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Early Awareness and Action System for advanced materials (Early4AdMa) Pre-regulatory and anticipatory risk governance tool to Advanced Materials

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INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2023

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Early awareness and action system for advanced materials (Early4AdMa)

Early awareness allows early action to support safety and sustainability of materials during their whole life cycle

1. The progress in chemistry and (nano)technology has resulted in the development of materials with new functionalities and structures, often with greater complexities. These innovative materials, generally referred to as advanced materials, may offer many economic advantages and some of them could help to deliver solutions to societal problems such as the need to reduce reliance on fossil fuels or the transition towards a circular economy. However, some advanced materials may pose risks to human health or the environment, as well has having the potential to create other unintended, sustainability issues. Further, it is not clear whether the existing (inter)national legislation and assessment methods for chemicals (including nanomaterials) are 'fit-for-purpose' to cover the potential issues posed by advanced materials. Timely identification of these issues is needed to prevent unacceptable risks or sustainability issues for society associated with the production and use of advanced materials.

2. Here, a systematic approach ('Early4AdMa') is proposed to identify and describe potential safety, sustainability and regulatory issues of advanced materials at the early stages of their development or use. The approach described here is an adaptation of a system developed by the RIVM (NL), BfR (DE), BAuA (DE) and UBA (DE) [1]. The outcome of the approach can inform regulatory decision makers, policy makers, risk assessors, and regulators and could facilitate regulatory preparedness and making timely decisions to avoid or reduce safety and/or sustainability impacts. As such, the Early4AdMa can be considered as a pre-regulatory and an anticipatory risk governance tool. Thereby, the system could be implemented in the development, production, use, and end-of-life of safer and more sustainable advanced materials and the products into which they are incorporated. Thereby, the Early4AdMa system may contribute to the delivery on solutions for societal and environmental challenges via application of advanced materials.

3. It should be noted that this adapted version of Early4AdMa has been developed based on the current state-of-the-art knowledge on advanced materials. As knowledge increases, the Early4AdMa system can be improved. Previous versions of the Early4AdMa system were used in two case studies (i.e. for MXenes, and a fibre-aerogel-mat for façade insulation) during two OECD WPMN workshops. The feedback collected during these workshops has been incorporated in the current version of the Early4AdMa system. It is foreseen that the Early4AdMa system will be further adapted based on experiences of additional case studies.

Introduction

Setting the global scene for advanced materials

4. Society is faced by environmental, economic, and sustainability challenges at a global scale, which threaten also planetary health. Needs to act on these challenges are recognised by (inter)governmental organisations, science, and industry [2-5] with strategies to achieve solutions being laid out in various (inter)national and/or cross-sector programmes and initiatives [3, 6].

5. In many of these strategies, the development of innovative 'advanced materials' is recognised as part of the solution of some major societal challenges [e.g., 6, 7]. Indeed, applications of advanced materials are being explored in a range of innovative technologies, materials and products including systems engineering, energy harvesting, energy storage, and biomedicine [6]. Specific applications are foreseen in e.g., solar and battery technologies, lighter and stronger construction materials, water filtration and environmental remediation systems [3].

6. In the European Union's (EU) growth strategy, the European Green Deal [2], the European Commission commits to tackle climate change and other environmental and economic challenges (e.g. circular economy, energy transition) and sets its ambition to achieve a toxic-free environment. An approach to achieve the latter is outlined in the EU's Chemicals Strategy for Sustainability (CSS) [6]. In the EU, major investments in research and innovation are put into place to achieve these goals, accompanied by the new research Framework Programme Horizon Europe [8]. The European Green Deal recognized the potential facilitating role of advanced materials in the transition to a safer and more sustainable society [2]. One of the European Commission's activities to implement the CSS was the adoption of a recommendation establishing a European assessment framework for 'safe and sustainable by design' chemicals and materials [9], based on scientific work by the Joint Research Centre (JRC) [10]. The framework addresses all chemicals and materials and, thus, includes advanced materials. Safe and sustainable advanced materials are, therefore, in the focus of policy in the European Union.

7. In Europe, industry, innovation and research partners founded the European Advanced Materials 2030 Initiative (AMI2030) and developed the Materials 2030 Roadmap [3]. This roadmap lays out how, according to the AMI2030, advanced materials can benefit society by providing a facilitating role in various transitions. Further, it recognizes the role of governance and policy in successfully developing AdMa.

8. Responding to the progress in technological innovations on materials, the Organisation for Economic Co-Operation and Development (OECD) Working Party on Manufactured Nanomaterials (WPMN) recognised that its focus should be expanded from more 'simple' nanomaterials to advanced (nano)materials [11].

What are advanced materials?

9. Different terms may be used to describe innovative materials in scientific literature, industrial and innovation: e.g., advanced materials, materials for tomorrow, smart (nano)materials, or next-generation materials. Although these terms may not be fully synonymous, these materials have in common that they

are at the forefront of innovation, show or are rationally designed to show specific "new" or enhanced properties or functions and that often little is known about their potential adverse effects on human health or the environment, their potential sustainability issues, and/or whether existing regulation is sufficient to cover these potential issues. Note that the level of knowledge about the potential safety, sustainability and regulatory issues for some materials is higher than for other materials.

10. The challenges to precisely define the term advanced materials are recognised, and include that **advanced materials are subject to a time component and comprise a wide variety of material types in terms of size range, shape, and composition** [11-14]. Accordingly, different descriptions exist of what the term advanced materials means. For example, Kennedy et al. [12] described advanced materials as "materials that are specifically engineered to exhibit novel or enhanced properties that confer superior performance relative to conventional materials". Similarly, Schwirn et al. [13] understand advanced materials as "materials that are rationally designed through the precise control of their composition and internal or external structure in order to fulfil new functional requirements."

11. Recognizing the need for a common understanding of the term 'advanced materials', in 2022 the OECD's WPMN published a working description [11] which is used in this document:

> *"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 advanced material will change with time."*

Why a screening approach for advanced materials is needed

12. The development of new chemicals and materials comes with uncertainties regarding their safety and sustainability and whether existing regulation is sufficient to cover potential risks. Early identification of those issues is a first step for regulators (and innovators) to become prepared for possible action. Indeed, it enables early anticipation actions like pointing out information gaps, concerns, and regulatory needs. Thus, providing the basis for relevant research and the development of guidance, appropriate test systems or adaptation of legislation to prevent possible negative impacts of newly developed chemicals and materials.

13. So far, several screening approaches to identify potential issues of new and emerging chemicals have been developed, some of which are internationally in use [15-17]. These existing systems, however, are focused on safety issues and do not consider sustainability. Further, owing to their unique properties (i.e., physical-chemical characteristics), safety and sustainability assessments of advanced materials may require some different considerations than, for example, those for chemicals in general. Therefore, there is a need for a screening approach that can identify potential safety, sustainability, and regulatory issues of advanced materials that is able to anticipate those possible issues in a fast-moving technological field.

14. The development of an anticipatory screening approach has benefits beyond those for safety and sustainability [18]. Over the last ten years, important lessons have been learned within the nanotechnology domain. One of these is that the innovation process itself can benefit from a timely identification of potential implications for human health and environmental risks, and of any sustainability issues. It is recognised that (inter)national innovation policies not only need to focus on the promotion of technology development but should also include the development of appropriate risk governance that can keep up with the pace of innovation [19]. Experiences within the nanotechnology field have shown that a lack of balance between innovation and policy, results in uncertainty amongst innovators (e.g., regarding regulatory compliance), but also in a risk governance increasingly lagging innovation [20, 21]. Uncertainties regarding regulatory acceptance of a new technology can act as a major barrier to innovation. Thus, an anticipatory screening approach may not only benefit society by preventing impacts on human health, the environment or sustainability issues. It could also benefit innovation through the early identification of issues which may be avoided by re-design, or which subsequently may be acted on by policy makers.

Aims of the Early4AdMa system

15. Here, an early awareness and action system (‘Early4AdMa’) is presented that helps to systematically identify potential human health, environmental, sustainability and regulatory issues of advanced materials. Specifically, the Early4AdMa system aims to:

- identify and describe potential safety, sustainability and regulatory issues of advanced materials in a systematic manner and identify potential follow-up actions,
- support regulatory preparedness by giving policymakers, decision makers and regulators the opportunity to early anticipate on innovations regarding materials and,
- provide a tool for anticipatory risk governance to facilitate and enhance innovation and safe and sustainable development of advanced materials.

16. It should be noted that the field of advanced materials is developing fast and that accordingly, with time the understanding of the properties and potential risks of advanced materials may change rapidly as well. The system described in this document has been developed based on the current state-of-the-art knowledge on advanced materials. Over time, the Early4AdMa system can be adapted to better fit to the latest understanding of the field. In addition, the Early4AdMa system will be further developed based on case studies. The scope and limitations of the system are further detailed below.

General considerations on how to use Early4AdMa

The system in brief

17. The system described here is an adaptation of the former Early4AdMa system that was developed by the RIVM (NL), BfR (Ger), BAuA (Ger) and UBA (Ger) [1]. The current version of the Early4AdMa system described in this document is intended for expert use (see paragraph below for details) and should support regulatory decision making. As such, it could be regarded as a pre-regulatory risk governance tool. The system is composed of two tiers (**Figure 1**).

