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The SERENADE project - a step forward in the Safe by Design process of nanomaterials: Moving towards a product-oriented approach

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Abstract: Recent research efforts have gone into formalizing and standardizing the Safe by Design process of nanomaterials. This usually results in a structured and (most often) sequential approach deliberately putting the focus on hazard and exposure issues regarding the nanomaterial itself in a bottom-up progression of material development. However, this general strategy lacks flexibility. Within the project SERENADE, a case study examining photocatalytic paint failed to validate the generally accepted Safe by Design scheme. This example examined the product (paint in this case) rather than the nanomaterials it contains. It was found that the essential parameters, namely product specification and functionality, failed to fit into a rigid bottom up approach and indicated the need for alternative Safe by Design strategies.

Focusing on the nanomaterial (NM): available tools and their benefits

A lot of attention has been paid to the Safe(r) by Design (SbD) approach applied to nanomaterials. Some of this research has been part of- or the primary focus of European Union (EU) funded projects, such as Nanoreg and Nanoreg 2 and, more recently, the EU projects targeting nano SbD research Asina, SbD4Nano, Sabydoma and Sabyna. A more comprehensive and detailed view of the nano-related projects can be found on the website of the EU Nano Safety Cluster. [Nanosafety-Cluster, #91] This large deployment of efforts is, in part, an answer to concerns regarding a technology sector for which the risk assessment is still in progress and the regulatory framework is sketchy at best. The strategy is clearly to address safety issues as early as possible in the R&D process to avoid problems further down the value chain.

SbD is a concept that existed well before nano-related concerns have been reported. The most notable example is probably the pharmaceutical industry, where SbD is a long-established cornerstone of drug development. Considering that an estimated one third of the drugs not-passing clinical trials do so because of safety issues,² even a modest reduction in the number of tested molecules would represent substantial savings in a traditionally costly approval process [³]

Since nano-safety concerns have focused on human health, similar to the pharmaceutical industry, it has been suggested that the same tools could be applied to nanomaterials
However, in contrast with the pharmaceutical industry, nanotechnologies cover a much wider range of application fields, thus requiring a more diversified approach. For instance, nanomaterials only represent an ingredient or a component of the overall product and their long-term stability will depend on the nano-matrix interactions. Exposure to nanomaterials should be controlled through encapsulation, use of embedding matrix or of core-shell structure to limit contact and potential release to workers, consumers and the environment.

A popular SbD approach is the stage-gate model that was developed by industry in the 1980s and has recently been reformalized [5-7]. It consist of a linear process that breaks down the development of a new product into a series of phases, separated by gates that are crossed when the requirements of the preceding stage are met. In recent years, this general concept has been translated into nano-SbD, in part leaning on the work developed in EU projects [8-11]. In this linear stage-gate process, the nanomaterial itself is and remains the primary focus throughout the entire decision-making (and thus, development) process. Indeed, failures to progress beyond the iterative development at stage #n can be resolved by corrective measures at stage #n-1, while #n-2 and preceding stages are assumed to be sound. The obvious benefit of this SbD strategy is that flaws in the development of nanomaterials prevent progression to the next stage and only materials passing the sequential validation process are considered for production and commercialization.

Nano SbD can also be considered under the three-pillar approach, known as Safe Product-Safe Use-Safe Production. [12] Within this concept, the three pillars are informed at each gate of the stage-gate model. It should be noted here that, since the three pillars are derived from the stage-gate model, the nanomaterial remains the central focus in this SbD process. The most obvious appeal of the pillar approach, in comparison with the stage-gate model, is that the life cycle of the nanomaterial and worker safety are explicitly addressed (Safe Use and Safe Production). However, while the stage-gate model has an easy-to-follow decision-making process, the general material validation within the three-pillar approach is less obvious.

The French project SERENADE, specifically dedicated to nanomaterial SbD, funded a series of coordinated interdisciplinary case studies sharing resources for toxicity assessments. [13] There were some difficulties that revealed inadequacies of the stage-gate- and the three pillar- approaches to address the SbD of nanomaterials properly. It should be noted here that the present work will examine only technical aspects of the SbD validation process. More general nanosafety concepts such as nano-risk governance (which includes for instance public and stakeholder perception), are not addressed here (see reference [13] for more details). Also, the examination of these technical aspects is outside the coordination strategy of a set of case studies, as it regards the process within a single case study, i.e. a given material or product.

Limitations of current Safe(r) by Design models

At initial technology readiness levels (TRLs), virtually any SbD-driven product development de facto follows a process that strictly is (or resembles) the stage-gate process whether intentionally or not. Indeed, at this stage, the three-pillar model cannot be implemented, since safe use cannot be assessed yet. The first synthesis and formulation steps easily accommodate the linear "trial and error" process of the stage gate model. For example, at the earliest stages of development, it is easy to modify size and shape or even the nature of a nanoparticle, or to correct the coating or embedding procedure... Indeed, such design adaptations mostly necessitate switching back and forth between adjacent stage-gates. When done early, this process is in general easy to implement from a technical point of view, and should not be an unacceptable financial burden. In fact, high throughput screening, inspired by pharmaceutical SbD, where the goal is to limit the number of molecules entering costly clinical
trials to a minimum, is sometimes recommended for the development of nanomaterials, although, except for biomedical applications, the stakes are vastly different.

