

## PAPER

View Article Online  
View Journal | View Issue



Cite this: *Environ. Sci.: Nano*, 2024, **11**, 2948

## Advanced materials earliest assessment (AMEA)<sup>†</sup>

Wendel Wohlleben,<sup>a</sup> Michael Persson,<sup>b</sup> Blanca Suarez-Merino,<sup>c</sup> Anders Baun,<sup>d</sup> Veronica Di Battista,<sup>ad</sup> Susan Dekkers,<sup>e</sup> Eugene P. van Someren,<sup>e</sup> Dirk Broßell,<sup>f</sup> Burkhard Stahlmecke,<sup>g</sup> Martin Wiemann,<sup>h</sup> Otmar Schmid<sup>i</sup> and Andrea Haase<sup>j</sup>

Advanced materials are rapidly being developed in different material categories. They share little commonalities apart from their novelty, which raises concerns that these materials may fall into a regulatory gap with potentially inappropriate risk management. But how to assess materials that are still under development? Here we present the Advanced Materials Earliest Assessment (AMEA) approach to fill this gap by proposing simple assessment steps and guidance for design rules meant to be applied by innovators in early material development phases (ideation, business case and lab phases). AMEA provides a structured approach to exploit the available knowledge at each phase, starting from the intended product, application and global region, starting also from the conventional material in the same application, of which the sustainability benefits and sustainability challenges often constitute the motivation for advanced material development. During the lab phase, AMEA recommends focusing on acquisition of data with discriminating power, and triggers more requirements and/or specific testing methods depending on the positioning of the material with respect to the three dimensions “nano-enabled?”, “advanced?”, and “containing particles?”. The methodological part can be amended for other material classes without relevance of nanostructures. Similarity and ranking approaches compare material versions synthesized in lab phases against each other and the conventional material in terms of performance, lifecycle emissions/exposures and hazards. AMEA prioritizes the discriminating power of specific data to refine the design targets instead of using generic assumptions with high uncertainties. It is the entry point of the HARMLESS decision support system covering the ensuing pilot and launch phases of innovation management to fulfill safe-and-sustainable-by-design material development.

Received 15th November 2023,  
Accepted 10th May 2024

DOI: 10.1039/d3en00831b

rsc.li/es-nano

### Environmental significance

Advanced materials are novel by their very nature. The assessment of their potential sustainability benefits, environmental safety and human safety, is more uncertain than with conventional materials, and should start at the earliest phases of innovation. Here we provide structured guidance for the design and assessment of advanced materials, supported by categorizations and comparative screening approaches. We strongly differentiate the recommended consideration and testing between the ideation phase, business case phase and laboratory phase. Comparison to known sustainability issues of the sector of intended use or known safety issues of specific material classes can direct industrial research resources towards the most sustainable alternative. However, none of the screening approaches targets the level of certainty of regulatory assessment, which remains reserved for the few materials that reach market introduction.

<sup>a</sup> BASF SE, Carl-Bosch-Str. 38, 67056 Ludwigshafen, Germany.

E-mail: [wendel.wohlleben@basf.com](mailto:wendel.wohlleben@basf.com)

<sup>b</sup> Chalmers CIT, Chalmers Industriteknik, Sven Hultins Plats 1, 412 58 Göteborg, Sweden

<sup>c</sup> TEMAS Solutions GmbH, Lätteweg 5, 5212 Hausen, Switzerland

<sup>d</sup> DTU Sustain, Technical University of Denmark, Building 115, 2800 Kgs. Lyngby, Denmark

<sup>e</sup> TNO, Risk Analysis for Products in Development, The Netherlands

<sup>f</sup> Federal Institute for Occupational Safety and Health, Nöldnerstr. 40-42, 10317 Berlin, Germany

<sup>g</sup> Institut für Umwelt & Energie, Technik & Analytik e. V, Bliersheimer Str. 58-60, 47229 Duisburg, Germany

<sup>h</sup> IBE R&D Institute for Lung Health gGmbH, Münster, Germany

<sup>i</sup> Helmholtz Zentrum München, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

<sup>j</sup> German Federal Institute for Risk Assessment (BfR), Department of Chemical and Product Safety, Germany

<sup>†</sup> Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3en00831b>



# 1. Introduction

The term “advanced materials” (AdMa) is frequently used in innovation steering, but is often open to interpretation. The term obviously relates to a material, which is also not a properly defined term, but in the innovation context it does not designate a raw resource, nor a consumer product, nor waste. The comparative qualifier advanced invokes the existence of other materials that are not as advanced, and one could denote these as “conventional materials” (CoMa). Motivated by this positioning in the value chain, which matched the focus of chemical industry, and further motivated by the connotation of technological progress, many producers in the chemical industry have designated their research and development units as “advanced” or “smart”. To name a few: “DuPont Advanced Materials”, “Altech Advanced Materials”, “Dow Advanced Building Materials”, “BASF SE, Advanced Materials & Systems Research (2012–2022)”, “Evonik Operations, Smart Materials”.

However, with *regulators* the connotation of novelty<sup>1</sup> also raised concerns that advanced materials (AdMa) may fall into a regulatory gap of unnoticed risks, or inappropriate methods of risk assessment and risk management.<sup>2</sup> It is also frequently questioned if advanced or smart materials create new hazards or new risks not known from conventional materials.<sup>3,4</sup> To structure the unknown territory, national authorities<sup>5</sup> and the OECD working party on manufactured nanomaterials (WPMN) have taken the lead. The discussions among global regulators resulted in a description of the term AdMa released by the OECD WPMN in July 2022, shown in Box 1.<sup>6</sup> The WPMN did not intend to develop a formal definition for AdMa, but noted that work is ongoing in ISO TC 229 on such a formal definition, which has not yet been released. The WPMN also noted that synonyms were conceivable for the terms “manufactured”, “enhanced”, “targeted”, “rationally designed” or “improved” like “specifically engineered”, “superior”, “novel”. This vague terminology creates ambiguity and uncertainty among innovators, who do not know if their existing or future products are considered as AdMa, and if yes, what implications this might have.

Innovators in *industry* and academia founded the Advanced Materials Initiative (AMI2030). The recent AMI2030 Roadmap is probably the most reliable foresight on the intended uses and very diverse types of materials that industry will commercialize in the coming decade.<sup>7</sup> The present draft has a very broad scope (Box 1) and has been co-created by the signatories of the Materials 2030 Manifesto,<sup>7</sup> the relevant European Technology Platforms EUMAT (European Technology Platform for Advanced Engineering Materials and Technologies), SUSCHEM (European Technology Platform for Sustainable Chemistry Technologies), MANUFUTURE (European Technology Platform for assuring the future of a competitive, sustainable and resilient European manufacturing) and the Energy Materials Industrial Initiative (EMIRI). The Manifesto focused

on solution-oriented AdMa which will offer faster, scalable and efficient responses to the challenges of the green and digital transition of the European Union (EU), and is thus a response to the United Nations Sustainability Goals<sup>8</sup> – if the innovations are safe and sustainable.

Also in *science*, the term “Advanced Materials” has a history. Since more than 30 years, the scientific journal “*Advanced Materials*” publishes “the very best in materials science”, and describes its scope by yet another list (Box 1) that is very diverse, and not all categories may require special assessment approaches. The long and successful history of this journal supports the WPMN notion of “what are

## Box 1: Descriptions of advanced materials by different stakeholders

*Advanced Materials* journal description (accessed 2023, representing a scientific perspective): “Keywords: materials science, nanotechnology, liquid crystals, semiconductors, superconductors, optics, lasers, sensors, porous materials, light emitting materials, ceramics, biological materials, magnetic materials, thin films, colloids, energy materials, photovoltaics, solar cells, biomaterials, photonics, ferroelectrics, multiferroics, metamaterials, drug delivery, cancer therapy, tissue engineering, imaging, self-assembly, hierarchical materials, batteries, supercapacitors, thermoelectrics, polymers, nanomaterials, nanocomposites, nanotubes, nanowires, nanoparticles, carbon, diamond, fullerenes”. “Progress in materials science every week for over 30 years. Cutting edge of the chemistry and physics of functional materials. Pronounced interdisciplinarity”.<sup>14</sup>

OECD WPMN description (2022),<sup>6</sup> representing a regulatory perspective: “In this context, AdMa are understood as materials that are rationally designed to have

- new or enhanced properties, and/or

- targeted or enhanced structural features

with the objective to achieve specific or improved functional performance. This includes both new emerging manufactured materials, and materials that are manufactured from traditional materials. This also includes materials from innovative manufacturing processes that enable the creation of targeted structures from starting materials, such as bottom-up approaches. It is acknowledged that what are currently considered as AdMa will change with time”.

*Advanced Materials Initiative AMI2030* (2022),<sup>7,15</sup> representing an innovator perspective: the Materials 2030 Manifesto exemplifies how advanced materials share much more cross-cutting commonalities across all the different markets they serve than apparent at first sight, notably to address four major materials’ challenges: circularity, zero-pollution, climate contribution, traceability. Nine materials innovation markets (MIMs) in the areas of health, construction, new energies, transport, home & personal care, packaging, textiles, agriculture, and electronic appliance have been selected as a first basis for the creation of the Materials 2030 initiative. Cross cutting R&D challenges related to materials processing and scale up match the previously defined industrial needs and priorities: 1) process optimization; 2) decarbonization; 3) mass customization; 4) zero defect production; 5) circular economy; 6) multi-materials processing; and 7) new materials processes.



currently considered as AdMa will change with time". In a visionary scoping strategy, now a decade ago, the platform "Design and Advanced Materials As a Driver of European Innovation" (DAMADEI) has structured the term "advanced materials" into several material categories, among them "nanomaterials", and a very similar list was provided by the temporary committee "Materials Science and Engineering Expert Committee" (MatSEEC).<sup>9,10</sup> The AdMa categories of DAMADEI and MatSEEC are mostly consistent and can be easily merged as follows:

- Active material (*e.g.* stimuli-responsive)
- Composite (advanced if *e.g.* multi-structural)
- Manufacturing (advanced if *e.g.* additive manufacturing/3-D-printing)
- Textiles or Fibers (advanced if *e.g.* sensing)
- Biobased and/or biodegradable
- Nanomaterials
- Ceramic or cementitious
- Coating or targeted surface properties
- Foils and films
- Gels and foams
- Alloys
- Polymers (advanced if *e.g.* "high-performance")

With these differences in how AdMa is perceived among regulators, innovators, and scientists, it becomes challenging to guide an AdMa risk assessment – and especially during early innovation phases where the materials are under development with very little data available. In the absence of a unifying technological AdMa feature (such as *e.g.* the size scale for nanomaterials),<sup>2</sup> a categorization is needed, which firstly must differentiate AdMa from CoMa,<sup>11</sup> but also between different AdMa classes (*e.g.* by industry sector, or by

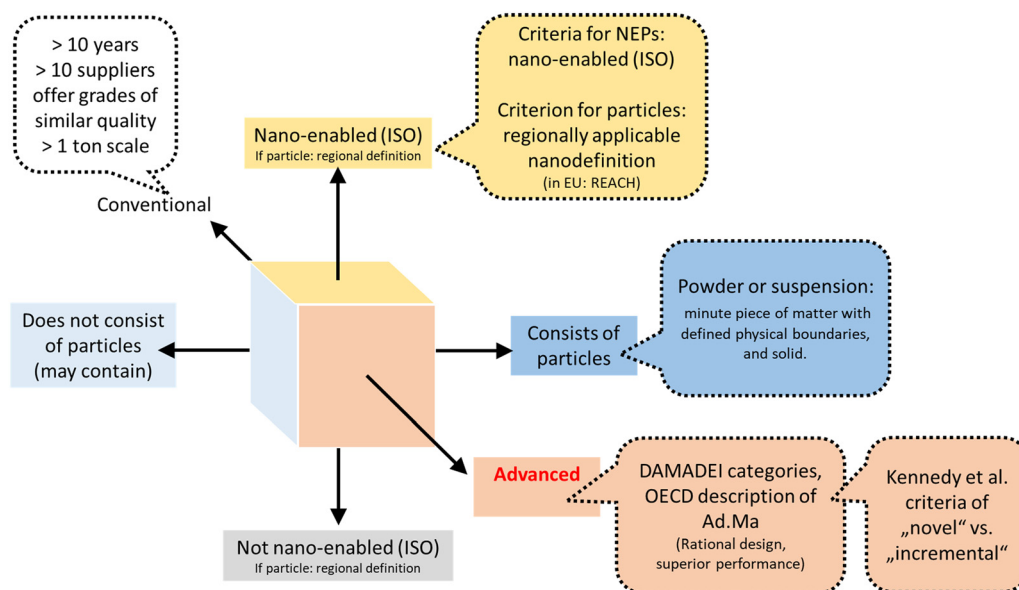
toxicological mode of action, or other criteria).<sup>12</sup> Here we present such a categorization framework and targeted recommendations to enable identification of specific concerns for screening and assessment and to provide criteria to guide safe and sustainable development of AdMa at the earliest innovation phases, namely the ideation, business case, and laboratory phases.<sup>13</sup> To reflect this positioning of the framework, it is termed Advanced Materials Earliest Assessment (AMEA). The AMEA is meant to be used by innovators in a small or median enterprise (SME) as well as in industry, who are supported by an interactive online version (see <https://diamonds.tno.nl/projects/harmlesspublic>) which does not include the intricate scientific reasoning outlined in the present paper.