18. Tier 1 is optional and is a broad screening assessment in which developments in the field of advanced materials are recorded, and a quick screening for potential issues is conducted. When an advanced material of potential concern has already been identified (e.g. based on expert knowledge and judgement regarding a specific concern in a use case) users can skip Tier 1 and start at Tier 2. The assessment part of Tier 1 is partly based on the NESSI system that was developed by BfR [13]. At the end of Tier 1, materials for which an issue is identified may be selected for further assessment in Tier 2.

19. In Tier 2, a more detailed screening for environmental and human safety, sustainability, and regulatory issues is conducted for the selected material through four sets of questions. Based on the identified concerns in Tier 2, suggestions for follow-up action (e.g. research and/or regulatory activities) are identified. These can be communicated to regulatory decision makers, policy makers and risk assessors so that potential issues can be addressed early on.

20. It should be noted that the focus of the development of the current version of the system was on Tier 2. Therefore, Tier 2 is more developed and ready-to-use, whereas part of Tier 1 (e.g., scanning of the field) should be regarded as a suggestion for screening considerations, but not as a concrete guideline. In future versions of the system, Tier 1 may be further developed or may refer to approaches published elsewhere.

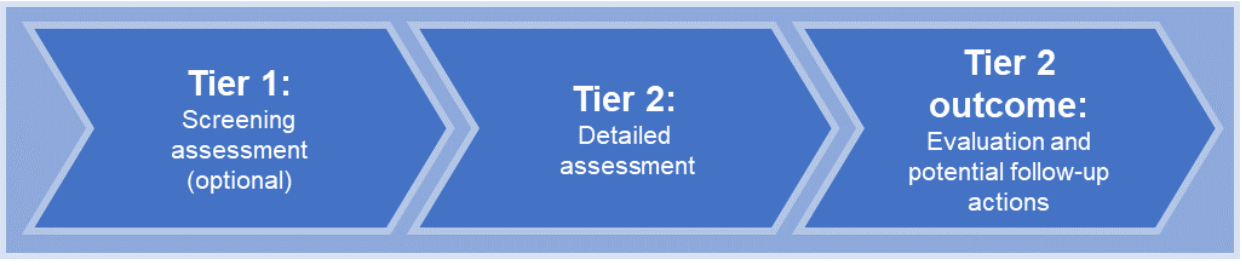

Figure 1. The different Tiers of the Early4AdMa system.

Who should use the system?

21. As indicated before, the system is developed for use as a pre-regulatory risk governance tool. The outcome should help regulatory decision makers to take action (e.g., fund research, develop policy, facilitate cross-sector discussions) so that potential issues posed by advanced materials can be addressed at an early stage. As such the system could contribute to achieving regulatory preparedness. **Although the system's output is designed for use by regulators, decision makers and risk assessors, input from research, industry and innovators is required** to obtain the information needed to conduct the assessment. Thus, cross-collaboration is essential for a successful assessment.

22. For optimal use, it is envisioned that the **assessments within the system are conducted by a group of experts, ideally with representation from different sectors** (i.e., regulation, academia and, industry and innovation) and **different expertise** (i.e., environmental safety, human health safety, sustainability, and regulation). To get a balanced overarching view, it is important that every topic in Tier 2 (i.e., environmental safety, human health safety, sustainability, and relevant regulatory frameworks) is considered. Although not recommended, when a group of experts misses certain expertise, some topics can be left unanswered if this is made clear in the final reporting of the outcome. Furthermore, it is recognized that, as a result of missing information or (scientific) knowledge, it might not be possible to answer certain questions for some materials. Those questions can help to identify information gaps and, thus, in which direction it may be relevant to gather or generate information.

23. Although the system is developed to inform policy making, **the system may also be used for other purposes** e.g., industry or other stakeholders may use it to identify safety, sustainability and/or regulatory issues of their material. Insight in these potential concerns may help industry with, for example, the safe-and-sustainable-by-design of materials.

Box 1**: **Descriptions of the selected stakeholders

This document uses several terms describing stakeholders. These terms may have different meanings in different contexts. For clarity the meaning of some of these terms as used in this document is briefly explained here:

- ***User**: the experts that use the Early4AdMa system to assess potential issues of an advanced material. Note that that by no means the term user refers to the user of an advanced materials in e.g., a product.*

- ***Innovator**: an innovator can be any person, company or organisation that contributes to the development of new materials and/or their applications.*

- ***Decision maker**: someone working for a(n) (international) governmental organisation that makes decisions (or strongly contributes to the decision making) regarding public funding allocations, setting of policy/research agendas, and/or is involved in regulations.*

How to consider different forms during the life cycle?

24. Advanced materials are rationally designed (be it embedded within a product or not embedded) to achieve a certain function. Throughout the life cycle, the physical-chemical form of the advanced material may change through multiple transformation pathways. In the Early4AdMa system, **potential issues for**

any anticipated form throughout the life cycle should ideally be considered. Different transformation pathways may be recognised.

25. The simplest case is when the advanced material does not change through its whole life cycle. In such a case, evaluation can be done based on the advanced material as produced. However, when the physical-chemical properties of an advanced material might change throughout their life cycle (e.g., during product manufacturing, after release to the environment during use, during waste treatment), the impact of the transformed material should be considered.

26. To address these transformations, experts are asked to identify the (anticipated) transformation forms of the material along the life cycle (see 'Context' section in Tier 2). It is recognised that it represents a major challenge to identify all possible forms throughout the life cycle. This is even more challenging at early market entry stages or when the applications of a material are not clear. However, it should be noted that the basis for this assessment is an expert judgement where an indication rather than definitive evidence is sufficient (see also below section on uncertainty). For some of these aspects, innovators could provide knowledge on their material or application, respectively, e.g., regarding physical behaviour / chemical reaction(s) during product manufacturing. In some cases, knowledge on different but similar (advanced) materials can be used for an expert assessment of the life cycle of the material under investigation.

What kind of materials can be considered?

27. In the Early4AdMa system there are no limitations regarding which advanced materials can be considered, as long as the material is clearly described in the assessment. The assessment may be conducted for a **specific advanced material or for a group of advanced materials**. There are also **no inclusion or exclusion criteria regarding the innovation stage** of the assessed material(s). Indeed, for any material in any innovation stage, the system can provide insights into which information is missing. Of course, the system works best when specific information is available, therefore, Early4AdMa may be more suitable for materials in the later innovation stages.

28. For choosing a material for the assessment, one may need to consider the desired specificity (low for a broad group of advanced materials, and high for a specific advanced material), the immediacy (low for early market stages, high for an advanced market stage) and relevance (low for a material with limited uses and societal impact, higher for a material with broad use with clear societal benefits) of the assessment. One may also consider the purpose of the assessment. For example, the information on a material or product is likely to be limited at an early innovation stage which increases the uncertainty of the assessment. Conversely, an assessment at an (early) innovation stage gives more flexibility to innovators to address safety or sustainability issues of their material early on.

29. It should be noted that during the development of the system the focus was on materials that consist of/contain nanomaterials or have a nanostructure. Firstly, this is because many innovations and advanced materials are enabled by nanotechnology, and secondly, there is a reasonable amount of knowledge on nanomaterials for the establishment of a science-based early awareness system. Nevertheless, this does not mean that the system is only relevant for advanced nanomaterials. Rather, the questions (especially in Tier 2) are tailored towards well-described issues that have been identified in more than a decade of small particle or nano-research. It can be assumed that many of these issues also apply to advanced materials without nano-components because in either case the physical and morphological aspects are likely to play a role in risks of materials. When over time knowledge on advanced materials increases, the Early4AdMa system can be adapted to better fit the latest understanding of the field.

How to deal with uncertainty?

30. It should be emphasised that **the Early4AdMa system is based on expert assessment**. It is recognised that, particularly in the early stages of product development, data on safety and sustainability of a material are scarce or lacking. This means that any assessment on potential issues of newly developed materials comes with a certain (relatively high) level of uncertainty. However, the goal of the system is not to provide a definitive safety/sustainability assessment, instead the goal is to identify potential issues including information gaps so that follow-up actions can be taken. Therefore, **assessments are performed in a conservative way.** Many questions (in Tier 1 or Tier 2) refer to specific information that may not be available at the time of the assessment, and therefore, **an indication, rather than definitive evidence, is sufficient to identify an issue of concern or gap of information**.

31. Experts may choose to fill-in 'unknown' when they are unsure about the plausibility of a particular issue. In some cases, this is the result of missing expertise on a specific subtopic, in other cases because this is generally not understood. In either case, it is recommended to briefly elaborate on why a question was scored as 'unknown' in the column "***comment***" included in the response sheets. This column should also be used to report the assumptions made during the answering of the question or specific considerations that may be relevant to the final evaluation. Furthermore, it is recognized that, because of missing information or (scientific) knowledge, it might not be possible to answer certain questions for some materials. Those questions can help to identify information gaps and, thus, in which direction it may be relevant to gather or generate information.

32. In the assessments, the **experts are sometimes asked to answer a more qualitative question**. For example, the list of questions in human health section contains a question on the persistency of the material:

> "Is there an indication of persistency due to low dissolution or degradation rate in any physiologically relevant media?"

