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1 The SERENADE project; a step forward in the Safe by Design process of
2 nanomaterials: The benefits of a diverse and interdisciplinary approach.

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29

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

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

39
40

41 **1. The necessity of more comprehensive research activities**

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

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

62 The general structure and strategy of SERENADE has been described in detail
63 previously.^[6] Briefly, the research activities centered around environmental- and human
64 exposure reduction, biocompliance, end of life and risk modeling fed into the central safe
65 nanomaterial design objective (Fig 1). In this work, the term biocompliance is used to include
66 applications with targeted toxicity for which "hazard reduction" would be inaccurate. More

67 recent reports dealing with the organization of the SbD process^[7] show strong resemblance
68 with the general SERENADE scheme, with the notable difference that risk, its hazard and
69 exposure components, and SbD appear as separate entities feeding into a larger nanosafety
70 loop. The approach addressing technical issues within SERENADE shows also clear
71 similarities with the five "S.A.F.E.R" (S: surface, structure; A: alternate material, F:
72 Functionalization, E: encapsulation; R: reduce quantity) principles proposed earlier.^[8]

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

79

80 **2. The implementation of a coordinated case study strategy**

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

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

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

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

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

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

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

107 The balanced hazard-exposure approach in criterion #3 appears under-represented (Fig
108 2, Table 1). As a matter of fact, exposure was examined with specific protocols according to
109 the targeted application and the diverse nature of the nanomaterials in the different case
110 studies. For example, while mechanical aging (abrasion, drilling) was a basic exposure
111 assessment for paint,^[12, 28] this was of course not an issue for sunscreens.^[28] As opposed to
112 exposure assessment, basic hazard assessment was not material- or application dependent. As
113 a consequence, instead of conducting a separate toxicity characterization in each case study,
114 the hazard assessment was handled in an action shared among all other case studies, and only
115 specific biological targets were examined within the individual case studies. The obvious
116 benefit of this process is that the same groups using the same experimental protocols
117 performed the toxicity assessment. The results obtained with this approach are particularly
118 valuable, since they are directly comparable across the set of case studies. To the best of our
119 knowledge, this was the first time that this shared hazard characterization has been applied to
120 a set of case studies examining nanomaterials along the life cycle. The EU H2020 project
121 Nanoreg 2 also launched a series of case studies without however implementing the shared
122 hazard assessment approach developed here.^[10]

123 Following the same strategy, the assessment of the end-of-life stage of the life cycle has
124 also been a shared effort. The approach consisted in examining the behavior of nanomaterials
125 in a wastewater treatment context. Indeed, for many nanomaterials reaching the end of the use
126 phase, the "sink" are the sewer and storm-drainage systems. Ideally, these systems lead to a
127 wastewater treatment plant (WWTP). The nanomaterials entering a WWTP differ greatly in
128 terms of aging/degradation; i.e. short-lived nanomaterials without significant modification
129 (e.g. cosmetics), to compounds exposed to years of weathering (e.g. paint). While the
130 nanomaterials themselves and their degradation stages show a large variety, the waste water

131 treatment technologies do not. Therefore, just as for the base toxicity assessment, the behavior
132 of nanomaterials in a WWTP has been shared with defined equipment and protocols to ensure
133 comparability of the results and to save resources.

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

145

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

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

163 also that in the life cycle coverage (Fig. 3) since some concerns/ problems become more
164 pressing as the TRL increases (see e.g. "quantity" in Table 1).

165 Even within a given hazard or exposure reduction measure, diversity is important.
166 Indeed, the implementation of these measures can take several forms depending on the
167 material and its intended use. For example, limiting the release is approached differently
168 whether sunscreens or self-cleaning paints and stains are considered: in the case of
169 sunscreens, release *per se* is unavoidable, therefore the strategy to avoid exposure to the
170 potentially harmful TiO₂ nanomaterial is to apply a protective coating with a durability
171 extending far beyond the intended use to protect not only the customer, but also the
172 environmental media these cosmetics are released to. At the opposite, in self-cleaning paint,
173 the same TiO₂ compound is used for its photocatalytic properties. Consequently, applying a
174 coating would be detrimental to the desired property, and exposure reduction then focuses on
175 strong attachment to a weathering- and TiO₂ resistant matrix.

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

196 hazard and end-of-life indicators, i.e. any opportunity characterization sharing should be
197 seized to overcome any differences/ in operational procedures.

198 As indicated above, the research developed in the SERENADE was not meant to
199 support grouping efforts which are mostly based on material characteristics and properties.^[31]
200 ^{32]} Nevertheless, by covering several application types (e.g. paints and stains, food
201 packaging...), the results of the SERENADE case studies may open the road for an
202 alternative kind of categorization. Products within a given application will undergo similar or
203 identical exposure and hazard testing. For example, lip-gloss and sunscreens, although
204 different in chemical nature, have the same aging/release mechanisms potentially affecting the
205 same biota, and therefore should be tested with the same experimental protocols. In this
206 context, diversifying the products tested in a given application type is actually an asset, since
207 trends identified with compounds of varied nature could be indicative of risk linked to a
208 specific type of use rather than the type of material. Of course, the findings of the
209 SERENADE case studies do not permit such a generalization on their own but they fit within
210 this type of extrapolation of results.