## 2. Development of the AMEA concept

The present contribution originated from the InnoMat.Life (BMBF) and HARMLESS (EU-H2020) projects, which focused on AdMa and nanomaterials, including nano-enabled AdMa. The specific call texts for these EU projects created a focus in our categorization approaches. Nevertheless, the tiered assessment scheme is designed to be generally applicable to all AdMa, and can easily be amended with respect to specific data/method requirements for other types of AdMa, such as biologicals or polymers or others.

### 2.1. Categorisation

Categories of AdMa were originally posited by DAMADEI and MatSEEC platforms, but these platforms had mixed more generic and highly specific categories.<sup>9,10</sup> Here we merged



**Fig. 1** Entry point to the "Advanced Materials Earliest Assessment" (AMEA): three dimensions (particles; nano-enabled; advanced) and their decision criteria. See Table 1 for implications of the "advanced" dimension for risk screening and assessment methods. See Fig. 3 for the implications of the "nano" and "particle" dimensions. The three dimensions and each of their implications together constitute the AMEA scheme. See the Glossary for abbreviations.



and amended the more general material categories, including those from AMI2030.<sup>7</sup> The InnoMat.Life scheme proposed to firstly sort materials by their material categories (as by the above DAMADEI/MatSEEC list), and then additionally to categorise them in three dimensions that have relevant implications for the risk assessment (criteria in Fig. 1). The considerations for the three dimensions are:

1. Does the material consist of particles (of any size and shape)? Does it contain particles?

As explained by the JRC report considering the implications of different definitions,<sup>16</sup> this criterion would be fulfilled for a powder, but not for a reinforced plastic composite, and not for a paint formulation, which contains particles but also contains the water phase with many other

constituents. All materials consisting of particles differ from other materials in their transport properties, and in their potential (eco)toxicological hazard concerns. Also materials that contain particles are in scope of the assessment, but will trigger different testing methods with a focus on lifecycle, because their use and disposal may induce releases of fragments, especially in cases of matrix degradation,<sup>17</sup> which induces releases also from materials that do not even contain particles. It is important to note, that the wording “consist” prepares, if the innovation progresses to registration and market launch, the regulatory distinction between substances (which may consist of particles) and articles (which in general do not consist of particles).

2. Is the material nano-enabled?

	MATERIAL MAY CONTAIN PARTICLES, BUT DOES NOT CONSIST OF PARTICLES	MATERIAL CONSISTS OF PARTICLES
NANO-ENABLED	<ul style="list-style-type: none"> <li>Composites, mostly conventional, including rubbers (CB, SAS in tires), coatings (e.g., transparent car coating) <i>Advanced if e.g. QLED™ colour converter or flexible display electrode, or dispersoid-pinned alloy</i></li> </ul>	<ul style="list-style-type: none"> <li>Pigments &amp; Fillers, mostly conventional: No. 1-5, 7, 9-12, 14-18 in R-nano<sup>90</sup> <i>Advanced pigment if e.g. Q-dots</i> <i>Advanced filler if e.g. graphene, mwCNT, swCNT, TiO<sub>2</sub> cubes, TiO<sub>2</sub> fibers, Ag wires</i></li> </ul>
	<ul style="list-style-type: none"> <li>Catalysts, mostly conventional <i>Advanced if e.g., 5-way exhaust cleaning functionality</i></li> </ul>	<ul style="list-style-type: none"> <li>Noble metal slurry</li> <li>Washcoat slurry: No. 6 in R-nano<sup>90</sup> <i>Advanced if e.g. perovskites, synthetic zeolites</i></li> </ul>
	<ul style="list-style-type: none"> <li><i>High-temperature superconductor cables</i></li> <li><i>Metal-organic framework CO<sub>2</sub> capture</i></li> <li><i>Aerogel insulation panels</i></li> <li><i>Metamaterials (for vis/NIR light)</i></li> </ul>	<ul style="list-style-type: none"> <li>Drug delivery formulation (if nano) <i>Advanced if e.g., active vector<sup>3</sup>, or DNA-origami (not commercial in this application)</i></li> </ul>
NOT-NANO ENABLED	<ul style="list-style-type: none"> <li>Coatings <i>Advanced if e.g., self-healing</i></li> <li>Paints <i>Advanced if e.g., anti-soiling or based on dendrimers</i></li> <li>Rubber <i>Advanced if e.g., low-wear tires</i></li> <li>Ceramics, Glasses</li> <li>Metal alloys <i>Advanced if e.g., shape memory</i></li> </ul>	
	<ul style="list-style-type: none"> <li>Plastics <i>Advanced if e.g., biobased, traceable, recyclable, biodegrading</i></li> </ul>	<ul style="list-style-type: none"> <li>Polymer pellets (~3mm)</li> </ul>
	<ul style="list-style-type: none"> <li>3D printed parts i.e., metal, polymer (also by filament process), concrete (not by SLS process)</li> </ul>	<ul style="list-style-type: none"> <li>Micronized powder (~100µm) e.g., metal, polymer</li> </ul>
	<ul style="list-style-type: none"> <li><i>Metamaterials (acoustic, radar)</i></li> <li>Textiles <i>Advanced if e.g., sensing</i></li> <li>Battery electrodes <i>Advanced if e.g., fast charging</i></li> <li>Solar cells, mostly conventional (silicon) <i>Advanced if e.g., halide-perovskites</i></li> <li>Composites, mostly conventional e.g., CFRP, GFRP <i>Advanced if e.g., recyclable, repairable</i></li> </ul>	<ul style="list-style-type: none"> <li>Pigments &amp; fillers, mostly conventional e.g., carbon fiber, glass fiber, TiO<sub>2</sub></li> </ul>

Fig. 2 Categories with examples sorted according to the three dimensions of the AMEA framework. Advanced materials or advanced processes are listed in italic red font; manufacturing processes are indicated as arrows. This categorization leads to four quadrants for each of which Fig. 3 provides assessment recommendations. See Glossary for abbreviations.





Inspired by the revised Swiss precautionary matrix, we recognize that often regionally different but legally binding regulatory definitions exist,<sup>18</sup> and specifically if consisting of particles, the revised EU recommendation of a regulatory definition of nanomaterials (2022) shall be applied as assessment criterion,<sup>19</sup> if the new material is developed for the EU region. The ISO term “nano-enabled” comprises also macroscopic materials with internal nano-porosity or with nanostructured surfaces, which are out of scope of the EU regulatory definition.<sup>20</sup>

3. Is the manufacturing process or the material itself considered as “advanced”?

We aligned with the OECD WPMN rationale (Box 1) that AdMa are made by rational design to have new or enhanced properties for specific performance, using precise control of its composition and internal structure, and/or are transformed through advanced manufacturing techniques.<sup>6</sup> We refine this description and differentiate incremental innovation from AdMa by additional qualitative characteristics,<sup>21</sup> specifically inherent physicochemical or biological attributes, or novel use of CoMa or unique combination of CoMa (examples in Fig. 2). We abstain from a quantitative metric, because for some sectors of use and material categories already a 1% improvement in functional performance is a significant achievement, while in others an order of magnitude is required to disrupt the status quo.<sup>7,21</sup> Advanced manufacturing processes can generate concerns on occupational safety in a similar manner as the use of advanced materials by conventional processes. However, the assessment of the use and disposal of parts made by advanced processes is identical to that of parts made by conventional processes.

By a tabular format, the three-dimensional categorisation can be easily displayed with four quadrants, listing for each quadrant some black (CoMa), and/or some red (AdMa) entries (to describe eight categories) (Fig. 2). Importantly, all entries in Fig. 2 are exemplary and not exclusive because numerous other examples of additional CoMa or AdMa exist. We strived to give examples of a property or feature that would identify a certain material in this category as advanced in the year 2023. In most cases this relies on a qualitatively different behavior (*e.g.* readily biodegradable by OECD TG 301 criteria instead of biopersistent), whereas an incremental advantage against the CoMa (*e.g.* 10% faster biodegradation rate) does not identify a material as advanced. The logic of excluding incremental innovations follows the proposals of Kennedy *et al.*, who posited that a material is no AdMa solely because it is used in a novel way, or because it was developed using advanced (or additive) manufacturing.<sup>21</sup> As also stated by the OECD WPMN, the relative novelty will cease to qualify a material as “advanced” after some time. For example, pigments were an AdMa in the 1920ies against the conventional dyes, and largely resolved their safety issues (such as leaching), but nowadays pigments are conventional materials. Typically, four criteria with “AND” logic support identification as CoMa (Fig. 1): if a material can be obtained

(1) for more than a decade, (2) from several (typically >10) suppliers, (3) in similar quality, and (4) in ton scale then we consider it a CoMa. Because the innovations of the AMI2030 roadmap do not match the CoMa description, they support the AMEA CoMa/AdMa criteria.<sup>15</sup> However, the criteria remain indicative and there may be borderline cases that fulfill both the above CoMa description and AdMa description.

The material category and the identification as nano-enabled and/or advanced and/or particle can be used to provide specific guidance for the safety assessment (section 2.2) and are relevant in several global jurisdictions. The material category additionally supports the sustainability assessment (section 3.2) in the European Safe-and-Sustainable-by-Design (SSbD) context and provides insights into regulatory preparedness (section 3.3).

## 2.2. Data requirements for early phases of StageGate

Data requirements for all dimensions of decision-making increase in number, specificity and required certainty from gate to gate in the StageGate® process (Fig. SI\_1†).<sup>22,23</sup> The iterative tiering of decisions and developments in “gates” and “stages” is the very heart of innovation management.<sup>22,23</sup> For all categories listed in Fig. 2, and especially for the AdMa, we aim to support the assessment and guidance at early stages of R&D, when essentially nothing is known except for the idea to serve a certain market need. At this stage, the combined technical and commercial probability of success is low (typically 2% in the idea phase),<sup>24–26</sup> and thus the introduction of the idea to the market is very unlikely. Accordingly, decision-support tools must reduce uncertainty at minimal cost by considering the most important factors only.<sup>22,23,27</sup> Many tools have been developed for sustainability assessment of chemicals in general or AdMa in particular (see section 3.1), but most of them do not consider adequately the different reasons of lack of data (see also ESI†). AMEA instead builds on best practice in industry, where criteria of safety and sustainability are integrated into the decisions to be made at each gate.<sup>28</sup> Examples were published *e.g.* by Unilever,<sup>29</sup> Solvay,<sup>30</sup> Evonik<sup>31</sup> or BASF.<sup>32</sup> In the following we introduce the tiered logic (Table 1), and then provide specific guidance for AdMa in section 3.3. The AMEA approach serves the need of SME and industry to perform very early screenings with tiered data requirements that are adapted to the ripeness of the innovation project:

- During the ideation phase (before gate 2, Fig. SI\_1†), the technology readiness level (TRL,<sup>36,37</sup> see also ESI†) is around 1 to 3: a market need has been identified, and a design is being developed for a certain P-A-R. Here design principles for exposure during lifecycle, hazard, and sustainability are key to guide the innovation:

- With respect to **sustainability**, design targets of the AdMa product are derived from the sustainability deficiencies of the CoMa product for the same application target.



◦ **Design principles** focus on warning signs from existing materials, *e.g.* the late lessons from early warnings (Harremoës *et al.* 2001)<sup>1</sup> and on circularity (Table 1).

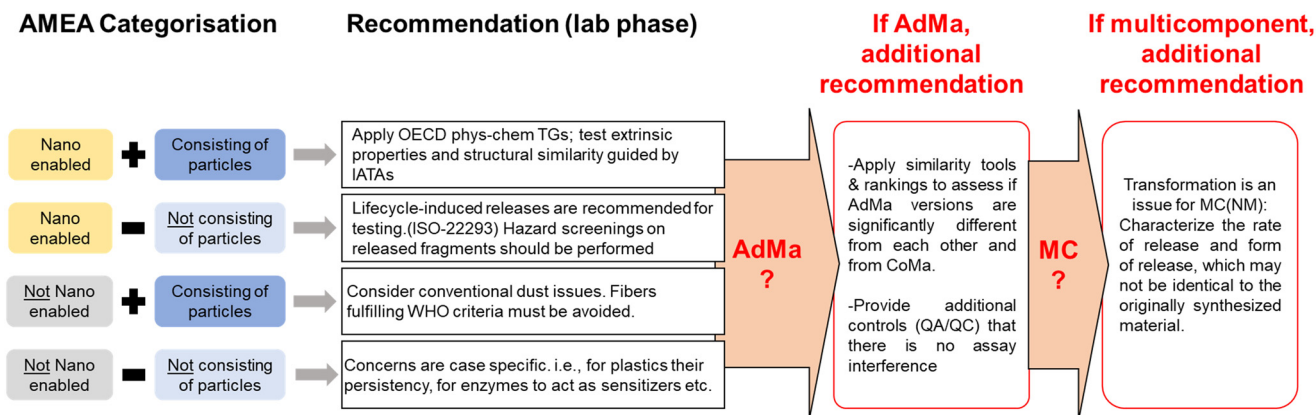
◦ The intended use that is captured by the P-A-R allows a qualitative identification of hot spots, where emission into the environment and/or exposure of humans is likely. Often, these hot spots are well known in the industry sector.

