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# 1 The SERENADE project - a step forward in the Safe by Design process of 2 nanomaterials: Moving towards a product-oriented approach

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15  
16 **Abstract:** Recent research efforts have gone into formalizing and standardizing the Safe by  
17 Design process of nanomaterials. This usually results in a structured and (most often) sequential  
18 approach deliberately putting the focus on hazard and exposure issues regarding the  
19 nanomaterial itself in a bottom-up progression of material development. However, this general  
20 strategy lacks flexibility. Within the project SERENADE, a case study examining  
21 photocatalytic paint failed to validate the generally accepted Safe by Design scheme. This  
22 example examined the product (paint in this case) rather than the nanomaterials it contains. It  
23 was found that the essential parameters, namely product specification and functionality, failed  
24 to fit into a rigid bottom up approach and indicated the need for alternative Safe by Design  
25 strategies.

## 26 27 **Focusing on the nanomaterial (NM): available tools and their benefits**

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

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

44 Since nano-safety concerns have focused on human health, similar to the pharmaceutical  
45 industry, it has been suggested that the same tools could be applied to nanomaterials

46 [4]. However, in contrast with the pharmaceutical industry, nanotechnologies cover a much wider  
47 range of application fields, thus requiring a more diversified approach. For instance,  
48 nanomaterials only represent an ingredient or a component of the overall product and their long-  
49 term stability will depend on the nano-matrix interactions. Exposure to nanomaterials should  
50 be controlled through encapsulation, use of embedding matrix or of core-shell structure to limit  
51 contact and potential release to workers, consumers and the environment.

52 A popular SbD approach is the stage-gate model that was developed by industry in the  
53 1980s and has recently been reformalized [5-7]. It consists of a linear process that breaks down  
54 the development of a new product into a series of phases, separated by gates that are crossed  
55 when the requirements of the preceding stage are met. In recent years, this general concept has  
56 been translated into nano-SbD, in part leaning on the work developed in EU projects [8-11]. In  
57 this linear stage-gate process, the nanomaterial itself is and remains the primary focus  
58 throughout the entire decision-making (and thus, development) process. Indeed, failures to  
59 progress beyond the iterative development at stage #n can be resolved by corrective measures  
60 at stage #n-1, while #n-2 and preceding stages are assumed to be sound. The obvious benefit of  
61 this SbD strategy is that flaws in the development of nanomaterials prevent progression to the  
62 next stage and only materials passing the sequential validation process are considered for  
63 production and commercialization.

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

72 The French project SERENADE, specifically dedicated to nanomaterial SbD, funded a  
73 series of coordinated interdisciplinary case studies sharing resources for toxicity assessments.  
74 [13] There were some difficulties that revealed inadequacies of the stage-gate- and the three  
75 pillar- approaches to address the SbD of nanomaterials properly. It should be noted here that  
76 the present work will examine only technical aspects of the SbD validation process. More  
77 general nanosafety concepts such as nano-risk governance (which includes for instance public  
78 and stakeholder perception), are not addressed here (see reference [13] for more details). Also,  
79 the examination of these technical aspects is outside the coordination strategy of a set of case  
80 studies, as it regards the process within a single case study, i.e. a given material or product.

81

## 82 **Limitations of current Safe(r) by Design models**

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

94 trials to a minimum, is sometimes recommended for the development of nanomaterials, [14-16]  
95 although, except for biomedical applications, the stakes are vastly different.

96 One of the SERENADE case studies examining the SbD of photocatalytic paint,  
97 benefited from the support of French paint manufacturer Allios. This support went well beyond  
98 a silent observation of the work and its implicit endorsement. The industrial partner participated  
99 actively in the experimentation and discussions [17-20] resulting in one of the most complete case  
100 studies in terms of life cycle coverage and advanced development stage. Indeed, the products  
101 tested were actual paint formulations prepared by the manufacturer. The linear bottom-up  
102 approach of the stage-gate model was followed since the process aimed at adapting existing  
103 solutions to address a niche market. Regarding the three-pillar model, the requirements were *a*  
104 *priori* met: the Safe Production pillar leaned on the experience of the manufacturer in  
105 formulating paint, including the handling of (nano-) powders, which ranks high in terms of  
106 potentially hazardous production steps. [21] The Safe Product and Safe Use pillars, although not  
107 validated at that point, were not a severe concern since paint, and especially indoor paint, is  
108 usually not considered as a high risk product. In a first approximation, release of nanomaterials  
109 from the paint matrix might be an obstacle for validating the Safe Use pillar since aging can  
110 cause measurable release. [22, 23] In fact, releases from the paints as a result of weathering and  
111 mechanical aging (e.g. sanding during building renovation) were determined as part of the paint  
112 case study to address this concern.