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

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

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

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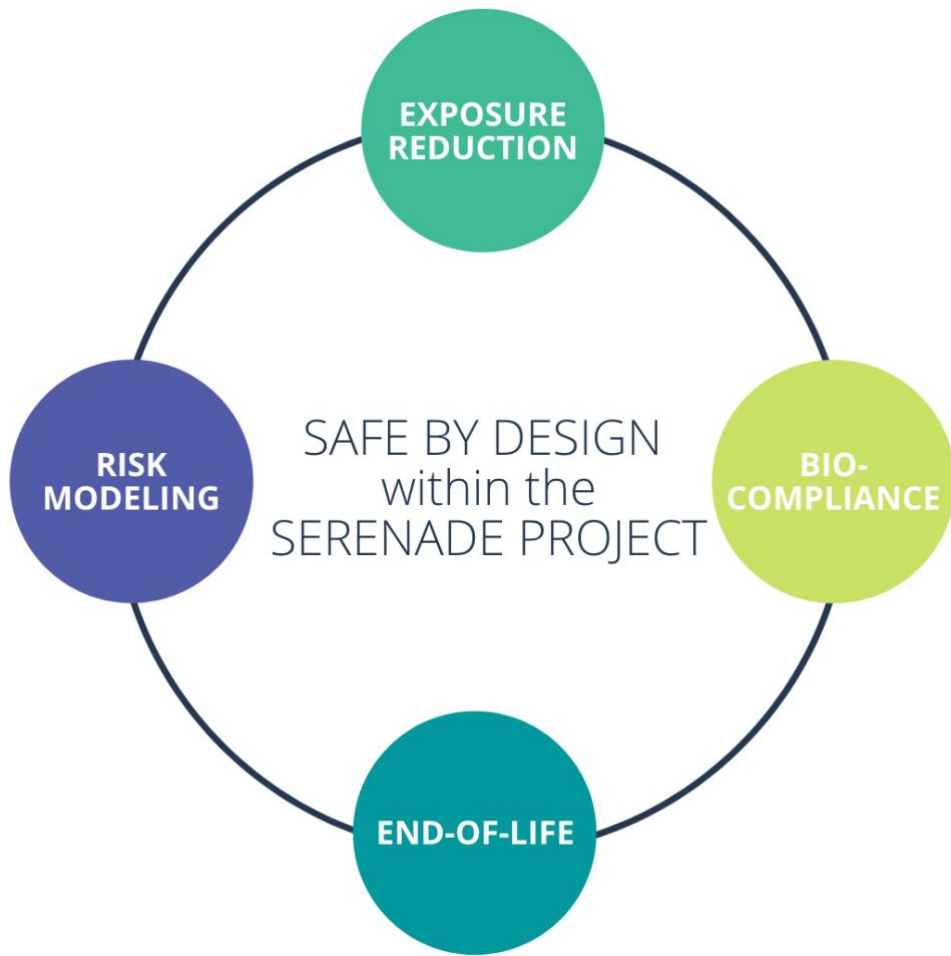
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254 Fig 1: Overall organization of the SERENADE project