33. Some guidance is provided in **Annex 1** to help experts to answer questions like these. However, it should be noted **that the answering of questions remains largely an expert judgement**. For example, related to the example question above, for the human health assessment, experts are referred to EFSA guidance on dissolution/degradation [22] which may help to decide whether a material can be considered persistent. Even following the EFSA guidance though, due to a lack of data, an accurate estimation of the persistency may not always be possible**. The absence of definitive evidence does not mean that experts should fill in 'unknown' by default**. Quite the contrary, experts are asked, based on their expertise in e.g., material science and particle toxicology, to judge whether the material should be considered persistent within the context of the risk assessment. For example, when a (complex, composite) (advanced) material is largely composed of a material for which it is known that is does not (or hardly) dissolve (e.g., titanium dioxide), experts may choose to consider the material to be persistent even though specific data on the material under examination is missing.

The Early4AdMa system

34. The Early4AdMa is composed of two tiers and in total seven steps (**Figure 2**). Tier 1 is optional. When an advanced material of potential concern has already been identified (e.g., based on expert knowledge, a specific concern in a use case) users can skip Tier 1 and start at Tier 2:

Tier 1 (optional):

1. **Scanning the field and AdMa selection**
2. **Screening assessment:**
    - NESSI (Novelty, Exposure, Severity, Scope, Immediacy)
    - Sustainability
    - Applicability of regulatory framework
3. **Preliminary evaluation**

Tier 2:

4. **Collection of additional information and context**
5. **Detailed assessment by experts**
    - Safety assessment - Human Health
    - Safety assessment – Environment
    - Applicability of Regulatory Frameworks
    - Sustainability
6. **Evaluation and potential follow-up actions:**
    - Description of the identified potential issues
    - Proposal for follow-up actions
    - Communication to decision makers, policy makers and regulators
7. **Monitoring of the impact of the assessment and follow-up action(s), and lessons learned**
    - The steps are described in more detail below.

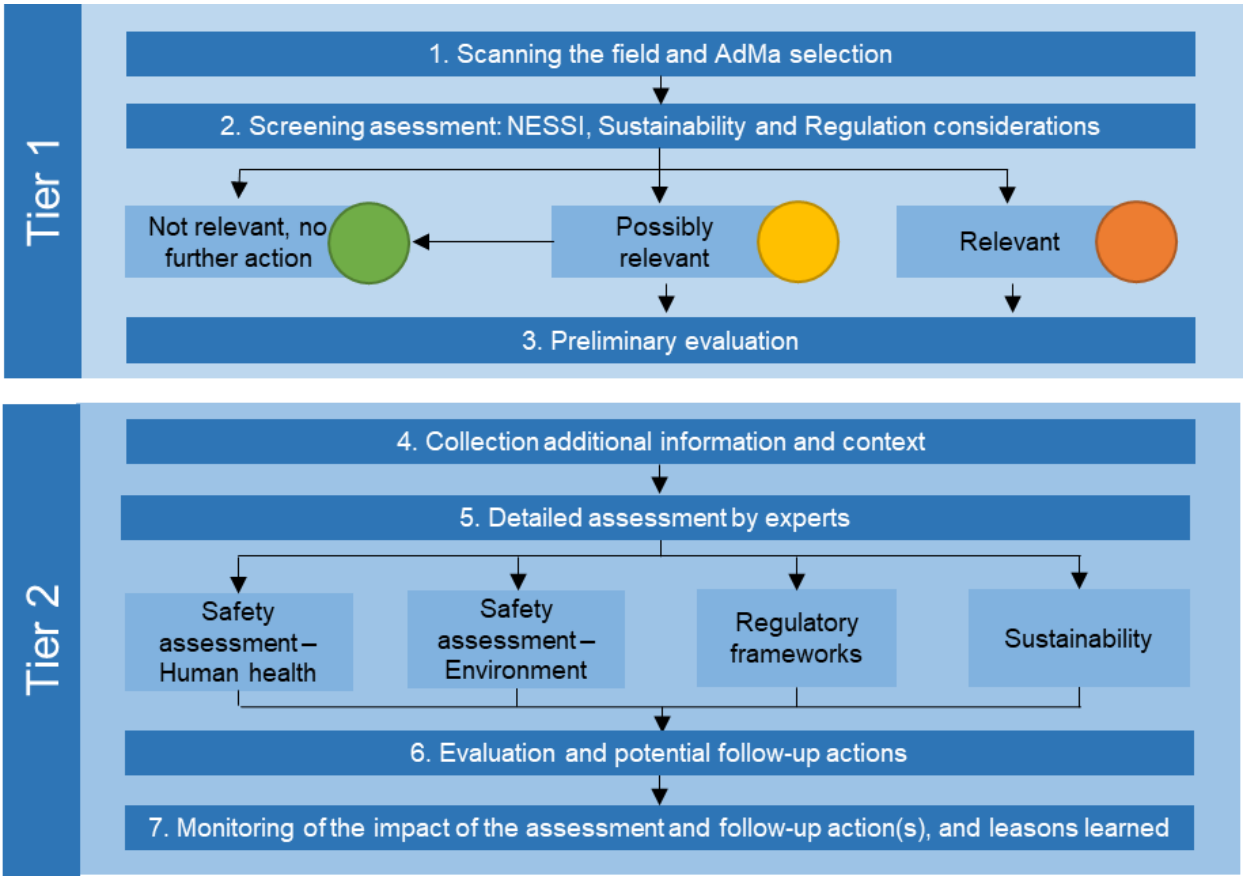

Figure 2. Schematic overview of the steps within the Early4AdMa system for early identification of potential safety, sustainability, and regulatory issues of advanced materials.

Step 1: Scanning the field and AdMa selection

35. To identify an advanced material for the assessment, one needs to obtain an overview of the current developments in the field of advanced materials. Recently, researchers from the European Commission Joint Research Centre developed an approach to identify and describe developments in the field of advanced materials [23]. This document does not aim to provide a concrete approach to conduct such a horizon scanning activity but merely provides suggestions for activities that may be undertaken to this end.

36. Activities that may be undertaken include, but are not limited to, periodic scanning of:

- The scientific literature (e.g. via searches in PubMed and Web of ScienceTM)
- Chemical/material science news websites (e.g., ChemWatch)
- Patent records (e.g., PATSTAT)
- Industry/technology networks or platforms (e.g., SusChem, EuMaT, AMI2030)
- Conferences and workshops (e.g., Thematic Conferences on Advanced Materials; Safe and sustainable smart materials workshop)

37. Based on the field scan, one single type or a group of advanced material(s) may be selected for further consideration. Examples of such selections are:

- A broad group of structurally or functionally related materials and/or combinations of materials, e.g., metal-carbon hybrids or antibacterial AdMa.
- A specific group of structurally or functionally related materials, such as, antibacterial advanced materials that act via photocatalysis. One may start with such a smaller group, or the smaller group may be identified as a sub-group of a broad group during assessment.
- A single type of advanced materials, e.g. graphene oxide.
- For choosing a material for the assessment, one may need to consider the desired specificity, immediacy, relevance, and purpose of the assessment (see also the section 'what kind of materials can be considered?' above). The broader the group of material, the more potential issues may be identified and the lower the specificity of the outcome.

Step 2: Screening assessment: NESSI, Sustainability and Applicability of Regulation

38. The second step of Tier 1 is an initial assessment of the selected (group of) advanced materials by experts. This step is composed of three parts: 1) an initial assessment of human health or environmental risks through the NESSI approach (see below for details), 2) an initial sustainability assessment and 3) an initial assessment of the applicability of current regulation. Based on the outcome of each part experts have to decide whether no further action for the (group of) advanced material(s) is needed or that a more detailed assessment of potential issues is needed through escalation to Tier 2 of Early4AdMa. Details of these steps are provided below.

The NESSI approach

39. The NESSI approach is developed by the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) to assess potential human health risks of chemicals and materials [13]. For advanced materials, NESSI comprises an initial human health and environmental risk assessment of the following items:

- ***Novelty***: including all factors making the issue relevant as an emerging risk, as opposed to a known one. This can include materials that are either entirely novel or appear in new forms or new applications.
- ***Exposure***: describes the expected exposure of the advanced material or components of that material. This can relate to either the exposure levels of people coming into contact with the materials, or to environmental exposure.
- ***Severity***: describes the severity of the expected level of harm caused by the material, either regarding health concerns or environmental impact. This may relate to both acute and chronic (environmental) health issues.
- ***Scope***: describes the expected scope of the issue regarding either the number of people affected or the geographical range that may be impacted.
- ***Immediacy***: describes the time frame until the issues becomes relevant and the resulting urgency to act.
- Each item is given a score between 1 to 5 where higher scores indicate more or greater potential issues. The scores are added up to a total "NESSI" score ranging from 5 to 25. Based on this score the assessed advanced material(s) is/are considered to fall under one of three categories, represented by a traffic light:

- A green light (NESSI score 5-9) means that the issue is not relevant and there is (likely) no need to follow up on this issue
- A yellow light (NESSI score 10-15) represents a situation where there is a possible relevant issue regarding a human or environmental risk that may needs a closer look
- A red light (NESSI score 16-25) shows an issue where a potential concern is expected, and follow-up actions are likely required

Sustainability assessment

40. Here experts initially assess whether there are potential issues related to sustainability. Topics that experts could assess include (but are not limited to) the materials' resource use (critical raw materials), environmental footprint and recyclability/reusability options to support circular economy. Here the whole life cycle of the advanced material should be considered (i.e., during manufacturing, production, transport, use and end-of-life). Based on expert assessment, experts are asked to determine whether there are 1) no; 2) possible; or 3) clear sustainability issues.