One of the SERENADE case studies examining the SbD of photocatalytic paint, benefited from the support of French paint manufacturer Allios. This support went well beyond a silent observation of the work and its implicit endorsement. The industrial partner participated actively in the experimentation and discussions resulting in one of the most complete case studies in terms of life cycle coverage and advanced development stage. Indeed, the products tested were actual paint formulations prepared by the manufacturer. The linear bottom-up approach of the stage-gate model was followed since the process aimed at adapting existing solutions to address a niche market. Regarding the three-pillar model, the requirements were a priori met: the Safe Production pillar leaned on the experience of the manufacturer in formulating paint, including the handling of (nano-) powders, which ranks high in terms of potentially hazardous production steps. The Safe Product and Safe Use pillars, although not validated at that point, were not a severe concern since paint, and especially indoor paint, is usually not considered as a high risk product. In a first approximation, release of nanomaterials from the paint matrix might be an obstacle for validating the Safe Use pillar since aging can cause measurable release. In fact, releases from the paints as a result of weathering and mechanical aging (e.g. sanding during building renovation) were determined as part of the paint case study to address this concern.

Another important part of this study was to test a range of TiO₂ concentrations within the product for optimal results. In a first approximation, the higher the TiO₂ concentration, the more efficient the photodegradation process. However, high TiO₂ content also translates to high levels of harmful volatile organic compounds (VOCs) released from the paint, indicating that optimizing the amount of photocatalytic agent is not a straightforward process in terms of product safety. This strategy was an iterative process, modifying the amount of TiO₂ in the paint with subsequent measurement of the effects to find the best compromise, without challenging the core formulation of the paint. In parallel, it was demonstrated that the paint can have reduced photocatalytic performance after aging as a result of degradation of the paint matrix through photocatalysis and the subsequent accelerated loss of TiO₂. This matrix degradation was predictable to a certain extent, and has been observed before with less photocatalytic compounds. However, the implicit adherence to the stage-gate model (in part because it leans on a series of "certainties") delayed the in-depth re-design of the paint with a matrix capable of withstanding photocatalysis. Stage-gate and three-pillar models failed to lead to a viable product. Indeed, the stage-gate model with its sequential progression scheme led to an aggravation of the situation, since intuition-guided modifications to enhance performance (i.e. the adjustment of TiO₂ concentration to limit the production of harmful VOCs) did not address degradation of the matrix and, thus, the release of TiO₂. This shows that the stage-gate process is ill-adapted to handle the present paint development example since it turned out that an effective SbD was required to backtrack over multiple stage-gates, thus de facto invalidating the sequential validation process.

Product oriented approach

This case study raises the question of how the SbD of nanomaterials should be approached in practice. The stage-gate model has a definite appeal in the earliest development stages. Indeed, inadequate material choices for a targeted application will not pass the validation process. This is also the point when a stage-gate-compliant high-throughput screening can be implemented. As the product development progresses, the three-pillar approach, which leans...
on the stage-gate model, adds an operational dimension by explicitly examining worker and consumer safety.

Unfortunately, the paint case study reveals that the strict progression scheme, which is undeniably a strength of the stage-gate model for early stage design steps, becomes less effective at later development stages. The reason for the limitations of the model is its lack of flexibility; indeed, at an "advanced" development level, the validation of earlier stage-gates is, in practice, not questioned since this would undermine the relevance of the entire process. Nevertheless, the paint case study shows that unexpected problems, which are hardly predictable, may require the design process to be resumed not one, but multiple stage-gates before, to address the issue properly. This demonstrates that a bottom-up design strategy focusing primarily on the nanomaterial may fail at a higher TRL.

This limitation is lifted when the focus is shifted from the nanomaterial to the product itself. Indeed, still using the paint case study, the product initially met the requirements of both the stage-gate and three-pillar models, but proved to be unfit for further development because of the effects of aging. Once the product became the predominant focus, the desired functionality and the expected service life duration naturally led to a profound re-design of the paint to include the development of a base matrix that is resistant to photocatalytic effects over time (see Fig 1) while the active compound remains the same. Admittedly, a product-oriented top-down design is more difficult to implement than a traditional approach, since the initial safety validation steps of a stage-gate based model are no longer verified but become assumed. The benefit of putting the product functionality first is, of course, placing it in a life cycle perspective: the function of the product needs to be maintained until it is discarded. This becomes more difficult if the intended use has a long lifetime, but this is precisely when a top-down design approach makes the most sense. For instance, in the case of products with a limited life-time (e.g. cosmetics), matrix stability issues are far less pressing than for products intended to last multiple years. Allowing for the flexibility to re-initiate the design process at an early stage i) avoids wasting time and resources attempting to resolve problems that passed early validation but turned out to be limited at later development stages and (ii) recognizes that not all problems are necessarily foreseeable, resetting the entire design process may become necessary despite stage-gate generated "certainties".

An obvious consequence of a product-oriented design process is the need to rethink the testing strategy. Most of the regular physical-chemical and (eco) toxicity assessments become inoperative in this context. Indeed, there are very few "whole product" tests available. Some standardized aging procedures partially address this issue. [26] Mesocosm testing is probably one of the best fits to test entire products, [27-29] but it addresses only the latest stages of the life cycle. Current efforts to streamline the testing strategy in a nanosafety context rely on grouping and read-across strategies already defined. [30] Unfortunately the main initiatives (e.g. H2020 Gracious) focus on a bottom-up process [31] but leave little- to no- room for a top-down approach.

Currently, the main European initiatives do not favor a product-oriented SbD approach because it supposedly conveys a false sense of adherence to an ineffective and tedious case-by-case assessment strategy. In fact, a product-oriented approach does the exact opposite: when the focus is on the functionality, all materials meeting the criteria are on the same level, so grouping can be thought of in terms of the application. A product-, or product-family, based approach admittedly implies a more difficult process, but it also promises far more effective design and testing strategies.

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Figure 1: Example of the non sequential feedback capability for a product oriented value chain validation approach. Stage numbers 1-5 refer to Cooper’s stage gate approach (see refs 5-7).
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