113 Another important part of this study was to test a range of TiO<sub>2</sub> concentrations within  
114 the product for optimal results. In a first approximation, the higher the TiO<sub>2</sub> concentration, the  
115 more efficient the photodegradation process. However, high TiO<sub>2</sub> content also translates to high  
116 levels of harmful volatile organic compounds (VOCs) released from the paint, {Gandolfo, 2018  
117 #29} indicating that optimizing the amount of photocatalytic agent is not a straightforward  
118 process in terms of product safety. This strategy was an iterative process, modifying the amount  
119 of TiO<sub>2</sub> in the paint with subsequent measurement of the effects to find the best compromise,  
120 without challenging the core formulation of the paint. In parallel, it was demonstrated that the  
121 paint can have reduced photocatalytic performance after aging as a result of degradation of the  
122 paint matrix through photocatalysis and the subsequent accelerated loss of TiO<sub>2</sub>. [20] This matrix  
123 degradation was predictable to a certain extent, and has been observed before with less  
124 photocatalytic compounds. [25] However, the implicit adherence to the stage-gate model (in  
125 part because it leans on a series of "certainties") delayed the in-depth re-design of the paint with  
126 a matrix capable of withstanding photocatalysis. Stage-gate and three-pillar models failed to  
127 lead to a viable product. Indeed, the stage-gate model with its sequential progression scheme  
128 led to an aggravation of the situation, since intuition-guided modifications to enhance  
129 performance (i.e. the adjustment of TiO<sub>2</sub> concentration to limit the production of harmful  
130 VOCs) did not address degradation of the matrix and, thus, the release of TiO<sub>2</sub>. This shows that  
131 the stage-gate process is ill-adapted to handle the present paint development example since it  
132 turned out that an effective SbD was required to backtrack over multiple stage-gates, thus *de*  
133 *facto* invalidating the sequential validation process.

134

### 135 **Product oriented approach**

136 This case study raises the question of how the SbD of nanomaterials should be  
137 approached in practice. The stage-gate model has a definite appeal in the earliest development  
138 stages. Indeed, inadequate material choices for a targeted application will not pass the validation  
139 process. This is also the point when a stage-gate-compliant high-throughput screening can be  
140 implemented. As the product development progresses, the three-pillar approach, which leans

141 on the stage-gate model, adds an operational dimension by explicitly examining worker and  
142 consumer safety.

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

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

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

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

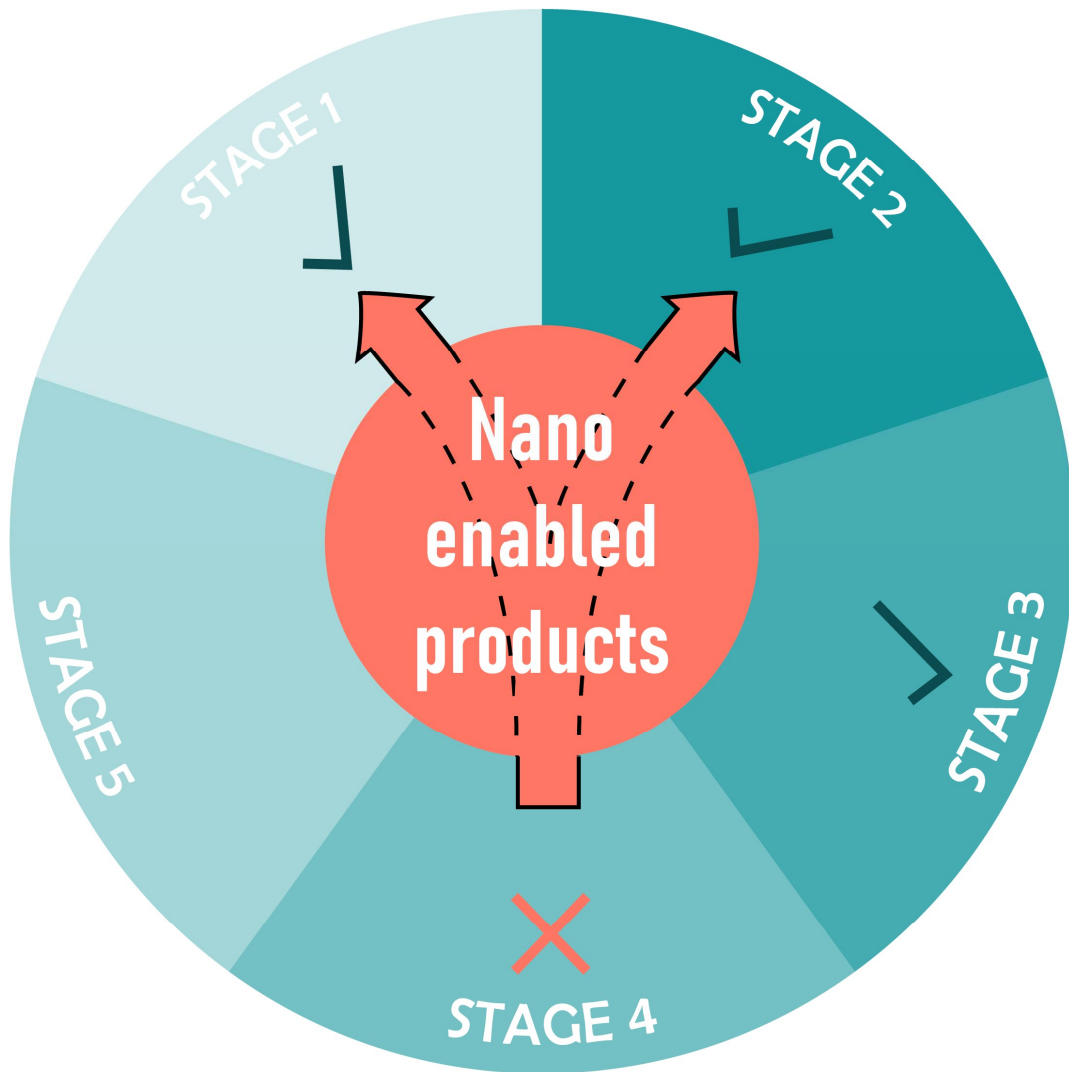
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199 Figure 1: Example of the non sequential feedback capability for a product oriented value chain  
200 validation approach. Stage numbers 1-5 refer to Cooper's -stage gate approach (see refs 5-7).

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