Considerations on applicability of regulation

41. Here experts initially assess whether the material or product is covered in current chemical/product legislation, and whether any potential concerns can be assessed based on the information that is to be provided in a regulatory dossier.

Decision making

42. After the assessment of each of the three parts, experts must decide whether to progress to Tier 2 of Early4AdMa. Three different scenarios can be distinguished:

- **No further action needed** (**Green** in **Figure 2**):
    a. NESSI score between 5-9 (green light), and no sustainability issues are foreseen

- **Potential need for action** (**Orange** in **Figure 2)**:
    a. NESSI score between 10-15 (yellow light), or
    b. NESSI score between 5-9 (green light) and possible sustainability issues

- **Clear need for action** (**Red** in **Figure 2**):
    a. NESSI score between 16-25 (red light), or
    b. NESSI score between 10-15 (yellow light) and possible sustainability issues, or
    c. clear sustainability issues, or
    d. current chemical legislation does not adequately cover the AdMa.

43. The scoring is meant to help the experts to make a decision. However, this part still requires expert judgement to decide whether to escalate to Tier 2 of Early4AdMa, especially when the assessment indicates that there is a **potential need for action**. For example, if a yellow NESSI score is mostly be attributed to a specific topic with (great) concern, the experts may decide that further assessment of the material (for all or a specific topic) in Tier 2 is needed. Furthermore, if an advanced material is not covered by existing legislation, experts may also choose to decide that an in-depth evaluation is needed. On the other hand, for a material that received a yellow NESSI score but for which the experts think that the issues are covered by existing regulation, the experts may decide that no further escalation to Tier 2 is needed (**Figure 2**).

Step 3: Preliminary evaluation

44. When a potential issue has been identified by the initial assessment, the third step is to evaluate and describe the potential identified issues. In this description the key potential issue identified in each of the topics of this step (i.e., NESSI, Sustainability, Regulatory frameworks) should be described.

Step 4: Collection of additional information and context

45. When potential issues were identified for an advanced material (or a group of advanced materials) in Tier 1, the advanced material is assessed in greater detail in Tier 2. First, in step 4, additional information is collected. The user should aim to identify as much relevant information as possible to address the items under the context section (see below, step 4), and for each of the four main topics (i.e., safety assessment for human health, safety assessment for the environment, applicability of regulatory frameworks and sustainability) of the detailed assessment in step 5. It is recommended to work in an iterative way and start with finding information to address the context, while also assessing what kind of information is required in step 5. Information on the advanced material may also be collected through collaboration with industry and innovators.

46. The context information should help to streamline and focus the further assessment of the case, by describing the application area, whether the material or the advanced material-enabled product is addressed, the market-entry stage and scale of application, what the expected benefit is etcetera. To answer the questions in step 5, it is important to also **collect information on the anticipated release of the advanced material or its transformation products during the life cycle**, and to which compartment such release takes place. It is recognized that the identification of all possible forms through-out the life cycle is a major challenge. This is especially true for materials at earlier market entry stages for which this kind of information is typically unavailable. However, it should be noted that the basis for this assessment is based on expert judgement. An indication rather than clear evidence is sufficient. Thus, experts may consider potential transformation forms based on their general knowledge of material science or specific examples from related materials. Considerations on the release during life cycle enable identification of possible exposure hotspots. This background information is for example relevant in the assessment of the likelihood for exposure to workers, consumers and the environment and the associated hazard (step 5). Note that an advanced materials is generally developed with a specific function or purpose, for example to support the energy efficiency of a product, to enable energy storage from renewable energy, to make a product easier recyclable, or to iavoid hazard substances in a specific product. This functionality and benefit can be reported in this section and may be taken into consideration in the final report. **Figure 3** provides an overview of the topics that should be described in the context section. An example of what the context section could look like is provided in **Annex 2.**

47. Most important, the information in the context section provides the setting for describing a potential concern and information gaps as well as its weighing. For example, information on the focus of assessment, benefit, market-entry stage, and scale of application can be used by the expert to finetune the wording related to the weight or urgency of a potential concern and information gaps. Socio-economic considerations are not addressed in step 5 of the assessment. Therefore, these considerations can be raised in the context section.

Context

- Application area[1]

1 Health-care and medicine	2 Con-struction	3 (New) energy	4 Trans-portation	5 Home and personal care	6 Packaging	7 Agri-culture	8 Textiles	9 Electronic appliance	10 Other

- Focus of assessment: material (as a whole incl. all its applications) or material in (one or more) specific product
- Benefit, benefit for whom, and anticipated magnitude of benefit (as compared to a conventional material/product)
- Socio-economic considerations (criticality raw materials, child labor etc)
- Market-entry stage
- (Anticipated) scale of application (of material, and if specific product(s) are considered, fraction related to product(s))
- Relevant **anticipated** release compartment and (transformation) forms during life cycle (see table):

	During production[2]	During use	End-of-life	Other[3]
Compartment(s) of release (e.g. air, water, soil)				
Form(s) of release (e.g. pristine, embedded in matrix, transformed, corona formation)				
Mechanism(s) of release (e.g. due to use, weathering, sanding)				

Figure 3. Schematic overview of step 4 of the Early4AdMa system.[1] These application area categories were taken from the manifesto of the Advanced Materials 2030 Initiative.[2] During production of the material and/or during production of an AdMa-enabled product. [3] Other life stages like mining of raw materials or transport.

Step 5: Detailed assessment by experts

48. In this step, a more detailed assessment is performed. The assessment is divided in four major topics (i.e., safety assessment for human health, safety assessment for the environment, applicability of regulatory frameworks and sustainability). Each topic is broken down into sub-topics (see **Table 1**) with each sub-topic having multiple questions. Each question can be answered by 'Yes', 'No', 'Unknown' and 'Not applicable'. The questions are phrased so that a 'Yes' always indicates a potential issue. The outcomes of the assessment can be graphically shown in a donut charts. Examples of the graphical output is provided in **Annex 2**.

49. As explained above in the section **'General considerations on the Early4AdMa',** ideally the assessment should be conducted by an interdisciplinary group of experts. Further, the answering of the question should be done in a conservative manner, i.e., indications rather than clear evidence is sufficient to provide 'Yes' as an answer to a question. Further details of the assessment the set of questions per topic are explained below in the main section '**Early4AdMa assessment system (details on step 5)**'.

Table 1. An overview of major topics and sub-topics that are part of step 5. Questions related to each subtopic can be found in '**Early4AdMa assessment system (details on step 5)**'.

Topic	Sub-topic
Safety assessment for human health	– Physico-chemical properties – Hazard – Kinetics – Exposure
Safety assessment for the environment	– Physico-chemical properties – Hazard – Fate – Exposure/environmental release
Applicability of regulatory frameworks	– Sample preparation and analytics – Applicability regulatory frameworks
Sustainability	– Raw materials and resources – Manufacturing, production, transport and use – End-of life (recyclability and reusability)

Step 6: Evaluation and potential follow-up actions

50. In this step, the users evaluate their assessment in a written report. The evaluation may contain the following sections:

51. A context section that describes the material, the focus of the assessment (i.e., all known applications vs. a specific application), the potential benefits of the advanced materials to society, the relevant (release) forms throughout the life cycle etc.

52. A summary of the detailed assessment conducted in step 5. Here, the most relevant identified potential issues should be described per topic. The overall outcome of the assessment may be also visualized in e.g., a donut chart (see **Annex 2** for an example).

53. A proposal for potential follow-up actions (see **Table 2** for suggestions).

54. The exact form of the evaluation is not strictly defined, and users are free to write a report according to their own discretion. Important is that the final evaluation is communicated to decision makers, policy makers and regulators to inform them about the potential risks, potential sustainability barriers, and information gaps and to provide recommendations about actions.

55. A non-exhaustive list of potential follow-up actions is provided in **Table 2.** Furthermore, in **Annex 2** a hypothetical example is provided of how a report on step 4-6 could look like, including the identification of potentials issues and suggestions to address these issues with potential follow-up actions and actors.

Table 2. Overview of potential follow-up actions related to topics as can be identified in step 5. Note: the list of potential actions are merely examples and is not exhaustive.

Topic	Some Suggestions For Follow-Up Actions
Safety assessment (human health and environment)	• Reduce uncertainties by generating additional (safety) data. • Consider substitution of materials of concern and/or regulatory action. • Consider risk management measures, e.g., to reduce exposure or release.
Applicability of regulatory frameworks	• Share knowledge with the involved Institutions, Regulatory Agencies, Ministries, Authorities and Committees to allow timely consideration whether/ which current regulatory frameworks need adaptations. • Develop guidance and best practices. • Encourage research to underpin the development of suitable (standardised) test methods and improve assessment strategies. • Encourage development of suitable (standardised) test methods or improve assessment strategies.

