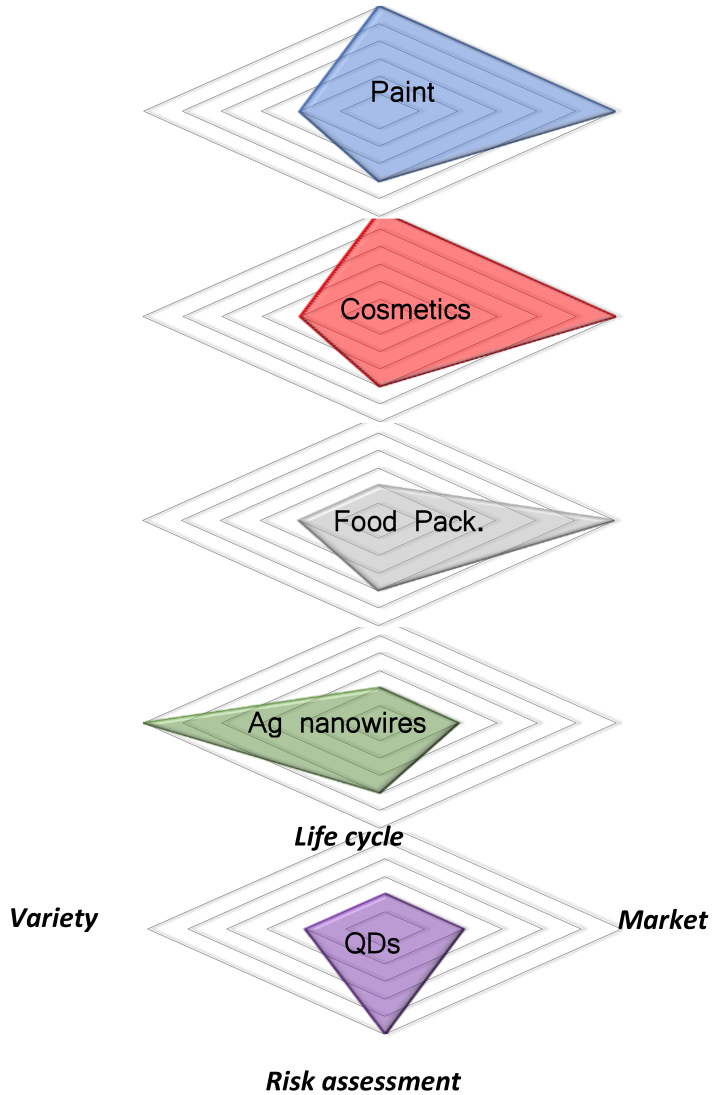

Fig 2: Case studies within the SERENADE project and their relevance to the four selection criteria

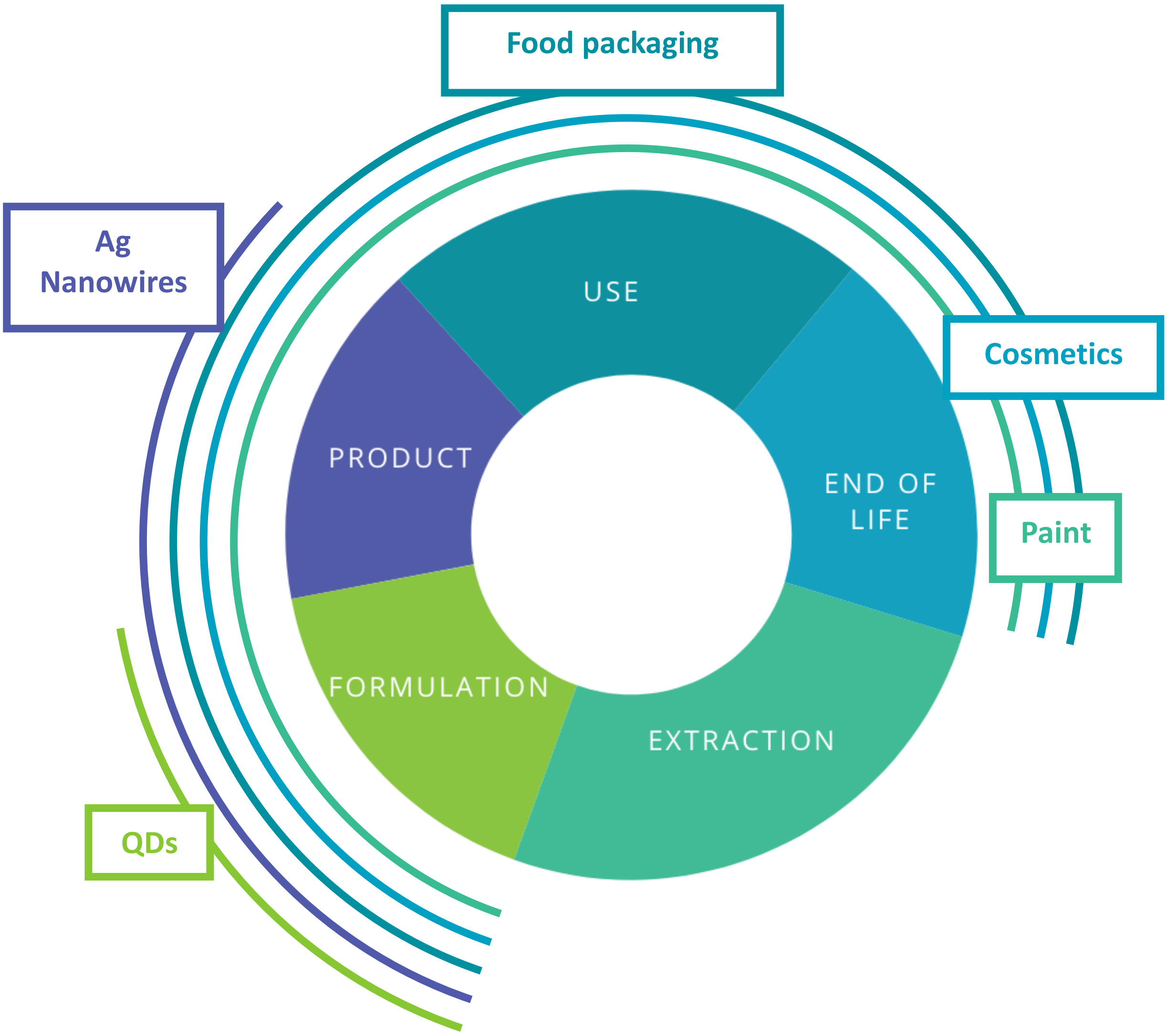

Fig 3: Life cycle coverage of the case studies

Table 1

		Paint	Ag nanowires	Food packaging	Cosmetics	QDs
Hazard reduction	Material substitution			x		x
	Mineralogy					
	Surface properties	x	x		x	x
	Size/texture optimization		x		x	
Exposure reduction	Dissolution rate (biodegradability)		x			
	Preventing the release	x		x	x	x
	Quantity	x			x	

Table 1: Hazard and exposure strategies applied in the case studies

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