• During the business case phase (before gate 3, Fig. SI\_1†), the TRL is still unchanged, but the commercial readiness is being improved by estimates of profitability (and ECV) of key customers. The resources that would be needed for further development in the next phases are planned, including budgets and technical capabilities (in-house or at partners). If all these considerations did not stop the project,

**Table 1** Tiered guidance for assessment with specific implications of categorization as advanced (AdMa) or multicomponent (MC) material shown in italic font. The tiered structure is consistent with industrial best practice on chemicals in general<sup>33</sup> and is not specific to nanomaterials. In HARMLESS, the framework follows the agile StageGate model, but still we differentiated here between the two earliest phases for those companies following the full five-stage process (Fig. SI\_1†)<sup>22,23</sup>

Agile stage-gate	Full stage-gate	Guidance for the assessment of safety and sustainability to be done during the specific phase to support the investment decision (stop/go) in the next gate
Idea and screening phase	Ideation phase (before gate 2)	<p><b>Sustainability: design idea for an innovation project</b></p> <ul style="list-style-type: none"> <li>Market need that is currently filled by unsustainable technology</li> </ul> <p><b>Design principles: lifecycle</b></p> <ul style="list-style-type: none"> <li>Consider end-of-life, design for circularity</li> <li>Describe P-A-R = product, application, region<sup>33</sup> and qualitatively identify potential hot spots</li> </ul> <p><b>Design principles: properties to avoid, based on slate lessons from early warnings:<sup>1</sup></b></p> <ul style="list-style-type: none"> <li>Fibers fitting the World Health Organisation (WHO) criteria</li> <li>Persistence</li> <li>Widespread use</li> <li>Bioaccumulation</li> <li>Irreversible effects</li> <li><i>Novelty (= trigger of AdMa discussion)</i></li> <li>Heavy metals &amp; other groups in generic approach</li> </ul> <p><b>Exposure during lifecycle: refine design by known principles and benchmark cases:</b></p> <ul style="list-style-type: none"> <li>Refine hot spot analysis by SPERC of benchmark cases for the same P-A-R.<sup>34</sup></li> </ul> <p>Focus on use map of intended use and sector</p> <ul style="list-style-type: none"> <li><i>In case of advanced manufacturing: consider non-chemical hazards, e.g., process-generated concerns</i></li> </ul> <p><b>Hazard: refine design by intrinsic properties</b></p> <ul style="list-style-type: none"> <li><i>In case of MC, assess hazard of individual components, of most similar CoMa</i></li> <li><i>Does structural similarity rank the AdMa target design significantly different from CoMa?</i></li> </ul> <p><i>Assume H-phrases from the CLP regulation of CoMa as specific concerns to avoid regrettable substitution</i></p> <ul style="list-style-type: none"> <li><i>Consider if enhanced technical property is likely to change biological interaction: derive additional specific concerns</i></li> </ul> <p><b>Sustainability: specifications</b></p> <ul style="list-style-type: none"> <li><i>AdMa specifications derived from the sustainability deficiencies of the CoMa product for the same A-R target</i></li> </ul>
	Business case phase (before gate 3)	<p><b>Exposure during lifecycle: release testing: use phase, end-of-life phase:</b></p> <ul style="list-style-type: none"> <li>Use stresses that are representative of intended use, <i>e.g.</i> ISO standards of durability &amp; performance testing</li> <li><i>Especially if MC: characterize the rate and form of release (check for transformation or degradation of MC (NM))</i></li> </ul> <p><b>Hazard: extrinsic properties = testing for specific concern:</b></p> <ul style="list-style-type: none"> <li>Perform physical-chemical characterization (by IATA)</li> <li>Apply similarity tools &amp; rankings to assess if AdMa versions are significantly different from each other and from CoMa</li> <li>Derive NAMs from guidance, where possible. <i>If AdMa, perform QA/QC that AdMa properties do not interfere with NAM</i></li> <li>Apply same NAM, same descriptor for new material and CoMa</li> <li><i>If MC(NM), perform test on released (transformed?) entities</i></li> <li><i>Option to show by data that AdMa is not similar to a group from initial generic risk assessment and prioritization<sup>35</sup></i></li> </ul> <p><b>Sustainability: indicative rankings</b></p> <ul style="list-style-type: none"> <li>Data on performance, exposure, hazard that is specific to each version enables an indicative ranking and re-design priorities</li> <li>Re-assess the potential contribution of the AdMa to UN Sustainable Development goals as compared to CoMa</li> </ul>
Lab phase	Lab phase (before gate 4)	





**Fig. 3** Implications of the “nano” and “particle” dimensions for the prioritization of concerns and for the selection of appropriate methods during the lab phase screenings. For either of the four combinations (corresponding to the four quadrants categorized in Fig. 2), lab-phase recommendations are given; additional action may be necessary, if a material is advanced and/or consists of multiple components.

it is worthwhile to refine the design by known principles and benchmark cases. At the end of the business case, the design specifications are established as goals for the next phase. Recommendations include:

- **Exposure during lifecycle:** for many sectors and uses, one can rely on the preconfigured ECHA “use maps”, or Specific Environmental Release Category (SPERC)<sup>34</sup> of benchmark cases for the same P-A-R (Table 1), or the HotSpotScan tool.<sup>38</sup> This type of generic data applies the same values to AdMa and CoMa, and thus does not differentiate them, but allows expert judgement by lifecycle thinking to prioritize hot spots and corresponding hazard endpoints.<sup>13</sup>

- **Hazard:** one can refine the design of intrinsic properties (structure) by digital (*in silico*) tools of structural similarity to known benchmark cases with well-known hazard classes. Suitable digital tools do not exist yet for all material classes and endpoints, but are increasingly powerful.<sup>39–41</sup> If the design space is very wide (many possible solutions for the market need), this step consumes a lot of time and would be shifted to the next phase, after narrowing of the design space.

- **Sustainability:** as in the ideation phase.

- **Budgeting for the lab phase:** the project budget needs to cover both innovation development and prioritized SSbD screenings, to enable decision-making at gate 3. It must be justified by the expected commercial value (ECV)<sup>42</sup> of the targeted product, application and region (P-A-R).<sup>33</sup>

- During the Lab phase (after gate 3, before gate 4, Fig. SI\_1†), the TRL must increase to 5 or 6,<sup>36</sup> otherwise the project will not pass gate 4. In this phase, the new material comes into physical existence. Recommendations include:

- **Synthesis:** small quantities of many different versions are generated, ideally guided by systematic variation of parameters and systematic characterization.

- **Physical-chemical characterization:** this goes hand-in-hand with the synthesis to check the properties against the design specifications of the new material.

- **Performance:** as soon as lab-scale demonstrators are generated, testing of the performance starts and allows benchmarking of the AdMa against the CoMa for the same market need (same A-R). A demonstrator means the integration of the new material into the final product or formulation and would be considered as an article (if ever launched to market) in regulatory terms.

- **Exposure during lifecycle:** using the same lab-scale demonstrators, testing of releases during the use phase and end-of-life phase is possible, and ideally uses the same stresses as relevant for the intended use, *e.g.* by using the same standardized test with additional characterization (of dust, leachates *etc.*).<sup>43–45</sup> The assessment should address the extent to which materials containing particles release these particles.

- **Hazard:** digital (*in silico*) tools of structural similarity can now be supported and refined by targeted testing of the relevant extrinsic properties (NAM: in chemico, *in vitro*) for the specific concern derived from the hot spots. IATAs, if available, can guide the selection of relevant properties and methods. Extensive research is ongoing to support by AOPs, NAMs, tools, assays, and it is beyond scope of the present contribution to recommend specific tools.

- **Sustainability:** sustainability assessment (by *e.g.* the LICARA innovation scan<sup>46</sup> or other tools) will still have to use a lot of generic data copied from the CoMa benchmark, but discriminating power may be good enough to provide an indicative ranking of the different AdMa versions, based on the data in raw materials, performance, exposure, and hazard that is specific to each AdMa version.

Pilot and launch phases are out of scope of the present AMEA scheme but are in scope of the other modules of the HARMLESS framework and DSS. Typically, only one version of the AdMa is continued in the pilot phase, and the value chain from raw materials to consumer is being demonstrated. Hence, from pilot phase, a life-cycle inventory can be established by trained experts, to enable specific LCA and sustainability assessment of the AdMa compared to the



CoMa.<sup>13</sup> By definition, a launch constitutes TRL 7 to 8.<sup>36</sup> In the above tiered approach, the certainty of assessment increases from phase to phase as required for product development. The assignment of data requirements and criteria to certain innovation phases must remain flexible, as explained in the following. Flexibility of data requirements is routine practice in performance testing during industrial R&D, where performance is often assessed only by screening tests during lab phase, whereas standardized tests are required for investment decision with high impact. Furthermore, performance testing on demonstrator articles of the integration into the customer's final product are decisive, but more typical for the next phase (pilot phase). Accordingly, also the release testing (for exposure) may need

to be shifted to pilot phase, because it depends on demonstrators. The above assignment of data requirements is adequate for an investment decision with high impact, such as an innovation project that would lead (if passing all gates) to the construction of a production facility in the multi-ton scale, incurring costs of several million Euros. For a more modest investment decision and/or more incremental innovation goal, criteria would be shifted from ideation and business phases to lab phase, and from lab phase to pilot phase, and the overall probability of late surprises due to failed safety criteria would still be low.

In the HARMLESS project, the ideation & business case are considered as one phase, followed by the Lab phase, and by the pilot & launch phase. This three-stage approach is

### Box 2: Implications of categorization for data requirements and testing methods

- During the ideation phase, apply the universal design principles.<sup>13</sup> One of the conventional warning signs, the “novelty”<sup>1,50</sup> is in fact the trigger for the entire elaborate concept on AdMa that we discuss here.
- If made by advanced manufacturing, consider non-chemical hazards, *e.g.* process-generated concerns. Examples include the intense laser radiation used in the selective laser sintering process of powder-based 3D-printing, or large-scale robots that are used for 3D printing of concrete on construction sites.
- For all materials in the lab phase, it is recommended to perform physical–chemical characterization. Loosli *et al.* highlighted that among all physical–chemical properties, dissolution was requested most frequently by IATAs for comparative assessment of nanomaterials.<sup>51</sup>
- If AdMa has multiple components, transformation is a bigger issue than for AdMa made of single substances.<sup>12</sup> One should characterize the rate of release and form of release, which may not be identical to the originally synthesized material, *e.g.* preferential leaching from advanced composite materials, or unintentional triggering of the rare “active” AdMa.<sup>11</sup> All composites are MC by definition.
- If AdMa has multiple components, hazards must be identified initially from the hazard of each component, even if mixture effects have to be considered at higher TRL.<sup>11,12</sup> For example on aerogel-glass fiber mats, one may initially screen for the hazard of the glass fiber and separately for hazard of the aerogel, where the latter can be approximated by a CoMa of similar extreme porosity. One should, in later phases, perform hazard screenings not on the originally synthesized material but also consider the released entities. This was originally demonstrated for nano-composite materials.<sup>43,52–55</sup> To extrapolate dose-related effects from screening tests to higher-tier tests, it may be necessary to test also a reconstituted pure form of a key transformation product, *e.g.* AgS<sub>2</sub> when testing a MCNM that leaches Ag. A MC-AdMa case study is given in the next section.
- In case of AdMa, apply similarity tools & rankings to assess if AdMa versions are significantly different from each other and from CoMa. If not, the design space is less restricted in the next phase, and can be guided by performance and cost. If significantly different, such as in the example in the ESI,† trade-offs must be weighed, which will require dedicated tools during the lab phase, before entering the pilot phase (to avoid investment decisions leading to failure). As a default assumption, the H-phrases of the CoMa constitute the initial specific concerns of the AdMa.
- If AdMa, one must provide additional controls (QA/QC) that the methods are appropriate, *e.g.* by using several methods with complementary measurement principles. For the prioritized endpoints of the specific concerns, NAMs incl. screenings tests of extrinsic properties should be compatible with or derived from guidance or test guidelines, or from AOPs.<sup>11,33</sup>
- If nano-enabled and consisting of particles (upper right quadrant in Fig. 2), appropriate methods must be used for structural similarity (*e.g.* nanoQSARs, although these may not be fully validated), in physical–chemical characterization and in the testing of extrinsic properties (*e.g.* screenings derived from nano-specific test guidelines,<sup>56</sup> IATAs for selection of most relevant properties<sup>57–60</sup>). At the lab phase, tests may, but do not need to fulfil guideline requirements, and do not need GLP status; as GLP largely impacts speed and costs.
- If nano-enabled but not consisting of particles (upper left quadrant in Fig. 2), lifecycle-induced releases are recommended for testing.<sup>61</sup> Hazard screenings on released fragments is possible and relevant, as demonstrated on the example of organic aerogels.<sup>62</sup>
- If not nano-enabled but consisting of particles (lower right quadrant in Fig. 2), the conventional dust issues are to be considered. Especially the presence of fibers fulfilling the criteria of the World Health Organisation (compare design principles, Table 1) must be avoided.
- If not nano-enabled and not consisting of particles (lower left quadrant in Fig. 2), other concerns should be prioritized. Examples are the sensitizing issues of enzymes,<sup>63</sup> or the persistence issue of plastics.





more agile, but still we differentiated here between the two earliest stages (ideation vs. business case) for those companies following the full five-stage process (as in Fig. SI\_1†).<sup>22,23,32</sup>

### 2.3. Implications of categorisation for data requirements and testing methods

While the implications of the three-dimensional categorization (Fig. 1) can be shown in any safety screening scheme, Box 2 and Fig. 3 specifically demonstrate the implications for the lab phase of the screening scheme in Table 1. The specific guidance for AdMa and MC materials in Table 1 and Fig. 3 is highlighted. The implications are cumulative: a material that is AdMa and nano-enabled triggers both of the requirements or recommendations.