Sustainability	• Encourage improved sustainability based on identified areas of most relevance, e.g.
	  ○ Minimalization of critical raw material use
	  ○ Reduction of global warming potential
	  ○ Minimalization of energy, water and land consumption
	  ○ Reduction of environmental footprint
	  ○ Effective recyclability and reusability

Other	• Encourage safe-and-sustainable-by-design in further material/product development, encourage substitution. • Facilitate interaction between relevant stakeholders. • Regularly monitor developments of innovations

56. The Safe-and-Sustainable-by-Design (SSbD) concept can be applied in the design phase of a material or product, as well as for substitution of e.g., specific harmful chemicals/components in existing products to safer and/or more sustainable alternatives. Design principles such as green chemistry and green engineering could be of help in early stages of innovation. These principles point the innovator to general considerations like attention to limit energy consumption or the impact on global warming potential, extraction of raw chemicals and the use of resources.

57. The OECD, via its work on the Safe(r) and Sustainable Innovation Approach (SSIA) provides working descriptions and developments in tools and approaches to bring SSIA into practice. Further details on SSbD can be found via the OECD website[1] in the section dedicated to the Safe(r) and Sustainable Innovation Approach (SSIA) [24].

[1] https://oe.cd/ssia

Step 7: Monitoring of the impact of the assessment and follow-up action(s), and lessons learned

58. Where relevant follow-up actions related to identified potential issues can be taken by the appropriate actors. It is important that, after some time, experts reflect on:

- the identified potential issues and information gaps (steps 1 to 5),
- the actual action(s) taken, and
- the impact of the actions.
- This reflection should help to maintain the overview of the field. It also helps to showcase the improvements made and learn from earlier actions, allowing to make improvements where appropriate.

Early4AdMa assessment system (details on step 5)

59. As part of step 5 the advanced material is further assessed in a more systematic manner by a group of different experts using a set of questions related to the following topics:

- Safety assessment Human Health (**Table 3**)
- Safety assessment Environment (**Table 4**)
- Applicability of Regulatory Frameworks (**Table 5**)
- Sustainability (**Table 6**)

60. Each topic is composed of several sub-topics, which together should cover the most critical safety, sustainability, and regulatory issues.

61. To increase the robustness of the assessment, it is recommended that the assessment is conducted by a group of experts and that expertise on each of the different topics (i.e., safety, sustainability, and regulatory frameworks) is represented. Questions can be answered by 'Yes', 'No', 'Unknown' (?) and 'Not applicable' (NA). Assessment is done in a conservative manner, i.e., **indications rather than clear evidence is sufficient to provide 'Yes' as an answer to a question**. AdMa may transform during the life cycle. Different (anticipated) (transformation) forms are identified in Step 4 (Context section). As explained above (see '**How to consider different forms during the life cycle?'**), one should keep these different forms through-out the life cycle in mind during the assessment of step 5. For example, if the pristine advanced material does not contain particles in the nanoscale, but during the life cycle it is expected that nanoscale particles may form, the group of experts should fill in 'Yes' for the first question of the Safety Assessment – Human Health (see below). Further considerations on how to conduct the assessment, including how to deal with uncertainty is provided above in the main section '**General considerations on how to use Early4AdMa'**.

Topic: Safety assessment - Human Health

62. The list of questions on 'Safety assessment - Human Health' provides insight in whether human health safety issues need further attention. These comprise issues relevant from both the chemical composition (e.g., whether substances of concern are present), and from a physical perspective (e.g., high aspect ratio). In addition, issues related to new or enhanced functionality, or multi-component nature of the material may – if applicable – give relevant indications for human health safety assessment. Questions on the availability and applicability of test methods (i.e., those related to measuring material properties, toxicokinetics and hazard characterization) are included in the set of questions on Applicability of Regulatory Frameworks in Table 5.

Table 3. Questions to assess potential issues related to 'Safety assessment - Human Health'. When a question is not applicable for the advanced material under investigation, this can be indicated in the '**NA**' column. '**?**' indicates unknown. Any relevant consideration may be provided in the comments section. For some questions, additional guidance on how to answer the question is provided in **Annex 1**. This is indicated by '**→Guidance**'.

Topic	Question[a]	Yes	No	?	NA	Comments
Physico-chemical properties	Does the material consist of, contain, or release particles at the nanoscale (i.e., in the size range 1 nm – 100 nm)?					
	Is there an indication of new or enhanced properties (e.g., electric, electromagnetic) related to the nano/multicomponent/advanced character of the material that may have an impact on risk?					
	Is there an indication of persistency due to low dissolution or degradation rate in any physiologically relevant media? **→ Guidance**					
	Is there an indication of high/enhanced reactivity? E.g., due to surface area, type of chemical, surface treatment.					
	Is there an indication of release of toxic ions or molecules in the human body?					
	Is there an indication that the material may cause frustrated phagocytosis, for example if it is a persistent and rigid fibre, i.e., a fibre fulfilling WHO criteria (length > 5 µm, diameter below 3 µm, aspect ratio > 3)? Also consider possible secondary structures. **→ Guidance**					
Hazard	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s), e.g.: • related to the new or improved functionality **or** • due to combination of materials or • due to morphological properties **or** • Based on information from similar AdMas **→ Guidance**					
	Is (one of) the (constituent) chemical(s) hazardous for human health? **→ Guidance**					
	Is there an indication of carcinogenicity/genotoxicity/mutagenicity of the material? **→ Guidance**					

Topic	Question[a]	Yes	No	?	NA	Comments
	Is there an indication of toxicity (e.g., immunotoxicity, sensitising properties, lung toxicity, endocrine toxicity) of the material? If yes, on which endpoint.					
Kinetics	Is there an indication of change in kinetic profile compared to the conventional material(s) (or individual components in case of a multicomponent material) and related to the new or improved functionality? For instance, because of improved dispersibility.					
	Is there an indication of uptake into the body?					
	Is there an indication of translocation across the blood-brain barrier, blood-testis barrier or placenta?					
	Is there an indication of accumulation/persistence in any tissue? E.g., due to low dissolution in phagolysosomal fluid. → **Guidance**					
Exposure	Are consumers likely to be exposed to the AdMas, or released substances/particles thereof, during the use phase?					
	Are workers likely to be exposed to the AdMas or released substances/particles thereof in an occupational setting, including during the production phase and the end-of-life or recycling process?					
	Are the AdMas used or likely to be used in many products and/or by a wide population?					
	Is exposure for consumers or workers likely to occur frequently (more than a few incidental times)?					
	Is exposure of vulnerable subgroups anticipated? (e.g., babies or elderly people)					
Total						

[a] If a more general material type is considered, e.g., metal carbon hybrids, provide the score for the application that may pose the highest likelihood for safety issues. This can be a different material for different questions. If applicable, specific materials for which only niche applications are foreseen may be disregarded.

Topic: Safety assessment - Environment

63. The list of questions on Safety assessment - Environment provides insight in whether environmental safety issues need further attention. Issues specific for advanced material are included comprising issues relevant both from the chemical composition (e.g., whether substances of concern are present) and from a physical perspective. Also, issues related to the new or enhanced functionality or multicomponent nature of the material may give relevant indications for environmental safety assessment. Questions on the availability and applicability of test methods (i.e., those related to measuring material properties, toxicokinetics and hazard characterization) are included in the set of questions on Applicability of Regulatory Frameworks in Table 5.

Table 4. Questions to assess potential issues related to 'Safety assessment – Environment'. When a question is not applicable for the advanced material under investigation, this can be indicated in the '**NA**' column. '**?**' indicates unknown. Any relevant consideration may be provided in the comments section. For some questions, additional guidance on how to answer the question is provided in **Annex 1**. This is indicated by '**→Guidance**'.

Sub-topic	Question[a]	Yes	No	?	NA	Comment/ clarification
Physico-chemical properties	Is there an indication of new or enhanced properties (e.g., electric, electromagnetic) related to the nano/multicomponent/advanced character of the material that may have an impact on risk?					
	Does the material feature a particulate nature (i.e. consisting, containing or releasing particles with a size at the nanoscale (1-100 nm)) or show other specific morphological properties that may impact risk? **→ Guidance**					
	Is there an indication of reactivity? **→ Guidance**					
	Is there an indication of release of toxic ions or molecules?					
Hazard	Does (one of) the (constituent) chemical(s) itself fall in one of the following categories? - Substance, material or constituent classified under GHS[b], relating to environmental hazards **or** - PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) **or** - PMT (persistent, mobile, and toxic) **or** vPvM (very persistence and very mobile) **→ Guidance**					
	Is there an indication of short- or long-term toxicity of (one of) the (constituent) chemical(s)?					
	Is there an indication of endocrine disruption? **→ Guidance**					
	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s)? - related to the new or improved functionality **or** - due to combination of materials **or** - due to morphological properties **or** - based on information from similar AdMa. **→ Guidance**					

Sub-topic	Question[a]	Yes	No	?	NA	Comment/ clarification
Fate	Is there an indication that fate of multicomponent material differs from that of the individual components of the material? → **Guidance**					
	Is there an indication of accumulation/persistence in one or more of the environmental compartments (of the AdMas or released substances/materials)?					
	Is there an indication of potential of mobility across one or more environmental compartments (of the AdMas or released substances/materials)? → **Guidance**					
	Is there an indication of uptake of the AdMa or released incorporated substances by animals or plants? → **Guidance**					
	Is there an indication of bioaccumulation of the AdMa or released incorporated substances by animals or plants? → **Guidance**					
Exposure/ environmental release	Is it likely that the AdMa will be produced in higher volumes, and/or in many applications? → **Guidance**					
	Is direct exposure of biota in one or more environmental compartments likely?					
	Is release of the AdMa itself or of incorporated substances/particles to one or more environmental compartments likely? → **Guidance**					
	Is environmental exposure to the AdMa likely to occur, based on production, use, end-of-life or recycling considerations?					
	Is one of the environmental compartments likely to act as a sink for the material?					
Total						

[a] If a more general material type is considered, e.g., metal-carbon hybrids, provide the response for the application that may pose the highest likelihood for safety issues. This can be a different material for different questions. Specific materials for which only niche applications are foreseen may be disregarded, if applicable.
[b] Globally Harmonized System of Classification and Labelling of Chemicals. Only substances on this list that relate to the environment are considered here.

