



HAL
open science

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

Jérôme Rose, Melanie Auffan, Camille de Garidel-Thoron, Sebastien Artous, Gregory Brochard, Simon Clavaguera, Delphine Truffier-Boutry, Henri Wortham, Armand Masion

► To cite this version:

Jérôme Rose, Melanie Auffan, Camille de Garidel-Thoron, Sebastien Artous, Gregory Brochard, et al.. The SERENADE project – A step forward in the Safe by Design process of nanomaterials: Moving towards a product-oriented approach. *Nano Today*, 2021, 39, pp.101238. 10.1016/j.nantod.2021.101238 . hal-03455690

HAL Id: hal-03455690

<https://hal.science/hal-03455690>

Submitted on 1 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3
4 Jerome ROSE¹, Melanie AUFFAN¹, Camille De GARIDEL-THORON¹, Sebastien ARTOUS², Gregory
5 BROCHARD³, Simon CLAVAGUERA², Delphine TRUFFIER-BOUTRY², Henri WORTHAM⁴, Armand
6 MASON^{1*}.

7
8 *: corresponding author

9
10 1: CNRS, Aix Marseille Univ, IRD, Coll France, INRAE, CEREGE, 13545 Aix-en-Provence,
11 France

12 2: Univ Grenoble Alpes, CEA, LITEN, DTNM, F-38000 Grenoble, France

13 3: ALLIOS, 185 Chemin de Saint-Lambert, 13821 La Penne Sur Huveaune, France

14 4: Aix Marseille Univ, CNRS, LCE, UMR 7376, 13331, Marseille, France

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,^[2] even a modest reduction in the number
42 of tested molecules would represent substantial savings in a traditionally costly approval
43 process ^[3]

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 TiO₂ concentrations within
114 the product for optimal results. In a first approximation, the higher the TiO₂ concentration, the
115 more efficient the photodegradation process. However, high TiO₂ 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 TiO₂ 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 TiO₂. [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 TiO₂ concentration to limit the production of harmful
130 VOCs) did not address degradation of the matrix and, thus, the release of TiO₂. 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. ^[26] Mesocosm testing is probably
175 one of the best fits to test entire products, ^[27-29] 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. ^[30] Unfortunately the main initiatives (e.g. H2020
178 Gracious) focus on a bottom-up process ^[31] 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.