Considering again the above-mentioned focus in our assessment schemes to nano-enabled materials, we maintain that the AMEA logical flow of Table 1 can be amended for other AdMa classes. As a specific example, the ECHA restriction of intentionally produced primary microplastic<sup>47</sup> and the upcoming plan to require registration of certain polymers under REACH define assessment priorities for materials containing polymers.<sup>48,49</sup> It is entirely possible, but beyond the scope here, to amend Table 1 by specific requirements *e.g.* for materials that are biologicals, polymers, or undefined and variable compositions. REACH has such requirements for the registration, and one could take inspiration from there for the early screenings at low TRL.

### 2.4. Exemplary case studies

Some of the entries in Fig. 2 reflect case studies that have been categorized according to the AMEA initial questions (Table SI\_1†). Since the present AMEA conceptualization precedes the demonstration, only one case study is published yet,<sup>64</sup> and all others are in the process of being evaluated against the design principles and of being screened with

methods recommended for the lab phase by Table 1 and Fig. 3. In short:

#### • AdMa with multiple components

Perovskites are oxides of multiple metals, some of which were studied by the HARMLESS project with a rational design for the qualitatively new functional performance<sup>21</sup> of oxygen storage capacity and catalytic activity, to replace traditional wash coats in the canned three-way automotive exhaust catalysts (Fig. 4, Table SI\_1†). They are not commercialized yet for this purpose, but due to the intended use, an “ex ante LCA”<sup>13</sup> identifies the hot spot of environmental fate of potential wastewater from the precipitation synthesis and potential occupational exposure during calcination. In contrast, the screening deprioritized exposure by installation and use in the car. Contrary to the AMEA recommendation, no ECHA use maps exist for this purpose. The perovskites are considered (Box 1) as AdMa with multiple components and were tested in several variations of the basic structure of  $\text{LaCo}_{0.475}\text{Ni}_{0.475}\text{Pd}_{0.05}\text{O}_3$  (Fig. 4). The AMEA scheme recommended to characterize the exposure during lifecycle, specifically the rate of release of the contained heavy metals and form of release (ionic or particle components) (Table 1). The screenings were implemented by screening methods that are compatible with OECD GD 318 (but not testing all the media required for a TG318 study), for both dispersion stability and leaching, and, incongruent leaching of the different metal components was observed.<sup>65</sup> Since the hot spots included aquatic compartments due to production waste water, point-of-entry bioaccumulation assessment was performed on crustacean studies in the lab phase. It could be followed up in later phases by algal interaction studies, and finally confirmatory fish bioaccumulation studies.<sup>66</sup> Furthermore, Table 1 recommended to apply similarity tools and rankings to assess if AdMa versions (variations of  $\text{LaCo}_{0.475}\text{Ni}_{0.475}\text{Pd}_{0.05}\text{O}_3$ ) are significantly different from each other and from CoMa. As CoMa,  $\text{CeO}_2\text{:Pd}$  was selected, to apply screenings of functional performance and of hazard.<sup>67</sup>



Fig. 4 Case study: perovskites intended for the use as canned automotive catalyst. AdMa versions differ in their mineralogical composition.



Changing the mineralogical composition was mentioned as under-used SSbD design strategy,<sup>68</sup> but no standardized methods exist to assess transformation of such inorganic AdMa (recommended by Table 1). An ongoing OECD project is developing guidance. As a next step *e.g.* LICARA innovation scan<sup>46</sup> or other tools of the HARMLESS DSS could be applied.

- Nano-enabled and consisting of particles

TiO<sub>2</sub> as white pigment and also nanoforms of TiO<sub>2</sub> serving as UV filter in transparent sunscreens are conventional materials that are available from numerous suppliers, are tested and approved in many countries (Table SI\_1†). However, TiO<sub>2</sub> nanofibers and nanocubes have targeted inherent structural features (Fig. SI\_2†) and are rationally designed for other functional uses than the pigments and UV filters. They are thus considered as AdMa (Box 1). The intended use of the TiO<sub>2</sub> cubes and fibers was not clearly defined by the producer, allowing no hot spot analysis. Following their production in powder form, the occupational hot spot of powder handling with inhalation concerns can be identified. Furthermore, the stiff and potentially biopersistent TiO<sub>2</sub> nanofibers violate design principles (Table 1) and differed by a description of the crystallinity by the supplier that was not usual for the CoMa. A suitable IATA exists and recommends testing of biodissolution, surface reactivity and *in vitro* macrophage interaction.<sup>58,59</sup> Benchmark materials were selected from the JRC repository with ample data from the EU Nano-Safety-Cluster. The results (Table SI\_1, Fig. SI\_3†) confirmed pronounced effects of the rigid TiO<sub>2</sub> nanofibers and attributed them by similarity and ranking (Fig. SI\_3†) to the fiber shape (excluding this part of the design space from further development), not the crystallinity (leaving the design open for crystallinity). The nanocubes, however, were similar to the CoMa benchmarks (Table SI\_2, Fig. SI\_3†). These investigations required several weeks by skilled labs. For the fibers (violating a design principle) the data requirement in the lab phase was considered adequate, but for the nanocubes (no violation of

design principles, and structurally similar to the CoMa), the postponement of benchmarking from lab phase to pilot phase would also have been adequate. The similarity to the well-known benchmark materials from the JRC repository allows the identification of safe uses.

- Nano-enabled and consisting of particles.

Quantum Dots, especially those with elaborate core-shell-coating structures (Fig. 5) clearly have targeted inherent structural features, and act as color converters by a qualitatively different mechanism than conventional color filters (Table SI\_1†). They are known since more than a decade, but can still be considered as AdMa, because the structural design is complex and their large-scale commercial use in TV screens is still recent and limited to few suppliers.<sup>68–70</sup> The recommendation (Table 1) to apply similarity tools & rankings to assess if AdMa versions are significantly different from each other and from CoMa was implemented by Di Battista *et al.* by testing of biodissolution and surface reactivity on a family of ZnCuInS–ZnS variations, benchmarked against pure CuO.<sup>64</sup> Additionally, reactivity was tested on the release-adjusted doses of the pure Cu, In, Zn ions, to fulfill also the recommendation to perform tests on released entities (Table 1). One reactivity test with potential AdMa interference (DCFH is among the recommended assays but relies on fluorescence)<sup>71</sup> was excluded. The functional performance was screened by testing the quantum yield and fluorescence spectra on the suspended particles, because a customer capable of producing the integrated demonstrator of light converter films was not involved at this low TRL phase. Similarity metrics of Euclidean distance were applied both to the hazard descriptors and to performance descriptors, and as a next step *e.g.* LICARA innovation scan<sup>46</sup> or other tools of the HARMLESS DSS could be applied.<sup>64</sup>

- Nano-enabled but not consisting of particles

Aerogel-fiber mats have inherent structural features that are different from CoMa such as mineral wool or polymer foams (Table SI\_1†). Specifically, the aerogel-fiber mats are a

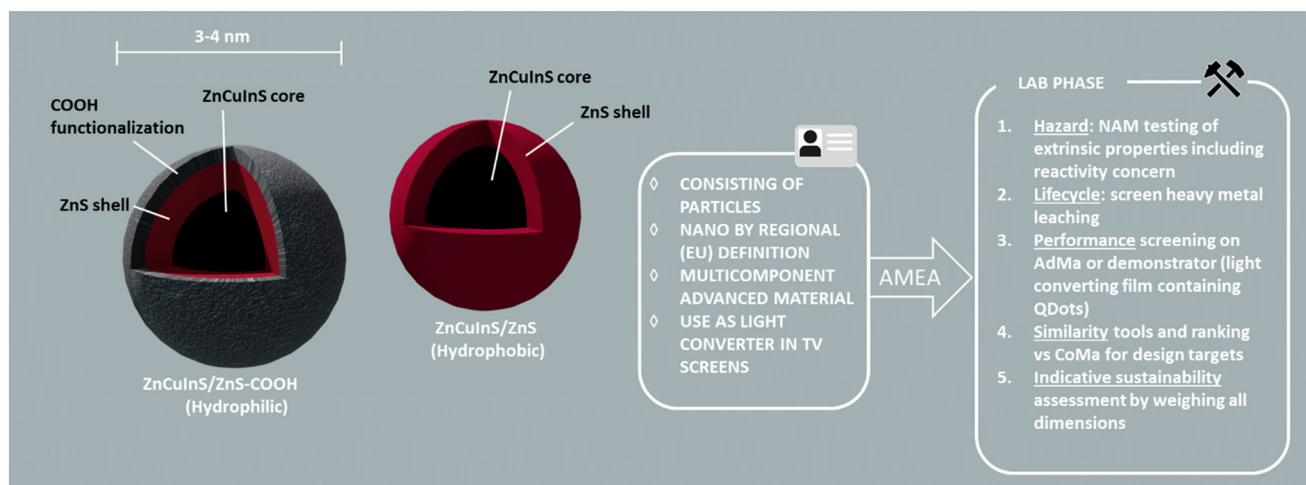


Fig. 5 Case study: quantum dots intended for the use as light converter in TV screens.



rationally designed nanoporous structure supported inside a fiber network, and achieve enhanced thermal insulation in a sector where 10% improvement is considered significant.<sup>72–74</sup> They are thus an AdMa now, but since they are increasingly established in higher-value niches of the insulation market,<sup>75,76</sup> some stakeholders may consider aerogels now or in a few years as CoMa. Following the recommendation to test lifecycle-induced releases, incl. end of life by nanospecific methods,<sup>61</sup> the aerosol emission during the scenario of “installation” and of “tear-down” was tested. Following the recommendation to assess the form of release (Table 1) and to ensure that the AdMa does not interfere with the assay (Table 1), several complementary methods of aerosol count and identification were combined in the tests.<sup>77</sup> Also the recommendation of hazard screenings on released fragments is possible and relevant, as demonstrated on the example of organic aerogels,<sup>62</sup> which serve different intended uses.

- Advanced manufacturing (some consisting of particles, some nano-enabled)

By the OECD description, all targeted structures by additive manufacturing are “advanced” (Box 1). In contrast, the intermediate (polymer filament or metal powder or concrete slurry), or the final 3D-printed part, is not necessarily an AdMa only due to the manufacturing process.<sup>21</sup> For example, steel parts are routinely fabricated from metal powders by the selective laser sintering process in industry,<sup>78,79</sup> and polymer filament printing is widespread for consumers and other uses. Hot spots of releases due to metal powder handling in industry and risk management by enclosure are easily identified, serving also the management of the non-chemical risk of high-intensity laser irradiation. Hot spots for consumers by polymer fume evaporation are known and are attributed to the combination of processing conditions and chemical material.<sup>80</sup> Additives in the materials, or novel processes, e.g. robots, may give reason to consider additive manufacturing as advanced manufacturing, and this would trigger (Table 1) more requirements, in the example on the leaching and release of the additives,<sup>81,82</sup> and on the non-chemical risks of the novel process.

### 3. Discussion

#### 3.1. Comparison of AMEA to other tools for AdMa screening during innovation process

Several recent reports support our position that – partially due to EU funding policy – current approaches to the AdMa field over-represent nano-enabled AdMa, especially those for the health sector, with too few approaches for the chemical space of AdMa in general, or alloys, or polymers, or biotechnology.<sup>13,83</sup> Some approaches focused entirely on the sub-topic of “smart nanomaterials”, which they understand as stimuli-responsive nanomaterials, which are currently emerging for uses in food, food packaging, cosmetics and agriculture. These materials are consistent with the “active materials” class in DAMADEI and MatSEEC schemes, due to

the stimuli-responsiveness. Gottardo *et al.* argued that these materials pose new challenges to safety and sustainability assessment due to their complexity and dynamic behavior.<sup>4</sup> Mech *et al.* also elaborated on smart nanomaterials as a case study of the challenges of SSbD.<sup>3</sup> But how many of the material categories in Fig. 2 are actually stimuli-responsive? One cannot generalize from this peculiar sub-topic to all AdMa.<sup>2</sup> An ECHA-mandated report on “next generation nanomaterials” found no major regulatory gaps<sup>84</sup> and instead noted in the outlook that industry also uses synthetic routes other than particles to induce internal nanostructure, pointing to a report of the nanomat network.<sup>69</sup> This is consistent with the choice of dimensions in AMEA (Fig. 1), leading to specific recommendations (Table 1).