Topic: Applicability of Regulatory Frameworks

64. The questions related to Regulatory Frameworks provide insight in whether the current regulatory frameworks are expected to address the advanced material and potential risks arising from their novel or enhanced properties in an adequate way.

Table 5. Questions to assess potential issues related to 'Applicability of Regulatory Frameworks'. When a question is not applicable for the advanced material under investigation, this can be indicated in the '**NA**' column. '**?**' indicates unknown. Any relevant consideration may be provided in the comments section. For some questions, additional guidance on how to answer the question is provided in **Annex 1**. This is indicated by '**→Guidance**'.

Sub-topic	Question	Yes	No	?	NA	Comment/ clarification
Sample preparation and analytics	Are there issues expected with the analysis of the characteristics of AdMa as pristine material? **→ Guidance**					
	Are there issues with sample preparation for determination of physicochemical properties, hazard, toxicokinetics, fate or exposure assessment of the specific material likely, e.g., due to the absence of guidance, protocols or existing protocols are not adequate? **→ Guidance**					
	Are there issues expected with the analysis of the AdMa in complex matrices in view of exposure, environmental fate or toxicokinetic analysis? **→ Guidance**					
Applicability Regulatory Frameworks	Is the material(s) or application(s) of the material outside of the scope of current chemical or sector specific legislation(s)?					
	If the material(s) or its application(s) falls within the scope of relevant (possibly sector-specific) legislation do the information requirements for substance identification **lack** provisions that **explicitly address** the nano/multicomponent/advanced character of the material? **→ Guidance**					
	If the answer to the previous question is "yes": If the material(s) or its application(s) falls within the scope of relevant (possibly sector-specific) legislation do the information requirements for substance identification **lack** provisions that **allow addressing** the nano/multicomponent/advanced character of the material?					
	If the material(s) or its application(s) falls within the scope of relevant (possibly sector-specific) legislation, do the information requirements lack provisions that cover the potential					

Sub-topic	Question	Yes	No	?	NA	Comment/ clarification
	human health safety issues (section 3.2) for the AdMa?					
	If the material(s) or its application(s) falls within the scope of relevant (possibly sector-specific) legislation, do the information requirements lack provisions that cover the potential **environmental** safety issues (section 3.3) for the AdMa?					
	Are any of the current existing test methods and assessment strategies (e.g., guidance) targeting potential **human health** safety issues considered unsuitable or are test methods missing applicable for the AdMa?					
	Are any of the current existing test methods and assessment strategies (e.g., guidance) targeting potential **environmental** safety issues considered unsuitable or a test method missing applicable for the **AdMa?**					
	Is the material or its application outside of the scope of (possibly sector-specific) legislation or guidance that address sustainability aspects besides safety (e.g., waste, energy demand)?					
	If the answer to the previous question is “no”: Does the legislation or guidance lacks provisions that address the AdMa of the material? → **Guidance**					
Total						

[a] If there are more than one application, the question should be answered for the application with the highest score. Niche applications/materials within a selected group of advanced material may be disregarded.

Topic: Sustainability

- The questions are related to sustainability aspects beyond safety and provide insight in whether the material is/can be sustainable over its entire life cycle. In the questions below, the following sustainability aspects are taken into consideration: use of critical raw materials, use of problematic substances during production, environmental footprints, and waste generation as well as recyclability/reusability to support circular economy. Social aspects regarding sustainability are not explicitly included. In a limited way, social aspects are included in the list of critical raw materials, because this list considers demographic considerations. Social aspects might be included more explicitly in the future.

Table 6. Questions to assess potential issues related to 'Sustainability'. When a question is not applicable for the advanced material under investigation, this can be indicated in the '**NA**' column. '**?**' indicates unknown. Any relevant consideration may be provided in the comments section. For some questions, additional guidance on how to answer the question is provided in **Annex 1**. This is indicated by '**→Guidance**'.

Sub-topic	Questiona	Yes	No	?	NA	Comment/ clarification
Raw Materials and Resources	Are critical raw materials used? **→ Guidance**					
	Are the raw materials used problematic substances? **→ Guidance**					
	Does the process of extracting the raw materials require high energy, water, or land consumption and/or have an impact on global warming potential (emission of greenhouse gases)? **→ Guidance**					
	Is a technically feasible and established process for recycling the raw material missing?					

Sub-topic	Questiona	Yes	No	?	NA	Comment/ clarification
Manufacturing, production, transport, and use	Does the process of manufacturing, production, transport, use or consumption require high energy, water or land consumption or have an impact on global warming potential (emission of greenhouse gases)? → **Guidance**					
	Do the processes of manufacturing and production include the use of problematic substances? → **Guidance**					
	Is waste generated during manufacturing, production, transport, or use? → **Guidance**					
	Are technically feasible and established possibilities for re-use and recycling of generated waste missing?					
	Does the waste generated during manufacturing, production, transport, and use contain problematic substances? → **Guidance**					
	Is a higher energy/material effort expected to achieve similar service performance than for a reference material/substance in a comparable application? → **Guidance**					
End-of-life (Recyclability and reusability)	Is the application of the AdMa short-lived, only? → **Guidance**					
	Is re-use of the materials in the same or another function technically infeasible/impractical?					
	Are different components used that are integrated, which might make recycling technically difficult?					
	Is a concept or plan to recover and recycle the individual materials missing?					
	Is a technically feasible and established process to recycle the AdMa/products containing AdMa missing?					

Sub-topic	Questiona	Yes	No	?	NA	Comment/ clarification
	Does the process of recycling require high amounts of energy, water, or land consumption and/or have an impact on global warming potential (emission of greenhouse gases)? → **Guidance**					
Total						

[a] If there is more than one application, the application with the highest score applies. Niche applications/materials may be disregarded.

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Annex 1: Guidance to answering questions in step 5

Safety assessment – Human health

Table 7. Guidance to answering the questions in Table 3.

Sub-topic	Question	Explanation
Physico-chemical properties	Is there an indication of persistency due to low dissolution or degradation rate in any physiologically relevant media?	EFSA (2021)[1] provides guidance on risk assessment of nanomaterials in food and feed. Section 5.2 and 7.2 provide guidance on dissolution and degradability of nanomaterials. Central question for the risk assessment of nanomaterials in the EFSA guidance is: is the particle form relevant for the potential risks. According to EFSA (2021), when 12% or less of the material is present as particles after 30 minutes in the intestinal conditions, there is no need to consider nano- or particle specific issues. When the material does not degrade in lysosomes within 72 h, the material may accumulate in tissues in time. For most new materials such specific data is not available. In those cases, experts should make an expert-based estimation of whether they expect the material to dissolve/degrade relatively quickly. This may be based on knowledge on the dissolution/degradability of similar materials, e.g. when a material is largely composed of TiO_2

Sub-topic	Question	Explanation
		(nano)materials, the experts can assume that the material will not quickly dissolve.
Physico-chemical properties	Is there an indication that the material may cause frustrated phagocytosis, for example if it is a persistent and rigid fibre, i.e. a fibre fulfilling WHO criteria (length >5µm, diameter below 3 µm, aspect ratio >3)[b] ? Also consider possible secondary structures (e.g., bundled fibres).	See Murphy et al. (2021)[2] for an Integrated Approach to Testing and Assessment (IATA) to grouping of High Aspect Ratio Nanomaterials (HARNs) based on their potential to cause frustrated phagocytosis and downstream effects. Different Decision Nodes that can be investigated with screening tests as well as more elaborated testing can provide insight in whether frustrated phagocytosis can be anticipated.
Physico-chemical properties	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s), e.g.: • related to the new or improved functionality **or** • due to combination of materials. **or** • due to morphological properties **or** • based on information from similar AdMas	Examples for AdMa featuring new or improved functionality might be so-called active/stimulus responsive materials or multicomponent (nano)materials that change properties based on a stimulus, i.e., pH, temperature, light, or multicomponent nature. In contrast, passive materials are 'stable during their use', see Roco (2018)[3]. Toxic effects of single materials might be altered in case different components enhance or overlap each other's effects. Particulate nature as well as morphological features like, edges, fibre or needle shape might indicate towards material-organisms interaction which may go beyond the chemical impact of the material on environmental organisms.
Physico-chemical properties	Is (one of) the (constituent) chemical(s) hazardous for human health?	Indications include, but are not limited to, GHS classifications, positive outcomes from predictive models (e.g. QSARs, ZZS similarity tool[3]) and *in vitro/in vivo* test methods. See also the guidance to '**Are the raw materials used problematic substances?**' in **Table 10** for a more complete list of potential resources.
Physico-chemical properties	Is there an indication of carcinogenicity/genotoxicity/ mutagenicity of the material?	Indications may include positive *in vitro/in vivo* genotoxicity test outcomes, CMR classification, predictive models (e.g. QSARs) but also expert assessment based on the properties of the materials.
Kinetics	Is there an indication of accumulation/persistence in any tissue? E.g. due to low dissolution in phagolysosomal fluid.	EFSA 2021[1] provides guidance on dissolution in lysosomal fluid.