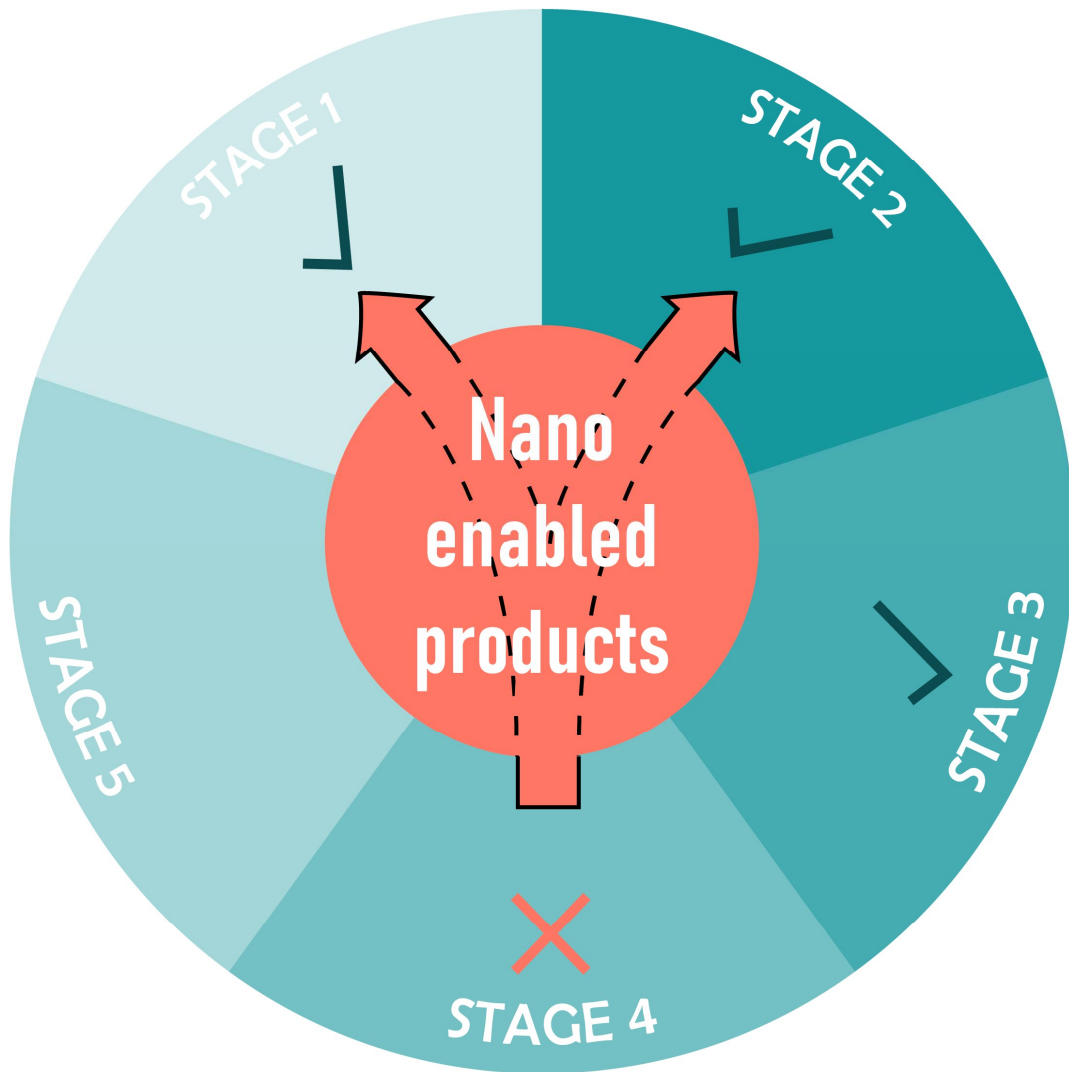
187

188 Acknowledgment:

189 The authors wish to thank Fanny Thavot for her help in designing the artwork. This work
190 is a contribution to the Labex SERENADE (No. ANR-11-LABX-0064) funded by the
191 “Investissements d’Avenir” French Government program of the French National Research
192 Agency (ANR) through the AMIDEX project (No. ANR11-IDEX-0001-02). The authors also
193 acknowledge the CNRS for the funding of the IRP iNOVE.

194

195



196

197

198

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).