In their seminal paper on risk assessment of AdMa, Kennedy *et al.* were unfortunately not aware of the visionary DAMADEI and MATSEEC contributions, stating in 2019 that no categorization scheme had been proposed, but they nicely clarified that AdMa only partially overlap with nanomaterials by AdMa “encapsulating the subset of engineered nanomaterials that demonstrate unique behavior”.<sup>21</sup> Kennedy *et al.* also stated that advanced materials do not all require an in-depth risk assessment, since they may be benign, or may transform to lose unique properties in the environment, or may not result in exposure.<sup>21</sup> In the present contribution we aimed to progress beyond the very generic “conceptual groupings” proposed by Kennedy *et al.*, such as “enhanced property, novel use” or “novel property, advanced manufacturing”, from which they could not guide the risk assessment without more specific identification of concerns and appropriate methods. More recently, Valsami-Jones *et al.* supported specifically that the categorization of AdMa enables a differentiation based on properties and technical criteria<sup>2</sup> (in our terminology: P-A-R), and Amorim *et al.* stressed that categorization enables measurable criteria, very much in support of our focus on data requirements.<sup>11</sup> They envisioned knowledge-based risk management to be developed with omics data, but in our interpretation this framework does not necessarily involve omics testing at low TRL for AdMa screening. Instead, a recent ASTM standard for SSbD innovation in one specific application was the first to consider the cost of performing SSbD screenings, and established that the tiered assessment is adjusted to the available funding and the innovation stage.<sup>27</sup>

A recent overview of lifecycle-derived approaches to SSbD during the early phases of innovation was excellent structured by Subramanian *et al.*<sup>13</sup> They assigned lifecycle thinking from TRL 1, ex ante LCA and *in silico* or *in vitro* screenings of hazard from TRL 3, but actual risk assessment with uncertainty estimation only from the pilot phase with TRL 7.<sup>13</sup> The initial focus on lifecycle thinking and the assignment of tools to innovation phases matches our assignment in Table 1. Subramanian *et al.* furthermore supported that full LCA and regulatory risk assessment is only possible from TRL 9.<sup>13</sup>





### Box 3: Comparative screening of sustainability concerns and sustainability benefits

AdMa often substitute CoMa, with the specific design target to remediate the CoMa deficiencies in certain dimensions of SSbD.<sup>33</sup> The assessment for SSbD at lab phase can be guided by the comparison to the CoMa for the same P-A-R. Using selected categories from Fig. 2, this could be done as follows (notes on AdMa in *italic*):

- Coatings: can contain particles (conventional nanomaterials such as pigments and fillers)
  - Typical SSbD concerns from solvent content, from dust generation during production of raw materials (pigment), from lifecycle releases (sanding dust) during repair operations
  - Typical SSbD benefit from extended service life of coated part
  - Advanced if *e.g.* self-healing – does it change SSbD concerns & benefits?
- Paints: always contain particles (conventional non-nano-materials such as TiO<sub>2</sub>, or natural nanomaterials such as Kaolin, or conventional engineered nanomaterials such as silica)
  - Typical SSbD concerns from waste release (primary microplastic) or weathering (secondary micropl.)
  - Typical SSbD benefit from water-borne formulation (no solvents)
  - Advanced if *e.g.* anti-soiling or based on dendrimers – does it change SSbD concerns & benefits?
- Rubber: in most cases contain fillers (Carbon Black, silica), which are conventional nanomaterials
  - Typical SSbD concern from raw materials (truck tire: natural rubber), from wear (secondary microplastics)
  - Advanced if *e.g.* low-wear tires (by rationally designed HD-silica grades, see OECD reports)
- Metal alloys (typically not nano-enabled, not typically handled as small particle)
  - Typical SSbD concern from raw materials (rare metals, mining operations, embodied energy)
  - Advanced *e.g.* if shape-memory, if replacing cobalt, *etc.* – does it change SSbD concerns & benefits?
- Plastics: most are not nano-enabled, but can contain particle and fiber fillers
  - Typical SSbD concern from raw materials (oil & gas) and from lack of circularity
  - Typical SSbD benefit from light weight function, packaging barrier function
  - Advanced if *e.g.* biobased, recyclable, biodegrading – does it change SSbD concerns & benefits?

Differing from the more tiered approaches by AMEA and by Subramanian *et al.*, the approach by Pizzol *et al.*, confronts the user with a list of more than 150 questions, trying to cover all SSbD dimensions from the earliest innovation phases.<sup>85</sup> Their questions were derived from the original draft of the regulatory awareness tool Early4AdMa<sup>86</sup> (revised since then, see section 3.3). A comparison between CoMa and AdMa was introduced, including a consideration of uncertainty from “I do not know” answers. AMEA agrees with Pizzol *et al.* that the SSbD approach must be always comparative, and is consistent with their assessment if “a modified MCNM or the respective product performs better in terms of safety, functionality and sustainability performance than another SSbD design alternative or than a conventional material/product that has the same or a similar function”. However, the experience from an OECD workshop on the example of aerogel-fiber-mats (see the exemplification in section 3.4) highlighted that some of the more than 150 questions of the original Early4AdMa and the Pizzol *et al.* approaches could not be answered at all, whereas many required expert judgment and the use of generic answers (see section 2.2) that grouped the entire sector of façade insulation, or grouped the entire category of aerogels. Without prioritization of hot spots leading to specific data for each SSbD version (see section 2.2), the assessment also did not provide SSbD feedback for design optimization. We believe that fewer, more targeted questions are needed.<sup>77</sup> One should add that the cost of the entire R&D project (including SSbD screenings) compared to the expected commercial value are important for industrial decision-making.<sup>42</sup>

All of the assessment frameworks consider exposure, and mention the specific lessons from nanomaterials,<sup>2</sup> but the SERENADE project most prominently explored risk management by exposure reduction.<sup>68</sup> Using commercially relevant products, an alternative kind of categorization was posited, namely that “products within a given application will undergo similar or identical exposure and hazard” to identify “risk linked to a specific type of use rather than the type of material”.<sup>68</sup> This thinking is highly consistent with the AMEA logic starting from the P-A-R to identify hot spots (Table 1) and SSbD challenges (section 3.2), and can be further supported with studies that group by use and matrix (instead of grouping by contained particles).<sup>87</sup>

The frequent characteristic of AdMa as being multi-component materials was recognized by many as challenge, and was often selected as case study to derive AdMa approaches.<sup>11,12,85,88</sup> Also some of the present cases (Fig. 4 and 5) address this challenge. The insufficient prediction of a MCNM effect by the effects of individual components, the potential transformation and mixture toxicity were raised as concern.<sup>11,12</sup> Interestingly, not only some AdMa are MC, but also some of the most conventional materials, *e.g.* stainless steel: alloys are MC materials by definition, and the testing for selective leaching and transformation from steel has been recognised as relevant.<sup>89</sup> Hence, the recommendations of





Table 1 apply in a comparative manner to CoMa and AdMa alike.

Finally, it is noted that AdMa categories exist with entirely different SSbD concerns and benefits, and hence entirely different priorities may arise during the earliest innovation phases. For example, a SSbD framework assessed innovative plastic food packaging primarily by packaging performance (preventing food loss),<sup>8</sup> aspects of circularity, and environmental footprint, but not by hazard.<sup>90</sup>

### 3.2. Comparison of AMEA to the European Commission's SSbD framework draft

The EU Commission has recommended a guidance framework establishing definitions of both “safety” and “sustainability” to foster substitutions for chemical products that may be phased out through stricter regulations. This includes a two-year test period. However, case studies have shown that even for established and REACH-registered CoMa (TRL 9), the data requirements for the four dimensions of the framework could not be fulfilled.<sup>63</sup> We consider this a serious shortcoming and concluded that between ideation and registration, a gradual transition from guiding principles to initial SSbD screening, to full SSbD assessment must be made. Hence, the AMEA follows this structure. It begins at ideation phase with design principles (Table 1), in line with the JRC draft framework. The categorisation (Fig. 2) and description of product, application, region (P-A-R)<sup>33</sup> has value in focusing the screenings in the next phases (business case, lab phase) on the hot spots that are all-too-often known for specific products and applications (Box 3). The present approach guides the sustainability screening by categorization (see section 2.1 and Box 3), and guides the safety screening by Table 1. The general recommendations at early phases (up to lab phase), and also the specific recommendations for AdMa and nanomaterials, can be mapped onto the five steps of the JRC draft framework, as shown in Fig. SI\_4.† The focus on hot spots, intended uses, and specific concerns of the P-A-R imply that elements of steps 4 and 5 precede and guide all other screenings. This is in line with the current industry best practice of assessing the most sensitive of the intended uses.<sup>32</sup> By considering both exposure and hazard (Table 1, Fig. SI\_4†), the screenings remain risk-based, covering the full life cycle in line with chemical and environmental regulations. A full LCA (by ISO14040/ISO 14044) is impossible for a new material for a new application,<sup>13</sup> but if the material category is known, elements of step 4 can be approximated *e.g.* by the SPERC from a CoMa for the same application.

The assessment for SSbD at lab phase must still remain lean (because the overall probability of launch is low, especially for AdMa), such that no full guideline tests can be performed. Only during pilot & launch phases, all dimensions of SSbD can be addressed, because the raw materials, production processes, uses and end-of-life options are defined during these phases. Those R&D projects that

survive to the launch on market are then seamlessly integrated in the portfolio sustainability assessment (PSA) of all products on the market, because our screening criteria are derived from the SSbD methodology on the PSA.<sup>32,33</sup>

With respect to the United Nations Sustainable Development goals,<sup>8</sup> and in line with the EU-SRIP,<sup>91</sup> AdMa should be assessed for their potential positive contribution to climate change & energy, resource efficiency, circular economy, pollution reduction, water protection, biodiversity, zero hunger & poverty, health & safety. Sustainability of AdMa on one hand relies on minimum resource consumption, maximum performance, long service life, ease of recycling. Performance in the intended functionality is a prerequisite for further development, as it is increasingly recognised by SSbD approaches.<sup>83</sup> Sustainability on the other hand relies on safety and a holistic lifecycle assessment. The assessment must consider the potential benefits of the material during the use phase on the integration in the final product (Box 3). Specifically for the above case studies, for the aerogel-fiber-mats, the energy savings by insulation must be considered, or for the perovskites, the cleaner air from exhaust catalysts. The weighing of sustainability benefits is not entirely clear in the drafted JRC SSbD framework yet.

When an early innovation phase is completed, the safety screenings may have indicated properties of a “most hazardous substance”, for which the JRC draft framework,<sup>63</sup> and also industrial best practice,<sup>30,32</sup> do not support the launch to the market. But during R&D, no fixed criteria should prevent the innovator from taking the commercial risk to proceed to the next phase. The innovator can then try to overturn the screening result by higher-tier testing and data, in order to evaluate safe uses and to successfully register before launch. It is common practice that tiered testing schemes overturn initial prioritization,<sup>39</sup> *e.g.* overturning groupings of intrinsic structure by testing the extrinsic properties.<sup>35</sup> In analogy, also the descriptors of economic viability and of performance are determined by tiered methods that achieve only in higher TRL phases a low uncertainty, but consume then more R&D resources.

### 3.3. Comparison of AMEA to the ongoing work in the OECD WPMN “Steering Group AdMa”

The OECD WPMN SG AdMa currently aims to develop a strategic approach for AdMa starting from advanced nanomaterials. A first version of the early awareness and action system for advanced materials (Early4AdMa) was originally proposed by the National Institute for Public Health and the Environment (RIVM, The Netherlands), the German Federal Institute for Risk Assessment (BfR), Federal Institute for Occupational Safety and Health (BAuA) and German Environment Agency (UBA) as a tool for an anticipatory risk governance approach as a basis for the discussions,<sup>86</sup> and was revised recently.<sup>92</sup> The Early4AdMa consists of two phases, an initial screening phase (tier 1) and a more detailed assessment phase (tier 2), which resulted



from combining two previously developed early warning systems, named NESSI (Novelty, Exposure, Severity, Scope, Immediacy) developed by the BfR<sup>5</sup> and a more detailed early warning system proposed by RIVM.

In the first screening tier of the Early4AdMa the user is mainly referred to the NESSI approach, which asks for expert judgements in five dimensions, namely Novelty (entirely novel materials or new applications of existing materials), Exposure (expected/estimated exposure of the AdMa or components for people and/or the environment), Severity (expected/estimated severity of harm for humans and/or the environment), Scope (expected scope in either the number of people affected or the geographical range) and Immediacy (expected time frame until the issues might become relevant). Each of these dimensions is scored from 1 to 5, resulting in an overall NESSI score. The NESSI score is complemented by some initial considerations on sustainability (e.g. the use of critical raw materials) and on the applicability of the existing regulations leading to a decision at the end of tier 1 whether or not a more detailed assessment within the second tier is required. The second tier consists of more than 150 specific questions sorted in five major topics, namely application/market entry-phase, safety assessment for human health, safety assessment for the environment, applicability of regulatory frameworks, and sustainability aspects.<sup>86</sup>

So far, the Early4AdMa has been tested in two case studies within the SG AdMa, one of which was the HARMLESS aerogel-fiber-mat (section 2.4) case study workshop comparing several concepts.<sup>21,93</sup> The strategic approach was revised<sup>92</sup> according to conclusions from the workshop.<sup>94</sup> Also the present AMEA approach takes into account the lessons from the workshop, e.g. adding consideration of lifecycle releases, adding more specific implications of the categorisation in Fig. 1 and 2, as now shown in Table 1.