[1] EFSA Scientific Committee, More S, Bampidis V, Benford D, Bragard C, Halldorsson T, Hernández-Jerez A, Hougaard Bennekou S, Koutsoumanis K, Lambré C, Machera K., et al. Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: Human and animal health. Efsa Journal. 2021 Aug;19(8):e06768 https://doi.org/10.2903/j.efsa.2021.6768.
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Safety assessment – Environment

Table 8. Guidance to answering the questions in Table 4

Sub-topic	Question	Explanation
Physico-chemical properties	Does the material feature a particulate nature (i.e., consisting, containing, or releasing particles with a size at the nanoscale (1-100 nm)) or show other specific morphological properties that may impact risk?	Particulate nature as well as morphological features like, edges, fibre or needle shape might indicate towards material-organisms-interaction which may go beyond the chemical impact of the material on environmental organisms.
Physico-chemical properties	Is there an indication of reactivity?	Indications for reactivity may be given due to e.g. type of chemical, surface treatment, light absorbance.
Hazard	Does (one of) the (constituent) chemical(s) itself fall in one of the following categories? - substance, material, or constituent classified under GHS, relating to environmental hazards or - PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) or - PMT (persistent, mobile, and toxic) or vPvM (very persistence and very mobile)	Environmental hazard categories according to GHS or national/regional inventories on classified substances. Criteria for PBT, vPvB , PMT and vPvB can be found e.g., in the European CLP regulation.
Hazard	Is there an indication of endocrine disruption?	Criteria for substances being an endocrine disruptor can be found, e.g. in the European CLP regulation.

Sub-topic	Question	Explanation
Hazard	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s)? - related to the new or improved functionality or - due to combination of materials or - due to morphological properties or - based on information from similar AdMa.	See guidance provided for the same question for Human Health in **Table 7** under sub-topic **Physico-chemical properties**.
Fate	Is there an indication that fate of multicomponent material differs from that of the individual components of the material?	Fate of a multicomponent material might differ of that of individual compounds e.g., in case a substance or material is incorporating into or bound to another substance or material.
Fate	Is there an indication of potential of mobility across one or more environmental compartments (of the AdMas or released substances/materials)?	An example for mobility across environmental compartments to be considered is e.g., the transfer from soil to ground water.
Fate	Is there an indication of uptake of the AdMa or released or incorporated substances by animals or plants?	Examples for released or incorporated substances include e.g. a released dissolved fraction or an active ingredient formerly incorporated/connected to the AdMa.
Fate	Is there an indication of bioaccumulation of the AdMa or released or incorporated substances by animals or plants?	Examples for released or incorporated substances include e.g. a released dissolved fraction or an active ingredient formerly incorporated/connected to the AdMa.
Exposure/ environmental release	Is it likely that the AdMa will be produced in higher volumes, and/or in many applications?	Here, production volumes of 100 t/a and higher are considered as “higher volumes”.
Exposure/ environmental release	Is release of the AdMa itself or of incorporated substances/particles to one or more environmental compartments likely?	Conceivable processes of release include intentional and unintentional processes e.g., leaching, weathering, abrasion, spraying or dumping.

Applicability regulatory Frameworks

Table 9. Guidance to answering the questions in Table 5.

Sub-topic	Question	Explanation
Sample preparation and analytics	Are there issues with sample preparation for determination of physicochemical properties, hazard, toxicokinetics, fate or exposure assessment of the specific material likely, e.g., due to the absence of guidance, protocols or the existing protocols are not adequate?	Proper and reproducible sample preparation is very important for obtaining valid science-based answers to all questions of the Early4AdMa system. This information is therefore crucial for properly applying it. Flotation on liquids, strong adsorption to e.g., surfaces or high tendency for agglomeration may pose challenges to proper sample preparation.
Sample preparation and analytics	Are there issues expected with the analysis of the characteristics of AdMa as pristine material?	Characterisation information is needed to obtain basic information for the pristine material. Some analytical methods are not compatible with the material to be analysed, and these must be addressed.
Sample preparation and analytics	Are there issues expected with the analysis of the AdMa in complex matrices in view of exposure, environmental fate or toxicokinetic analysis?	Guidance to be provided in a later version
Applicability Regulatory Frameworks	If the material(s) or its application(s) falls within the scope of relevant (possibly sector-specific) legislation do the information requirements for substance identification lack provisions that explicitly address the nano/ multicomponent/ advanced character of the material?	The legislation may not explicitly require certain information (particle size, distribution, listing the components and their %, listing specific advanced characterisers, information on 3-dimensional structure of complex materials), or it may not have (unspecified) room for additional identifiers (e.g., “list any other properties considered necessary for identification”).
Applicability Regulatory Frameworks	Are the existing test methods and assessment strategies (e.g., guidance) targeting potential human health (environmental) safety issues considered not applicable for the AdMa? Are any of the current existing test methods and assessment strategies (e.g., guidance) targeting potential human health safety issues considered unsuitable or are test methods missing applicable for the AdMa?	Are the test methods/assessment strategies unsuitable to consider the nano/multicomponent/advanced nature of the material?

Sustainability

Table 10. Guidance to answering the questions in Table 6

Sub-topic	Question	Explanation
Raw Materials and Resources	Are critical raw materials used?	For instance, critical raw material can be found for instance in the EU list of Critical raw materials (europa.eu)
Raw Materials and Resources	Are the raw materials used problematic substances?	In this document, "problematic substances" are considered as those which are e.g. • classified according to GHS or listed in regional/national inventories of classified substances. • mentioned in the candidate list for authorization under REACH: • mentioned in the list of priority and priority hazardous substances (Annex II) of the EU Water Framework Directive. • Considered as persistent organic compounds regulated under the UN POPs-Convention • listed on the priority lists of OSPAR (OSPAR: Convention on the protection of the marine environment of the North-East Atlantic) • HELCOM (HELCOM: Commission on the protection of the marine environment of the Baltic Sea; Annex II) • affecting the climate according to the Montreal- and Kyoto-Protocol (Annex A) • Ozone depleting substances according to the Montreal protocol • part of the SIN ("Substitute it now")-list
Raw Materials and Resources	Does the process of extracting the raw materials require high energy, water, or land consumption and/or have an impact on global warming potential (emission of greenhouse gases)?	Regarding energy, water, and land consumption, see the guidance to the question directly below.
Manufacturing production, transport, and use	Does the process of manufacturing, production, transport, use, or consumption require high energy, water or land consumption or have an impact on global warming potential (emission of greenhouse gases)?	Resource consumption in general comprises the use of renewable and fossil resources. For both cases the use of such resources can be associated with negative social and ecological consequences or not. Water consumption comprises the use of direct water and indirect water ("virtual water") consumption during the different life cycle stages of the material. This includes water that is used, evaporated, or polluted. The water thus consumed can be categorised into: - "Green water" is the naturally occurring soil and rainwater that is absorbed and evaporated by plants. It is relevant for agricultural products.

Sub-topic	Question	Explanation
		- "Blue water" is groundwater or surface water that is used to manufacture a product and is no longer returned to a body of water. - "Grey water" describes the amount of water that would be needed to dilute water pollution to such an extent that the water quality meets the legal or agreed requirements Land is used by humanity for mobility, housing, recreation, farming, extraction of raw materials, and production. Land consumption comprises the use of land for arable land, pasture, fishing grounds, commercial forests, and built-up areas. It denotes the biologically productive area that is available for the activities of, for example, an individual or within a country in a given period of time to produce all the products and services consumed and to absorb the waste and carbon emission produced. Unit of measurement is the global hectare (gha), which represents the average productivity of the biologically productive surface per hectare in one year. Impact on global warming comprises the emission of gases that affect the climate. Greenhouse gases are carbon dioxide (CO_2), methane (CH_4), nitrous oxide (N_2O), hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), and sulphur hexafluoride (SF_6). These gases have different potential to affect the climate. Therefore, the parameter emission of greenhouse gases is presented as CO2 equivalent. For example, methane has a CO_2-equivalent of 25, which means that the emission of 1 tonne methane has the same greenhouse effect as the emission of 25 tonnes CO_2 over a duration of 100 years. Energy consumption comprises energy from renewable and from fossil energy sources. The latter one is closely linked with the greenhouse gas emission. For manufacturing of a substance including the procurement of raw materials, the UBA Guide on sustainable chemicals proposes values of - More than 10 kg CO_2-equivalent/kg substance as high greenhouse gas production - More than 100 MJ/kg substance as high demand of energy sources - More than 100 L water/1 kg substance as high-water demand For comparison of different chemicals, it must be considered additionally how much of a substance is needed to achieve similar services.