201

202

203

204

205

206 **Cited references**

- 207 [1] Nanosafety-Cluster. <https://www.nanosafetycluster.eu/>. Accessed Apr 2021.
- 208 [2] I. Kola, J. Landis. Can the pharmaceutical industry reduce attrition rates? *Nature Reviews*
209 *Drug Discovery*, 3 (2004) 711-715.
- 210 [3] V.G. Sasseville, J.H. Lane, V.J. Kadambi, P. Bouchard, F.W. Lee, S.K. Balani, G.T. Miwa,
211 P.F. Smith, C.L. Alden. Testing paradigm for prediction of development-limiting barriers
212 and human drug toxicity. *Chemico-Biological Interactions*, 150 (2004) 9-25.
- 213 [4] R. Hjorth, L. van Hove, F. Wickson. What can nanosafety learn from drug development?
214 The feasibility of "safety by design". *Nanotoxicology*, 11 (2017) 305-312.
- 215 [5] R.G. Cooper. Managing technology development projects. *Research-Technology*
216 *Management*, 49 (2006) 23-31.
- 217 [6] R.G. Cooper. Perspective: The Stage-Gate (R) idea-to-launch process-update, what's new,
218 and NexGen systems. *Journal of Product Innovation Management*, 25 (2008) 213-232.
- 219 [7] R.G. Cooper. What's Next? After Stage-Gate. *Research-Technology Management*, 57
220 (2014) 20-31.
- 221 [8] A. Kraegeloh, B. Suarez-Merino, T. Sluijters, C. Micheletti. Implementation of Safe-by-
222 Design for Nanomaterial Development and Safe Innovation: Why We Need a
223 Comprehensive Approach. *Nanomaterials*, 8 (2018) 239.
- 224 [9] L.G. Soeteman-Hernandez, M.D. Apostolova, C. Bekker, S. Dekkers, R.C. Grafstrom, M.
225 Groenewold, Y. Handzhiyski, P. Herbeck-Engel, K. Hoehener, V. Karagkiozaki, S. Kelly,
226 A. Kraegeloh, S. Logothetidis, C. Micheletti, P. Nymark, A. Oomen, T. Oosterwijk, I.
227 Rodriguez-Llopis, S. Sabella, A.S. Jimenez, A. Sips, B. Suarez-Merino, I. Tavernaro, J.
228 van Engelen, S.W.P. Wijnhoven, C.W. Noorlander. Safe innovation approach: Towards an
229 agile system for dealing with innovations. *Materials Today Communications*, 20 (2019)
230 Unsp 100548.
- 231 [10] S.N. Sorensen, A. Baun, M. Burkard, M. Dal Maso, S. Foss Hansen, S. Harrison, R. Hjorth,
232 S. Loftis, M. Matzke, B. Nowack, W. Peijnenburg, M. Poikkimaki, J.T.K. Quik, K.
233 Schirmer, A. Verschoor, H. Wigger, D.J. Spurgeon. Evaluating environmental risk
234 assessment models for nanomaterials according to requirements along the product
235 innovation Stage-Gate process. *Environmental Science-Nano*, 6 (2019) 505-518.
- 236 [11] A.P. van Wezel, H. van Lente, J.J.M. van de Sandt, H. Bouwmeester, R.L.J. Vandenberg,
237 A. Sips. Risk analysis and technology assessment in support of technology development:
238 Putting responsible innovation in practice in a case study for nanotechnology. *Integrated*
239 *Environmental Assessment and Management*, 14 (2018) 9-16.
- 240 [12] A. Sanchez, R. Puelles, M. Pérez, I. Rodriguez, M. Apostolova, B. Shivachev, Y. Youdar,
241 H. Goede, N. Shandilya, R. Meier, C. Merino, E. Garcia, I. Tavernaro, A. Kraegeloh (2019)
242 Nanoreg2 Deliverable D4.6: Guidance on the practical implementation of SbD in the
243 nano-technology community.
244 [https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=0801](https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c3043cca&appId=PPGMS)
245 [66e5c3043cca&appId=PPGMS](https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c3043cca&appId=PPGMS). Accessed May 2020
- 246 [13] J. Rose, M. Auffan, C. de Garidel-Thoron, S. Artous, C. Auplat, G. Brochard, I. Capron,
247 M. Carriere, B. Cathala, L. Charlet, S. Clavaguera, T. Heulin, J. Labille, T. Orsiere, S.
248 Peyron, T. Rabilloud, C. Santaella, D. Truffier-Boutry, H. Wortham, A. Masion. The