We envision that the “ideation” and “business case” data requirements of the AMEA scheme (Fig. 1, Table 1) can be easily merged with tier 1 of Early4AdMa. The scope of AMEA is quite similar to the original NESSI scheme that became tier 1 of Early4AdMa, but AMEA is better focused on specific products, applications, regions (aligned with industrial WBCSD<sup>33</sup>). We furthermore anticipate that the more focused approach of the present “lab phase” data requirements (Fig. 1, Table 1) could be useful to subselect the most relevant ones from the currently very high number of questions in the original Early4AdMa tier 2. However, the frameworks will retain each a distinct perspective, since an “early” phase for regulatory preparedness, when first products of an AdMa appear on the market, is already a “late” phase for the innovator's SSbD process.

The WPMN also decided that “the considerations within the WPMN will build on the knowledge gained on manufactured nanomaterials, and possibly include other AdMa with relevance to safety, sustainability and regulatory issues considering their whole life cycle”. Fig. 2 supports four conclusions with relevance to the OECD WPMN discussion if nanomaterials are an appropriate

point of departure to develop approaches to AdMa risk screening:

a) Some AdMa are nano-enabled, but still not nanomaterials by the REACH definition, and are not made *via* particles (Fig. 2, top left quadrant). *E.g.* aerogels are not nanomaterials by EU Commission's recommended definition and hence not considered nanomaterial in REACH, but the fragments that they potentially release during their use and end-of-life phases can be assessed by methods and tiered testing schemes developed for nanomaterials.<sup>62,95</sup> The AMEA recommendations close the assessment gap on this quadrant.<sup>12</sup>

b) Many AdMa are not even nano-enabled. Examples include advanced (e.g. self-healing) coatings, gels and foams, advanced textiles, carbon-fiber-composites, shape-changing/memory materials, advanced alloys, advanced ceramics (Fig. 2, bottom left quadrant). This quadrant was mentioned<sup>2</sup> but mostly overlooked earlier.<sup>12</sup>

c) Not all nanomaterials are AdMa, e.g. silica, most pigments or carbon black are several decades old (Fig. 2, top right quadrant). Their nanoforms are now reported to the R-nano registry,<sup>96</sup> and the methodologies for their registration under REACH are mostly standardised by ISO or OECD. These materials rank high (ranks #1–5, 7, 9–12, 14–18) in the public list of production volumes above 100 tons to above 10 000 tons in France alone.

d) Some nanomaterials are AdMa, e.g. quantum dots as discussed above (Fig. 2, top right quadrant).

There is no unifying technological feature that would justify a common approach to the risk assessment on all materials in Fig. 2. In fact, materials that are not nano-enabled are prevalent (upper *vs.* lower part of Fig. 2). Furthermore, many AdMa are not based on particles (left *vs.* right part of Fig. 2), including many of the nano-enabled AdMa (top left quadrant of Fig. 2). Taken together, it is questionable if nanomaterials are a suitable point of departure for the development of generic concepts for all AdMa. Instead, Table 1 proposes a structured approach to identify the specific concern, with additional scrutiny for AdMa, and Fig. 3 adds the appropriate choice of methods for nano-enabled AdMa and CoMa. The HARMLESS DSS will be applicable to nano-enabled and nanoparticle-containing AdMa and CoMa.

## 4. Conclusions

The present assessment approach, termed AMEA (Advanced Material Earliest Assessment) fills a gap for design rules and simple assessments during the ideation and business case phases of innovation management. The AMEA also addresses the lab phase, where it recommends focusing on acquisition of data with discriminating power between the different versions of the innovative material and the conventional material (termed CoMa) for the same market need. That data can be processed by tools of sustainability screening that already exist<sup>46,97</sup> or that are currently being



developed and integrated *e.g.*, in the HARMLESS DSS, where the AMEA will be integrated as entry point. AMEA has been implemented as an online tool that provides SSbD prioritisation and guidance for each of the three innovation phases based on the categorization that follows answering the three main questions (<https://diamonds.tno.nl/projects/harmlesspublic>).

Data quality and data availability have often been addressed,<sup>83</sup> *e.g.* by database and read-across approaches, but we conclude that discriminating data is essential for SSbD decisions. AMEA recommendations for data acquisition are derived from a categorization that enables sector-specific, application-specific, potentially region-specific guidance, that is consistent with industrial best practice<sup>30–33</sup> and is workable at low TRL phases with tiered requirements. The AMEA approach triggers more requirements (Table 1) and/or specific testing methods depending on the answers to the three questions (Fig. 1): “is it nano-enabled?”, “is it an advanced material?”, “does it contain particles (such as a composite of formulation), or does it consist of particles (such as a powder), or none thereof?”

The exemplary categorization of many materials classes and their most advanced versions (Fig. 2) highlighted that not all AdMa are nano-enabled, but also that not all nanomaterials are advanced. AdMa have no unifying technological feature and no common concern. Several case studies from diverse industry sectors exemplified the AMEA approach *e.g.*, additive manufacturing of targeted structures, multi-component perovskite catalysts for automotive exhaust cleaning, multi-component aerogel-fiber mats for façade insulation, advanced and conventional forms of TiO<sub>2</sub>, and displays with color converters based on quantum dots.

During ideation phase, AMEA design principles prevail on both hazard and lifecycle considerations, which indeed can be considered in the design specifications. During the business case phase, AMEA asks users to identify hotspots of exposure during lifecycle, and -if the applicability domains fit- to apply digital tools of structural (intrinsic) similarity to known benchmark materials, since no lab work is possible yet. From the lab phase, AMEA recommends data acquisition with discriminating power for the most relevant intended use, and considers specificities of AdMa, multicomponent materials and nano-enabled products. The assignment of data requirements and criteria to certain innovation phases (Table 1) must remain flexible. The incentives are clear: it is in the interest of the innovator to reduce the probability of lost innovation budget by tiered and early screenings that discover potential failure due to safety and/or sustainability and/or commercial and/or technical reasons. Accordingly, the assignment of screening criteria is at the discretion of the innovator, as long as all SSbD dimensions are assessed before launch onto the market.

By mapping of the individual steps and recommendations, it was concluded that the AMEA approach serves the goals of the JRC draft SSbD framework, for which a starting point at

very low TRL was not originally developed. The present material categories and case studies suggested a more liberal approach than the strictly sequential steps of the JRC draft. Examples showed that already in early phases of innovation management, at the ideation phase before lab synthesis, the intended use in specific categories and industry sectors guides the assessment to typical SSbD challenges, where one can assess if the AdMa changes (alleviates or aggravates) a concern. The present AMEA approach will have to be combined with other tools that address socio-economic aspects, and with multicriteria decision-making to deal with trade-offs of risks *vs.* sustainability benefits during the use phase, considering that such benefits are the design target of many AdMa.<sup>15</sup>

## Glossary of abbreviations

AdMa	Advanced Material
AMI 2030	Advanced Materials Initiative 2030
AOP	Adverse Outcome Pathway
CFRP	Carbon fiber reinforced plastic
CLP	Classification and labelling of products
CoMa	Conventional Material
DAMADEI	Design and Advanced Materials As a Driver of European Innovation
DSS	Decision-support system
ECV	Expected commercial value
GLP	Good Laboratory Practice
GFRP	Glass fiber reinforced plastic
HARMLESS	Project acronym for: Advanced High-Aspect Ratio and Multicomponent materials: towards comprehensive intelligent testing and Safe-by-design Strategies
IATA	Integrated Approach to Testing and Assessment
LCA	Life cycle analysis
MC	Multicomponent
MatSEEC	Materials Science and Engineering Expert Committee
NAM	Novel approach methods
NM	Nanomaterial
NEP	Nano-enabled product
OECD	Organisation for Economic Cooperation and Development
P-A-R	Product-application-region
PSA	Portfolio Sustainability Assessment
QA/QC	Quality assurance/quality control
QSAR	Quantitative structure–activity relationships
R&D	Research and development
SPERC	Specific environmental release category
SME	Small and medium enterprise
SSbD	Safe-and-sustainable-by-design
TRL	Technology readiness level
WBCSD	World Business Council for Sustainable Development
WPMN	Working Party on Manufactured Nanomaterials (at OECD)



## Author contributions

Conceptualization: WW and all authors; methodology: BSM, AB, SD, EVS; investigation: MW, VDB, BS; visualization: VDB; writing – original draft: WW, AH, MW; writing – review & editing: AB, AH, BS, BSM, DB, EVS, MP, MW, OS, SD, VDB, WW

## Conflicts of interest

WW and VDB are employees of BASF SE, a company marketing conventional and advanced chemical and materials. The other authors declare no conflicts of interest.

## Acknowledgements

This work has received funding from BMBF (German Federal Ministry of Education and Research) within the project InnoMat.Life (03XP0216) and from EU-H2020 project HARMLESS (GA 953183). The initial dimensions and categories were developed in InnoMat.Life, and the HARMLESS project added the identification of specific concerns and SSbD assessment strategies. An earlier version of this scheme was compared against other screening approaches in an OECD-HARMLESS workshop in November 2022. We gratefully acknowledge the facilitation by Mar Gonzalez, and the lessons from the discussion with participants. We acknowledge Nathan Bossa and Veronique Adam for excellent comments on earlier versions of the manuscript.

## References

- 1 P. Harremoës, D. Gee, M. MacGarvin, A. Stirling, J. Keys, B. Wynne and S. G. Vaz, *Late lessons from early warnings: the precautionary principle 1896-2000*, Citeseer, 2001, ISBN: 9291673234.
- 2 E. Valsami-Jones, F. R. Cassee and A. Falk, From small to clever: What does the future hold for the safety and sustainability of advanced materials?, *Nano Today*, 2022, **42**, 101364.
- 3 A. Mech, S. Gottardo, V. Amenta, A. Amodio, S. Belz, S. Bøwadt, J. Drbohlavová, L. Farcas, P. Jantunen and A. Malyska, Safe-and sustainable-by-design: The case of Smart Nanomaterials. A perspective based on a European workshop, *Regul. Toxicol. Pharmacol.*, 2021, 105093.
- 4 S. Gottardo, A. Mech, J. Drbohlavova, A. Malyska, S. Bøwadt, J. R. Sintes and H. Rauscher, Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials, *NanoImpact*, 2021, 100297.
- 5 K. Schwirn, D. Völker, A. Haase, J. Tentschert, U. Bernauer, R. Packroff and V. Bachmann, Risk Governance of Advanced Materials - Considerations from the joint perspective of the German Higher Federal Authorities BAuA, BfR and UBA, accessible at <https://www.umweltbundesamt.de/publikationen/risk-governance-of-advanced-materials>, *Umweltbundesamt Texte*, 2021, vol. 156, p. 57.
- 6 OECD, *Advanced Materials: Working Description*, 2023, [https://one.oecd.org/document/ENV/CBC/MONO\(2022\)29/en/pdf](https://one.oecd.org/document/ENV/CBC/MONO(2022)29/en/pdf) (accessed).
- 7 EMMC, *Materials 2030 Manifesto*, it can be found under [https://ec.europa.eu/info/sites/default/files/research\\_and\\_innovation/research\\_by\\_area/documents/advanced-materials-2030-manifesto.pdf](https://ec.europa.eu/info/sites/default/files/research_and_innovation/research_by_area/documents/advanced-materials-2030-manifesto.pdf), 2022.
- 8 UN, *The Sustainable Development Goals Report*, 2023, ISBN 978-92-101460-0.
- 9 DAMADEI, *Design and Advanced Materials As a Driver of European Innovation*, 2013, ISBN: 87-90904-67-2.
- 10 MatSEEC, *Knowledge and Technology Transfer in Materials Science and Engineering in Europe*, 2015, ISBN: 978-2-36873-198-7.
- 11 M. J. B. Amorim, W. Peijnenburg, D. Greco, L. A. Saarimäki, V. I. Dumit, A. Bahl, A. Haase, L. Tran, J. Hackermüller, S. Canzler and J. J. Scott-Fordsmand, Systems toxicology to advance human and environmental hazard assessment: A roadmap for advanced materials, *Nano Today*, 2023, **48**, 101735, DOI: [10.1016/j.nantod.2022.101735](https://doi.org/10.1016/j.nantod.2022.101735).
- 12 F. Abdolapur Monikh, W. Peijnenburg, A. G. Oomen, E. Valsami-Jones, V. Stone, R. Kortet, J. Akkanen, P. Zhang, J. Kekäläinen, A. Sevcu and J. V. K. Kukkonen, “Advanced materials” and the challenges on the horizon for testing their (eco)toxicity and assessing their hazard, *Environ. Sci.: Adv.*, 2023, **2**(2), 162–170, DOI: [10.1039/D2VA00128D](https://doi.org/10.1039/D2VA00128D).
- 13 V. Subramanian, W. J. G. M. Peijnenburg, M. G. Vijver, C. F. Blanco, S. Cucurachi and J. B. Guinée, Approaches to implement safe by design in early product design through combining risk assessment and Life Cycle Assessment, *Chemosphere*, 2023, **311**, 137080.
- 14 *Advanced Materials*, <https://onlinelibrary.wiley.com/page/journal/15214095/homepage/productinformation.html>, (accessed, 15.11.2023).
- 15 Advanced\_Materials\_Initiative\_AMI2030, Materials 2030 Roadmap, can be found at <https://www.ami2030.eu/roadmap/>, 2022.
- 16 H. Rauscher, G. Roebben, A. Boix Sanfeliu, H. Emons, P. Gibson, R. Koeber, T. Linsinger, K. Rasmussen, J. Riego Sintes, B. Sokull-Kluettgen and H. Stamm, Towards a review of the EC Recommendation for a definition of the term “nanomaterial”: Part 3: Scientific-technical evaluation of options to clarify the definition and to facilitate its implementation, *JRC\_95675*, 2015, pp. 1–34.
- 17 T. V. Duncan, Release of Engineered Nanomaterials from Polymer Nanocomposites: the Effects of Matrix Degradation, *ACS Appl. Mater. Interfaces*, 2014, **7**, 20–39, DOI: [10.1021/am5062757](https://doi.org/10.1021/am5062757).
- 18 J. Höck, R. Behra, L. Bergamin, M. Bourqui-Pittet, C. Bosshard, T. Epprecht, T. Furrer, M. Gautschi, H. Hofmann and K. Höhener, *et al.*, Guidelines on the Precautionary Matrix for Synthetic Nanomaterials V4.0, can be accessed at <https://www.bag.admin.ch/pmx-en>, 2023.
- 19 H. Rauscher, A. Kobe, V. Kestens and K. Rasmussen, Is it a nanomaterial in the EU? Three essential elements to work it out, *Nano Today*, 2023, **49**, 101780.