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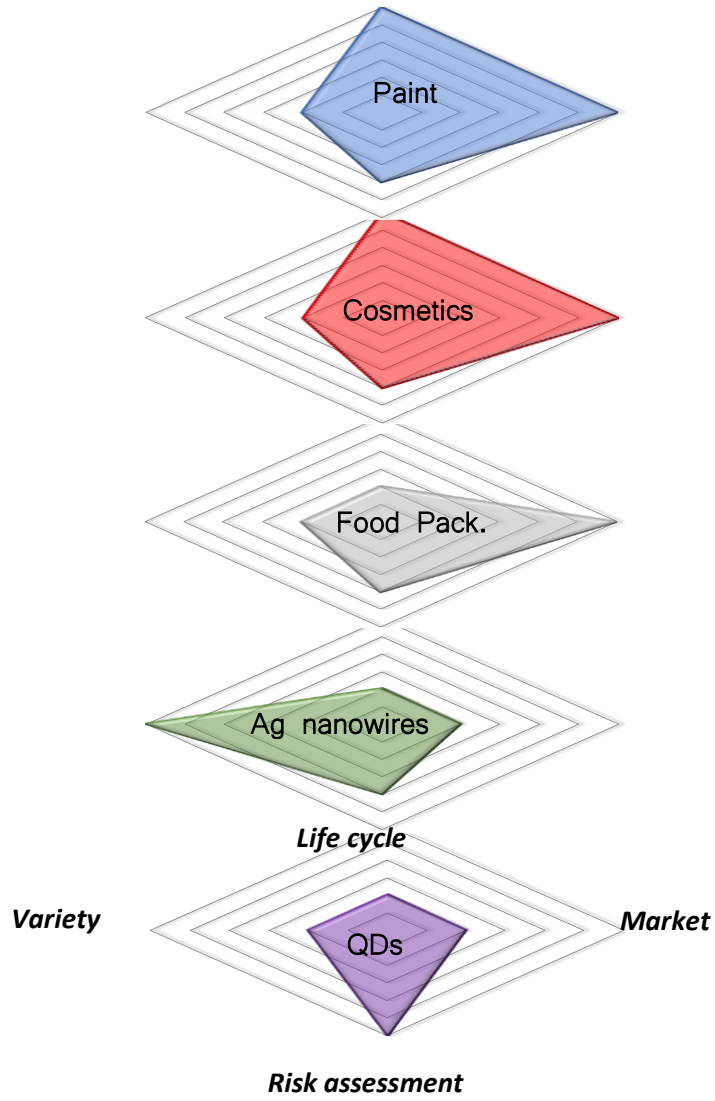
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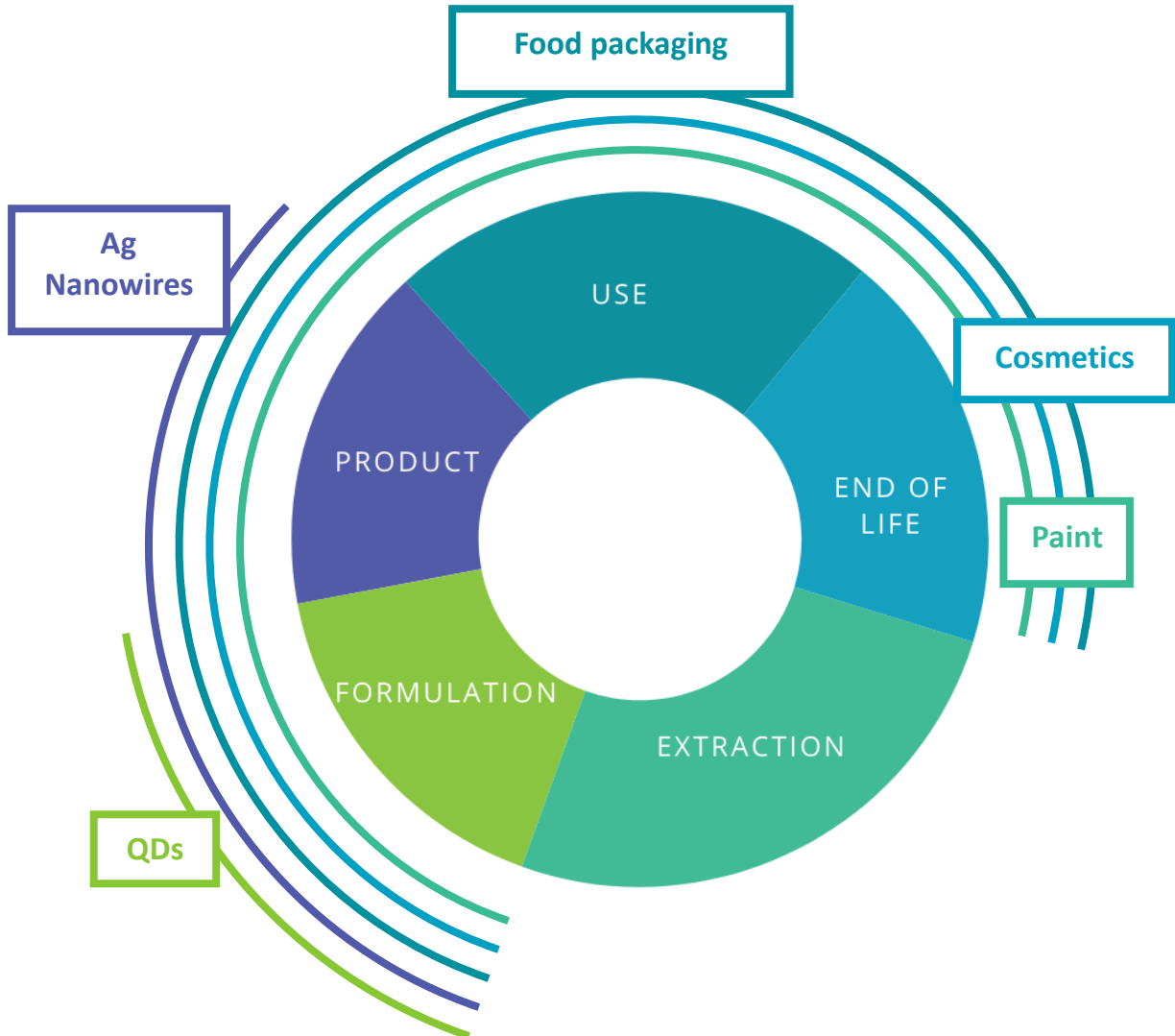
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Fig 2: Case studies within the SERENADE project and their relevance to the four selection criteria

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Fig 3: Life cycle coverage of the case studies

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284

285 Table 1

286

		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	

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

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