- 249 SERENADE project; a step forward in the safe by design process of nanomaterials: The
250 benefits of a diverse and interdisciplinary approach. *Nano Today*, 37 (2021) 101065.
- 251 [14] S. Ottofuelling, F. Von der Kammer, T. Hofmann. Commercial Titanium Dioxide
252 Nanoparticles in Both Natural and Synthetic Water: Comprehensive Multidimensional
253 Testing and Prediction of Aggregation Behavior. *Environmental Science & Technology*,
254 45 (2011) 10045-10052.
- 255 [15] C.R. Thomas, S. George, A.M. Horst, Z. Ji, R.J. Miller, J.R. Peralta-Videa, T. Xia, S.
256 Pokhrel, L. Maedler, J.L. Gardea-Torresdey, P.A. Holden, A.A. Keller, H.S. Lenihan, A.E.
257 Nel, J.I. Zink. *Nanomaterials in the Environment: From Materials to High-Throughput*
258 *Screening to Organisms*. *ACS Nano*, 5 (2011) 13-20.
- 259 [16] F. von der Kammer, S. Ottofuelling, T. Hofmann. Assessment of the physico-chemical
260 behavior of titanium dioxide nanoparticles in aquatic environments using multi-
261 dimensional parameter testing. *Environmental Pollution*, 158 (2010) 3472-3481.
- 262 [17] J.Y. Bottero, J. Rose, C. de Garidel, A. Masion, T. Deutsch, G. Brochard, M. Carriere, N.
263 Gontard, H. Wortham, T. Rabilloud, B. Salles, M. Dubosson, B. Cathala, D. Boutry, A.
264 Ereskovsky, C. Auplat, L. Charlet, T. Heulin, E. Frejafon, S. Lanone. SERENADE: safer
265 and ecodesign research and education applied to nanomaterial development, the new
266 generation of materials safer by design. *Environmental Science-Nano*, 4 (2017) 526-538.
- 267 [18] A. Gandolfo, V. Bartolomei, D. Truffier-Boutry, B. Temime-Roussel, G. Brochard, V.
268 Berge, H. Wortham, S. Gligorovski. The impact of photocatalytic paint porosity on indoor
269 NO_x and HONO levels. *Physical Chemistry Chemical Physics*, 22 (2020) 589-598.
- 270 [19] J. Morin, A. Gandolfo, B. Temime-Roussel, R. Streckowski, G. Brochard, V. Berge, S.
271 Gligorovski, H. Wortham. Application of a mineral binder to reduce VOC emissions from
272 indoor photocatalytic paints. *Building and Environment*, 156 (2019) 225-232.
- 273 [20] D. Truffier-Boutry, B. Fiorentino, V. Bartolomei, R. Soulas, O. Sicardy, A. Benayad, J.F.
274 Damlencourt, B. Pepin-Donat, C. Lombard, A. Gandolfo, H. Wortham, G. Brochard, A.
275 Audemard, L. Porcar, G. Gebel, S. Gligorovski. Characterization of photocatalytic paints:
276 a relationship between the photocatalytic properties - release of nanoparticles and volatile
277 organic compounds. *Environmental Science-Nano*, 4 (2017) 1998-2009.
- 278 [21] Nanoreg Deliverable D3.01 (2015) Gap analysis report, identifying the critical exposure
279 scenarios within the key value chains. [https://www.rivm.nl/sites/default/files/2018-
280 11/NANoREG%20D3.01%20DR%20Gap%20analysis%20report%2C%20identifying%20
281 the%20critical%20exposure%20scenarios%20within%20the%20key%20value%20chai
282 ns.pdf](https://www.rivm.nl/sites/default/files/2018-11/NANoREG%20D3.01%20DR%20Gap%20analysis%20report%2C%20identifying%20the%20critical%20exposure%20scenarios%20within%20the%20key%20value%20chains.pdf). Accessed May 2020 [https://www.rivm.nl/en/documenten/nanoreg-d301-dr-gap-
283 analysisreport-identifying-critical-exposure-scenarios-within-key](https://www.rivm.nl/en/documenten/nanoreg-d301-dr-gap-analysisreport-identifying-critical-exposure-scenarios-within-key). Accessed June 2021
- 284 [22] R. Kaegi, B. Sinnet, S. Zuleeg, H. Hagendorfer, E. Mueller, R. Vonbank, M. Boller, M.
285 Burkhardt. Release of silver nanoparticles from outdoor facades. *Environmental Pollution*,
286 158 (2010) 2900-2905.
- 287 [23] R. Kaegi, A. Ulrich, B. Sinnet, R. Vonbank, A. Wichser, S. Zuleeg, H. Simmler, S.
288 Brunner, H. Vonmont, M. Burkhardt, M. Boller. Synthetic TiO₂ nanoparticle emission
289 from exterior facades into the aquatic environment. *Environmental Pollution*, 156 (2008)
290 233-239.
- 291 [24] A. Gandolfo, S. Marque, B. Temime-Roussel, R. Gemayel, H. Wortham, D. Truffier-
292 Boutry, V. Bartolomei, S. Gligorovski. Unexpectedly High Levels of Organic Compounds