- 20 ISO, *ISO/TS 80004-4:2011. Nanotechnologies — Vocabulary — Part 4: Nanostructured materials*, 2011, <https://www.iso.org/standard/52195.html> (accessed, 5.04.2024).
- 21 A. Kennedy, J. Brame, T. Rycroft, M. Wood, V. Zemba, C. Weiss Jr., M. Hull, C. Hill, C. Geraci and I. Linkov, A Definition and Categorization System for Advanced Materials: The Foundation for Risk-Informed Environmental Health and Safety Testing, *Risk Analysis*, 2019, **39**(8), 1783–1795, DOI: [10.1111/risa.13304](https://doi.org/10.1111/risa.13304).
- 22 R. G. Cooper, S. J. Edgett and E. J. Kleinschmidt, Optimizing the Stage-Gate Process: What Best-Practice Companies Do—II, *Res.-Technol. Manag.*, 2002, **45**(6), 43–49, DOI: [10.1080/08956308.2002.11671532](https://doi.org/10.1080/08956308.2002.11671532).
- 23 R. G. Cooper, Stage-gate systems: a new tool for managing new products, *Bus. Horiz.*, 1990, **33**(3), 44–54.
- 24 F. Kerka, B. Kreigesmann and M. B. Schwering, Evaluating innovation ideas: a comprehensive approach to New Product Development, *Int. J. Technol. Intell. Plan.*, 2009, **5**(2), 118–137, DOI: [10.1504/ijtip.2009.024174](https://doi.org/10.1504/ijtip.2009.024174).
- 25 G. A. Stevens and J. Burley, 3,000 Raw Ideas = 1 Commercial Success!, *Res.-Technol. Manag.*, 1997, **40**(3), 16–27, DOI: [10.1080/08956308.1997.11671126](https://doi.org/10.1080/08956308.1997.11671126).
- 26 D. Baxter, P. Trott and P. Ellwood, Reconceptualising innovation failure, *Res. Policy*, 2023, **52**(7), 104811, DOI: [10.1016/j.respol.2023.104811](https://doi.org/10.1016/j.respol.2023.104811).
- 27 ASTM, *Standard Guide for Assessing the Environmental and Human Health Impacts of New Compounds for Military Use*, ASTM, 2023, p. E2552.
- 28 ISO, 21505 Project, programme and portfolio management - guidance on governance, 2017.
- 29 I. Malcomber, S. Sim, F. Bohnes, D. Mason, G. Riley, C. Rodseth and E. Vandenbossche-Goddard, SAFE AND SUSTAINABLE BY DESIGN WITHIN UNILEVER: Application of Safe and Sustainable by Design Approaches for a Biosurfactant, can be found at: <https://www.unilever.com/sustainability/safety-and-environment/safe-and-sustainable-by-design/>, 2023.
- 30 B. Van Parys, Solvay sustainable portfolio management guide: Driving long-term sustainable growth, 2021, <https://www.solvay.com/sites/g/files/srpend221/files/2022-07/Sustainable%20Portfolio%20Management%20%28SP-M%29%20Guide.pdf> (accessed, 5.04.2024).
- 31 Evonik, *Sustainability Report*, 2022, <https://sustainability-report.evonik.com/> (accessed).
- 32 W. Lölsberg and P. Kölsch, *Sustainable Solutions Steering - TripleS Manual*, 2023, [https://www.basf.com/global/documents/en/sustainability/we-drive-sustainable-solutions/sustainable-solution-steering/BASF\\_TripleS\\_Manual.pdf](https://www.basf.com/global/documents/en/sustainability/we-drive-sustainable-solutions/sustainable-solution-steering/BASF_TripleS_Manual.pdf) (accessed, 5.04.2024).
- 33 WBCSD, *Portfolio Sustainability Assessments (PSA) v2.0*, 2023, <https://www.wbcd.org/Programs/Circular-Economy/Resources/Portfolio-Sustainability-Assessment-v2.0> (accessed).
- 34 A. Reihlen, T. Bahr, C. Bögi, C. Dobe, T. May, F. Verdonck, T. Wind, L. Zullo and J. Tolls, SPERCS—A tool for environmental emission estimation, *Integr. Environ. Assess. Manage.*, 2016, **12**(4), 772–781, DOI: [10.1002/ieam.1745](https://doi.org/10.1002/ieam.1745).
- 35 W. Wohlleben, A. Mehling and R. Landsiedel, Lessons Learned from the Grouping of Chemicals to Assess Risks to Human Health, *Angew. Chem., Int. Ed.*, 2023, **62**, e202210651, DOI: [10.1002/anie.202210651](https://doi.org/10.1002/anie.202210651).
- 36 European Commission, ABOUT TECHNOLOGY READINESS LEVELS: Why using TRLs? can be found at: <https://euraxess.ec.europa.eu/career-development/researchers/manual-scientific-entrepreneurship/major-steps/trl>, 2012.
- 37 NASA, Technology Readiness Levels, can be found at: [https://www.nasa.gov/wp-content/uploads/2017/12/458490main\\_trl\\_definitions.pdf?emrc=da53fb](https://www.nasa.gov/wp-content/uploads/2017/12/458490main_trl_definitions.pdf?emrc=da53fb).
- 38 TNO, Hotspot Scan, can be accessed at <https://diamonds.tno.nl/projects/hotspotscan>.
- 39 T. Luechtefeld, D. Marsh, C. Rowlands and T. Hartung, Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility, *Toxicol. Sci.*, 2018, **165**(1), 198–212.
- 40 A. Maertens, E. Golden and T. Hartung, Avoiding Regrettable Substitutions: Green Toxicology for Sustainable Chemistry, *ACS Sustainable Chem. Eng.*, 2021, **9**, 7749–7758.
- 41 A. Maertens, E. Antignac, E. Benfenati, D. Bloch, E. Fritsche, S. Hoffmann, J. Jaworska, G. Loizou, K. McNally and P. Piechota, *et al.*, The probable future of toxicology - probabilistic risk assessment, *ALTEX*, 2024, DOI: [10.14573/altex.2310301](https://doi.org/10.14573/altex.2310301).
- 42 ACCOUNTING\_CPE\_COURSES&BOOKS, R&D funding decisions, can be accessed at: <https://www.accountingtools.com/articles/rd-funding-decisions>, 2023.
- 43 M. J. B. Amorim, S. Lin, K. Schlich, J. M. Navas, A. Brunelli, N. Neubauer, K. Vilsmeier, A. L. Costa, A. Gondikas and T. Xia, *et al.*, Environmental Impacts by Fragments Released from Nanoenabled Products: A Multiassay, Multimaterial Exploration by the SUN Approach, *Environ. Sci. Technol.*, 2018, **52**, 1514–1524.
- 44 D. Pantano, N. Neubauer, J. Navratilova, L. Scifo, C. Cividini, V. Stone, F. von der Kammer, P. Müller, M. S. Sobrido and B. Angeletti, *et al.*, Transformations of nanoenabled copper formulations govern release, antifungal effectiveness, and sustainability throughout the wood protection lifecycle, *Environ. Sci. Technol.*, 2018, **52**(3), 1128–1138.
- 45 N. Neubauer, L. Scifo, J. Navratilova, A. Gondikas, A. Mackevica, D. Borschneck, P. Chaurand, V. Vidal, J. Rose, F. von der Kammer and W. Wohlleben, Nanoscale Coloristic Pigments: Upper Limits on Releases from Pigmented Plastic during Environmental Aging, In Food Contact, and by Leaching, *Environ. Sci. Technol.*, 2017, **51**(20), 11669–11680, DOI: [10.1021/acs.est.7b02578](https://doi.org/10.1021/acs.est.7b02578).
- 46 TNO and EMPA, *LICARA Innovation scan*, can be reached at <https://diamonds.tno.nl/#licara>, 2022.
- 47 ECHA, Intentionally-added microplastics: Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU, can be found under <https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/22921/term>, 2020.
- 48 WOOD, Scientific and technical support for the development of criteria to identify and group polymers for Registration/



- Evaluation under REACH and their impact assessment, 40867-WOOD-XX-XX-RP-OP-002\_S3\_P03.5, 2020.
- 49 ECETOC, The ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers), *ECETOC Technical Report*, 2019, 133-1.
  - 50 L. Persson, B. M. Carney Almroth, C. D. Collins, S. Cornell, C. A. de Wit, M. L. Diamond, P. Fantke, M. Hassellöv, M. MacLeod and M. W. Ryberg, *et al.*, Outside the Safe Operating Space of the Planetary Boundary for Novel Entities, *Environ. Sci. Technol.*, 2022, **56**(3), 1510–1521, DOI: [10.1021/acs.est.1c04158](https://doi.org/10.1021/acs.est.1c04158).
  - 51 F. Loosli, K. Rasmussen, H. Rauscher, R. K. Cross, N. Bossa, W. Peijnenburg, J. Arts, M. Matzke, C. Svendsen and D. Spurgeon, *et al.*, Refinement of the selection of physicochemical properties for grouping and read-across of nanoforms, *NanoImpact*, 2022, **25**, 100375, DOI: [10.1016/j.impact.2021.100375](https://doi.org/10.1016/j.impact.2021.100375).
  - 52 A. T. Saber, A. Mortensen, J. Szarek, I. K. Koponen, M. Levin, N. R. Jacobsen, M. E. Pozzebon, S. P. Mucelli, D. G. Rickerby and K. Kling, *et al.*, Epoxy composite dusts with and without carbon nanotubes cause similar pulmonary responses, but differences in liver histology in mice following pulmonary deposition, *Part. Fibre Toxicol.*, 2016, **13**(1), 1–20, DOI: [10.1186/s12989-016-0148-2](https://doi.org/10.1186/s12989-016-0148-2).
  - 53 V. Gomez, M. Levin, A. T. Saber, S. Irusta, M. Dal Maso, R. Hanoi, J. Santamaria, K. A. Jensen, H. Wallin and I. K. Koponen, Comparison of Dust Release from Epoxy and Paint Nanocomposites and Conventional Products during Sanding and Sawing, *Ann. Occup. Hyg.*, 2014, **58**, 983–994.
  - 54 A. Saber, N. Jacobsen, A. Mortensen, J. Szarek, P. Jackson, A. Madsen, K. Jensen, I. Koponen, G. Brunborg and K. Gutzkow, *et al.*, Nanotitanium dioxide toxicity in mouse lung is reduced in sanding dust from paint, *Part. Fibre Toxicol.*, 2012, **9**(1), 4, DOI: [10.1186/1743-8977-9-4](https://doi.org/10.1186/1743-8977-9-4).
  - 55 W. Wohlleben, S. Brill, M. Meier, M. Mertler, G. Cox, S. Hirth, B. von Vacano, V. Strauss, S. Treumann and K. Wiench, *et al.*, On the lifecycle of nanocomposites: comparing released fragments and their in-vivo hazards from three release mechanisms and four nanocomposites, *Small*, 2011, **7**, 2384–2395.
  - 56 F. Abdulahpur Monikh, A. Praetorius, A. Schmid, P. Kozin, B. Meisterjahn, E. Makarova, T. Hofmann and F. von der Kammer, Scientific rationale for the development of an OECD test guideline on engineered nanomaterial stability, *NanoImpact*, 2018, **11**, 42–50, DOI: [10.1016/j.impact.2018.01.003](https://doi.org/10.1016/j.impact.2018.01.003).
  - 57 L. Di Cristo, G. Janer, S. Dekkers, M. Boyles, A. Giusti, J. G. Keller, W. Wohlleben, H. Braakhuis, L. Ma-Hock and A. G. Oomen, *et al.*, Integrated approaches to testing and assessment for grouping nanomaterials following dermal exposure, *Nanotoxicology*, 2022, **16**(3), 310–332, DOI: [10.1080/17435390.2022.2085207](https://doi.org/10.1080/17435390.2022.2085207).
  - 58 F. Murphy, S. Dekkers, H. Braakhuis, L. Ma-Hock, H. Johnston, G. Janer, L. di Cristo, S. Sabella, N. R. Jacobsen and A. G. Oomen, An integrated approach to testing and assessment of high aspect ratio nanomaterials and its application for grouping based on a common mesothelioma hazard, *NanoImpact*, 2021, **22**, 100314.
  - 59 H. M. Braakhuis, F. Murphy, L. Ma-Hock, S. Dekkers, J. Keller, A. G. Oomen and V. Stone, An Integrated Approach to Testing and Assessment to Support Grouping and Read-Across of Nanomaterials After Inhalation Exposure, *Appl. In Vitro Toxicol.*, 2021, **7**, 112–128.
  - 60 V. Stone, S. Gottardo, E. A. Bleeker, H. Braakhuis, S. Dekkers, T. Fernandes, A. Haase, N. Hunt, D. Hristozov and P. Jantunen, A framework for grouping and read-across of nanomaterials-supporting innovation and risk assessment, *Nano Today*, 2020, **35**, 100941.
  - 61 ISO, Evaluation of methods for assessing the release of nanomaterials from commercial, nanomaterial-containing polymer composites, 2021, TR-22293.
  - 62 J. G. Keller, M. Wiemann, S. Groeters, K. Werle, A. Vennemann, R. Landsiedel and W. Wohlleben, Aerogels are not regulated as nanomaterials, but can be assessed by tiered testing and grouping strategies for nanomaterials, *Nanoscale Adv.*, 2021, **3**(13), 3881–38893.
  - 63 JRC, *Safe and Sustainable by Design chemicals and materials, application of the SSbD framework to case studies*, 2023, <https://publications.jrc.ec.europa.eu/repository/handle/JRC127109> (accessed).
  - 64 V. Di Battista, K. R. Sanchez-Lievanos, N. Jeliaskova, F. Murphy, G. Tsiliki, A. Zabeo, A. Gajewicz-Skretna, A. Mikołajczyk, D. Hristozov and V. Stone, *et al.*, Similarity of multicomponent nanomaterials in a safer-by-design context: the case of core-shell quantum dots, *Environ. Sci.: Nano*, 2024, **11**, 924–941.
  - 65 V. Di Battista, K. Werle, L. M. Skjolding, W. Wohlleben and A. Baun, Behaviour of advanced materials in environmental aquatic media – dissolution kinetics and dispersion stability of perovskite automotive catalysts, *Environ. Sci.: Nano*, 2024, **11**(1), 91–102, DOI: [10.1039/D3EN00685A](https://doi.org/10.1039/D3EN00685A).
  - 66 C. Pang, L. M. Skjolding, H. Selck and A. Baun, A “point-of-entry” bioaccumulation study of nanoscale pigment copper phthalocyanine in aquatic organisms, *Environ. Sci.: Nano*, 2021, **8**(2), 554–564.
  - 67 V. Di Battista, A. Gajewicz-Skretna, K. Werle, L. M. Skjolding, N. Jeliaskova, A. Baun and W. Wohlleben, 24 Safe-by-Design Guidance for Multicomponent Nanostructured Materials (MCNM): Heavy Metals Containing Perovskites, *Ann. Work Exposures Health*, 2023, **67**(Supplement\_1), i46, DOI: [10.1093/annweh/wxac087.111](https://doi.org/10.1093/annweh/wxac087.111).
  - 68 J. Rose, M. Auffan, C. de Garidel-Thoron, S. Artous, C. Auplat, G. Brochard, I. Capron, M. Carriere, B. Cathala and L. Charlet, *et al.*, The SERENADE project; a step forward in the safe by design process of nanomaterials: The benefits of a diverse and interdisciplinary approach, *Nano Today*, 2021, **37**, 101065, DOI: [10.1016/j.nantod.2020.101065](https://doi.org/10.1016/j.nantod.2020.101065).
  - 69 W. Wohlleben, C. Punckt, J. Aghassi-Hagmann, F. Siebers, F. Menzel, D. Esken, C.-P. Drexel, H. Zoz, H. U. Benz and A. Weier, *et al.*, Nanoenabled Products: Categories, Manufacture, and Applications: Protocols and Industrial