- 293 Released by Indoor Photocatalytic Paints. *Environmental Science & Technology*, 52
294 (2018) 11328-11337.
- 295 [25] L. Scifo, P. Chaurand, N. Bossa, A. Avellan, M. Auffan, A. Masion, B. Angeletti, I.
296 Kieffer, J. Labille, J.-Y. Bottero, J. Rose. Non-linear release dynamics for a CeO₂
297 nanomaterial embedded in a protective wood stain, due to matrix photo-degradation.
298 *Environmental Pollution*, 241 (2018) 182-193.
- 299 [26] Nanoreg Deliverable D3.03 (2015) Methods for the use of simulation approaches.
300 [https://www.rivm.nl/sites/default/files/2018-12/NANoREG_D3_en/documenten/nanoreg-](https://www.rivm.nl/sites/default/files/2018-12/NANoREG_D3_en/documenten/nanoreg-d3-03_DR_Methods_-dr-methods-for_the_-use_-of_-simulation_-approaches%253AnSiipFASTyEgpl0INMZ2g.pdf)
301 [d3-03_DR_Methods_-dr-methods-for_the_-use_-of_-simulation_-](https://www.rivm.nl/sites/default/files/2018-12/NANoREG_D3_en/documenten/nanoreg-d3-03_DR_Methods_-dr-methods-for_the_-use_-of_-simulation_-approaches%253AnSiipFASTyEgpl0INMZ2g.pdf)
302 [approaches%253AnSiipFASTyEgpl0INMZ2g.pdf](https://www.rivm.nl/sites/default/files/2018-12/NANoREG_D3_en/documenten/nanoreg-d3-03_DR_Methods_-dr-methods-for_the_-use_-of_-simulation_-approaches%253AnSiipFASTyEgpl0INMZ2g.pdf). Accessed March 2020 June 2021
- 303 [27] M. Auffan, A. Masion, C. Mouneyrac, C. de Garidel-Thoron, C.O. Hendren, A. Thiery, C.
304 Santaella, L. Giamberini, J.-Y. Bottero, M.R. Wiesner, J. Rose. Contribution of mesocosm
305 testing to a single-step and exposure-driven environmental risk assessment of engineered
306 nanomaterials. *Nanoimpact*, 13 (2019) 66-69.
- 307 [28] M. Auffan, M. Tella, C. Santaella, L. Brousset, C. Pailles, M. Barakat, B. Espinasse, E.
308 Artells, J. Issartel, A. Masion, J. Rose, M.R. Wiesner, W. Achouak, A. Thiery, J.-Y.
309 Bottero. An adaptable mesocosm platform for performing integrated assessments of
310 nanomaterial risk in complex environmental systems. *Scientific Reports*, 4 (2014) 5608.
- 311 [29] A. Masion, M. Auffan, J. Rose. Monitoring the Environmental Aging of Nanomaterials:
312 An Opportunity for Mesocosm Testing? *Materials*, 12 (2019) 2447.
- 313 [30] A.G. Oomen, E.A.J. Bleeker, P.M.J. Bos, F. Van Broekhuizen, S. Gottardo, M.
314 Groenewold, D. Hristozov, K. Hund-Rinke, M.-A. Irfan, A. Marcomini, W.J.G.M.
315 Peijnenburg, K. Rasmussen, A.S. Jiménez, J.J. Scott-Fordsmand, M. Van Tongeren, K.
316 Wiench, W. Wohlleben, R. Landsiedel. Grouping and Read-Across Approaches for Risk
317 Assessment of Nanomaterials. *International Journal of Environmental Research and Public*
318 *Health*, 12 (2015) 13415-13434.
- 319 [31] A.G. Oomen, K.G. Steinhaeuser, E.A.J. Bleeker, F. van Broekhuizen, A. Sips, S. Dekkers,
320 S.W.P. Wijnhoven, P.G. Sayre. Risk assessment frameworks for nanomaterials: Scope,
321 link to regulations, applicability, and outline for future directions in view of needed
322 increase in efficiency. *Nanoimpact*, 9 (2018) 1-13.