- Innovations, in *Metrology and Standardization for Nanotechnology: Protocols and Industrial Innovations*, ed. E. Mansfield, D. L. Kaiser, D. Fujita and M. Van de Voorde, John Wiley & Sons, 2017, pp. 411–464.
- 70 J. S. Steckel, J. Ho, C. Hamilton, J. Xi, C. Breen, W. Liu, P. Allen and S. Coe-Sullivan, Quantum dots: The ultimate down-conversion material for LCD displays, *J. Soc. Inf. Disp.*, 2015, **23**(7), 294–305, DOI: [10.1002/jsid.313](https://doi.org/10.1002/jsid.313).
  - 71 D. Ag Seleci, G. Tsiliki, K. Werle, D. A. Elam, O. Okpowe, K. Seidel, X. Bi, P. Westerhoff, E. Innes and M. Boyles, *et al.*, Determining nanoform similarity via assessment of surface reactivity by abiotic and in vitro assays, *NanoImpact*, 2022, **26**, 100390, DOI: [10.1016/j.impact.2022.100390](https://doi.org/10.1016/j.impact.2022.100390).
  - 72 Z. Mazrouei-Sebdani, M. Naeimirad, S. Peterek, H. Begum, S. Galmarini, F. Pursche, E. Baskin, S. Zhao, T. Gries and W. J. Malfait, Multiple assembly strategies for silica aerogel-fiber combinations—a review, *Mater. Des.*, 2022, 111228.
  - 73 NASA, *Flexible aerogels*, it can be found under <https://www.nasa.gov/offices/oct/40-years-of-nasa-spinoff/flexible-aerogel>, 2016.
  - 74 S. Kiil, Quantitative analysis of silica aerogel-based thermal insulation coatings, *Prog. Org. Coat.*, 2015, **89**, 26–34, DOI: [10.1016/j.porgcoat.2015.07.019](https://doi.org/10.1016/j.porgcoat.2015.07.019).
  - 75 Polaris\_Market\_Research, Aerogel Market Share, Size, Trends, Industry Analysis Report, By Product (Silica, Polymers, Carbon, Others); By Form; By Technology; By End-Use; By Region; Segment Forecast, 2022 - 2030, can be found under <https://www.polarismarketresearch.com/industry-analysis/aerogel-market>, 2022.
  - 76 IndustryARC, *Aerogel Market - Forecast(2023 - 2028)*, it can be found under <https://www.industryarc.com/Report/15381/aerogels-market.html>, 2022.
  - 77 V. Di Battista, C. Ribalta, K. Vilsmeier, D. Singh, P. Demokritou, E. Günther, K. A. Jensen, S. Dekkers, V. Adam and W. Wohlleben, A Screening Approach to the Safe-and-Sustainable-by-Design Development of Advanced Insulation Materials, *Small*, 2024, 2311155.
  - 78 M. Agarwala, D. Bourell, J. Beaman, H. Marcus and J. Barlow, Direct selective laser sintering of metals, *Rapid Prototyp. J.*, 1995, **1**(1), 26–36.
  - 79 J.-P. Kruth, X. Wang, T. Laoui and L. Froyen, Lasers and materials in selective laser sintering, *Assem. Autom.*, 2003, **23**(4), 357–371.
  - 80 L. Stabile, M. Scungio, G. Buonanno, F. Arpino and G. Ficco, Airborne particle emission of a commercial 3D printer: the effect of filament material and printing temperature, *Indoor Air*, 2017, **27**(2), 398–408.
  - 81 G. Tedla, A. M. Jarabek, P. Byrley, W. Boyes and K. Rogers, Human exposure to metals in consumer-focused fused filament fabrication (FFF)/3D printing processes, *Sci. Total Environ.*, 2022, **814**, 152622.
  - 82 P. M. Potter, S. R. Al-Abed, F. Hasan and S. M. Lomnicki, Influence of polymer additives on gas-phase emissions from 3D printer filaments, *Chemosphere*, 2021, **279**, 130543.
  - 83 I. Furxhi, A. Costa, S. Vázquez-Campos, C. Fito-López, D. Hristozov, J. A. Tamayo Ramos, S. Resch, M. Cioffi, S. Friedrichs and C. Rocca, *et al.*, Status, implications and challenges of European safe and sustainable by design paradigms applicable to nanomaterials and advanced materials, *RSC Sustainability*, 2023, **1**(2), 234–250.
  - 84 M. Camboni, J. Hanlon, R. Pérez-García and P. Floyd, A state of play study of the market for so called “next generation” nanomaterials, ECHA-2019-R-14-EN, 2019, DOI: [10.2823/242422](https://doi.org/10.2823/242422).
  - 85 L. Pizzol, A. Livieri, B. Salieri, L. Farcial, L. G. Soeteman-Hernández, H. Rauscher, A. Zabeo, M. Blois, A. L. Costa and W. Peijnenburg, *et al.*, Screening level approach to support companies in making safe and sustainable by design decisions at the early stages of innovation, *Clean. Environ. Syst.*, 2023, **10**, 100132.
  - 86 A. Oomen, L. G. Soeteman-Hernández, W. Peijnenburg, E. Bleeker, E. Swart, C. Noorlander, A. Haase, P. Hebel, K. Schwirn, D. Völker and R. Packroff, *The Early4AdMa system*, 2022, DOI: [10.21945/brochure-advanced-materials](https://doi.org/10.21945/brochure-advanced-materials) (accessed).
  - 87 E. Ruggiero, K. Y. Santizo, M. Persson, C. Delpivo and W. Wohlleben, Food contact of paper and plastic products containing SiO<sub>2</sub>, Cu-Phthalocyanine, Fe<sub>2</sub>O<sub>3</sub>, CaCO<sub>3</sub>: Ranking factors that control the similarity of form and rate of release, *NanoImpact*, 2021, 100372.
  - 88 W. Peijnenburg, A. G. Oomen, L. G. Soeteman-Hernández, M. Groenewold, A. J. A. M. Sips, C. W. Noorlander, J. A. B. Kettelarij and E. A. J. Bleeker, Identification of emerging safety and sustainability issues of advanced materials: Proposal for a systematic approach, *NanoImpact*, 2021, **23**, 100342, DOI: [10.1016/j.impact.2021.100342](https://doi.org/10.1016/j.impact.2021.100342).
  - 89 X. Wang, J. Hedberg, H.-Y. Nie, M. C. Biesinger, I. Odnevall and Y. S. Hedberg, Location of cobalt impurities in the surface oxide of stainless steel 316L and metal release in synthetic biological fluids, *Mater. Des.*, 2022, **215**, 110524, DOI: [10.1016/j.matdes.2022.110524](https://doi.org/10.1016/j.matdes.2022.110524).
  - 90 X. C. Schmidt Rivera, C. Leadley, L. Potter and A. Azapagic, Aiding the Design of Innovative and Sustainable Food Packaging: Integrating Techno-Environmental and Circular Economy Criteria, *Energy Procedia*, 2019, **161**, 190–197, DOI: [10.1016/j.egypro.2019.02.081](https://doi.org/10.1016/j.egypro.2019.02.081).
  - 91 European Commission, DG Research and Innovation, *Strategic research and innovation plan for safe and sustainable chemicals and materials*, Publications Office of the European Union, 2022.
  - 92 OECD, *Early Awareness and Action System for Advanced Materials (Early4AdMa): Pre-regulatory and anticipatory risk governance tool to Advanced Materials*, 2023, <https://search.oecd.org/chemicalsafety/safer-and-sustainable-innovation-approach/early-awareness-and-action-system-for-advanced-materials-pre-regulatory-anticipatory-risk-governance-tool.pdf> (accessed).
  - 93 R. Arvidsson, G. Peters, S. F. Hansen and A. Baun, Prospective environmental risk screening of seven advanced materials based on production volumes and aquatic ecotoxicity, *NanoImpact*, 2022, **25**, 100393.
  - 94 OECD, *Advanced Materials Assessment Schemes HARMLESS - OECD Working Party on Manufactured Nanomaterials (WPMN)*



Workshop Report, 2023, [https://one.oecd.org/document/ENV/CBC/MONO\(2023\)34/en/pdf](https://one.oecd.org/document/ENV/CBC/MONO(2023)34/en/pdf) (accessed).

- 95 D. Singh, A. Marrocco, W. Wohlleben, H.-R. Park, A. R. Diwadkar, B. E. Himes, Q. Lu, D. C. Christiani and P. Demokritou, Release of particulate matter from nano-enabled building materials (NEBMs) across their lifecycle: Potential occupational health and safety implications, *J. Hazard. Mater.*, 2022, **422**, 126771, DOI: [10.1016/j.jhazmat.2021.126771](https://doi.org/10.1016/j.jhazmat.2021.126771).
- 96 Ministère de la transition écologique et solidaire, Éléments issus des déclarations des substances à l'état nanoparticulaire exercice 2019: rapport d'étude, 2020.
- 97 T. van Harmelen, E. K. Zondervan-van den Beuken, D. H. Brouwer, E. Kuijpers, W. Fransman, H. B. Buist, T. N. Ligthart, I. Hincapié, R. Hischier and I. Linkov, *et al.*, LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts, *Environ. Int.*, 2016, **91**, 150–160, DOI: [10.1016/j.envint.2016.02.021](https://doi.org/10.1016/j.envint.2016.02.021).