Sub-topic	Question	Explanation
Manufacturing production, transport, and use	Do the processes of manufacturing and production include the use of problematic substances?	For a list of problematic substances see guidance to question '**Are the raw materials used problematic substances**?' in this **Table 10** under sub-topic **Raw Materials and Resources**
Manufacturing production, transport, and use	Is waste generated during manufacturing, production, transport, or use?	Waste could include for instant packaging, residual and/or contaminated feedstock, side products, broken or contaminated tools, other consumables.
	Does the waste generated during manufacturing, production, transport, and use contain problematic substances?	For a list of problematic substances see guidance to question '**Are the raw materials used problematic substances**?' in this **Table 10** under sub-topic **Raw Materials and Resources.**
Manufacturing production, transport, and use	Is a higher energy/material effort expected to achieve similar service performance than for a reference material/substance in a comparable application?	For example, it might be that the functionality (e.g., antibacterial properties) of the new material is lower than that of a reference which leads to the situation that higher volumes of the material (accompanied by e.g., higher demand of source materials, energy input, and/or waste) needs to be applied to achieve the same service performance. On the other hand, other properties of the material may lead to disadvantages for sustainability (e.g. higher weight comes along with higher energy demand for transport).
End-of life (Recyclability and reusability	Is the application of the AdMa short-lived, only?	An application is considered to be short-lived e.g., in case it features no long-term functionality or no reparability.
End-of life (Recyclability and reusability	Does the process of recycling require high amounts of energy, water, or land consumption and/or have an impact on global warming potential (emission of greenhouse gases)?	See guidance for question on "Does the process of manufacturing, production, transport, use or consumption require high energy, water or land consumption or have an impact on global warming potential (emission of greenhouse gases)?"

Annex 2: Examples of the contents of the final evaluation in step 6

65. In the future versions of the Early4AdMa system, links may be provided to the reports of actual case studies. For clarification, here examples are provided of how one could report the results of Step 4 (the context section), Step 5 (detailed assessment) and Step 6 (Evaluation and potential follow-up actions). **Note that the provided examples are merely suggestions of elements that could be included in the final evaluation**. The provided examples are not a formal format that the user should adhere to. The **users are free to evaluate and report on the outcomes according to their own discretion** as long as the main topics (i.e. the context, the outcomes of the detailed assessment, the evaluation of the potential issues and follow-up actions) are clearly described.

66. **Disclaimer:** the example is provided to help the user with their reporting and is based on a hypothetical advanced material. Any similarities with actual advanced materials are coincidental. Under no circumstance the example can be used for the assessment of a real case or in support of such a real case.

67. The example is based on a **hypothetical advanced material** (hereafter 'AdMaX') which has the following characteristics:

- AdMaX is a nanomaterial composed of multiple components. Individual particles have an aspect ratio ranging between of 3-10. The material can be used in its pristine forms (as nanomaterials themselves) or embedded in a matrix where it can form homo- and heteroaggregates.
- One of the components can dissolve, has a hazard classification under GHS (among others, toxic to aquatic environment, organ toxicity when inhaled) and is considered a critical raw material.

Example Step 4: Context section

68. Below an example of how to report the context of the material, in this case the hypothetical advanced material AdMaX:

- **Application area**: construction (insulation material), new energy (battery technology), home and personal care (paints and coatings), packaging (food contact material)
- **Focus of assessment**: construction (insulation material), home and personal care (paints and coatings)
- **Benefit, benefit for whom, and anticipated magnitude of benefit (as compared to a conventional material/product)**: for use in insulation material and compared to the conventional material, AdMaX is expected to increase insulation potential by 50-100%. Its use in paints and coating may improve durability of the product but specific data is lacking.
- **Socio-economic considerations (criticality raw materials, child labour etc)**: One of the components is a critical raw material. Dominant mining area of the material are in low- and middle-income countries.

- **Market-entry stage: depending on the product, the market stage ranges between early market stage (battery technology**: TLR 3; food contact material: TLR 3-5) and late market stage (insulation: TLR 7-9; paints and coating: TLR 7).
- **(Anticipated) scale of application (of material, and if specific product(s) are considered, fraction related to product(s))**: as the material can be generally applied to any building (as insulation material) and many paints or coatings, the potential scale of applications is very large. As insulation material, the material may be present up to 10% of the total mass. For paints and coating the material is applied at lower concentrations (no data available but based on expert estimate this is likely lower than 10%).

Relevant anticipated release compartment and (transformation) forms during life cycle: see Table 11.

Table 11. Identification of the (anticipated) relevant release compartments and (transformation) forms of release along the life cycle.

	During production[1]	During use	End-of-life	Other[2]
Compartment(s) of release (e.g., air, water, soil)	Air	Soil and water (paints and coatings) and air (construction activities)	Air	NA
Form(s) of release (e.g., pristine, embedded in matrix, transformed, corona formation)	Pristine	Transformed (paints and coatings): formation of homo- and hetero-aggregates/agglomerates In matrix (insulation): formation of hetero-aggregates, release of individual AdMa particles unlikely	Transformed (paints and coatings): formation of homo- and hetero-aggregates/agglomerates In matrix (insulation): formation of hetero-aggregates, release of individual AdMa particles unlikely.	NA
Mechanism(s) of release (e.g., due to use, weathering, abrasion, sanding)	Dustiness	Leaching, Weathering, and construction activities (sanding, drilling etc.)	Processing during manufacturing. During end of life through combustion.	NA

[1] During production of the material and/or during production of an AdMa-enabled product.
[2] Other life stages like mining of raw materials or transport.

Example Step 5: Graphical summary of the detailed assessment

69. The outcome of the detailed assessment by experts in step 5 may be graphically summarized. Examples are provided in **Figure 4.**

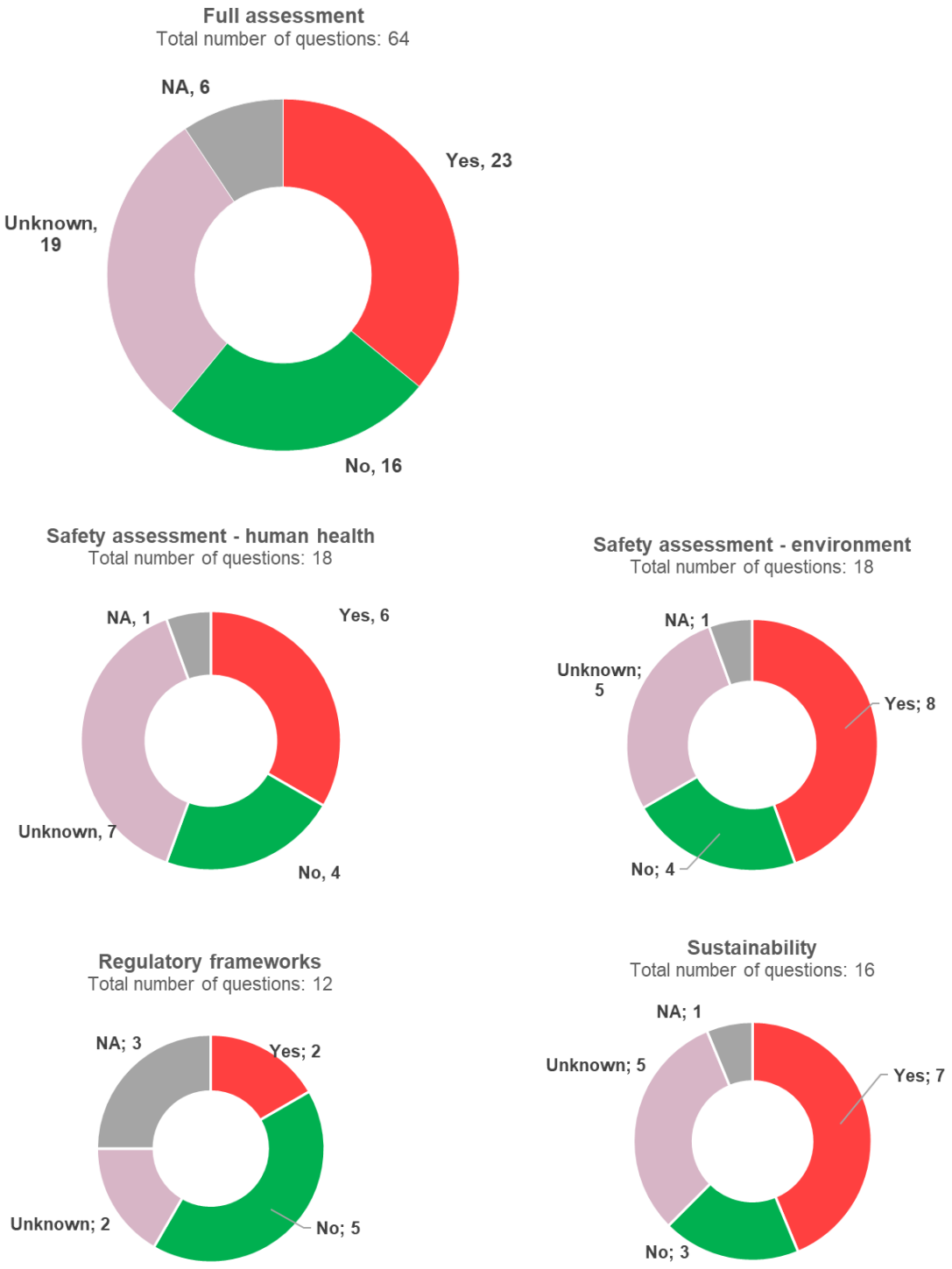

Figure 4: Example of a graphical summary of the detailed assessment in step 5. **The graphs in this figure are hypothetical and not based on an actual assessment**.

Example Step 6: Summary of potential issues and follow-up actions'

70. Below an example of how the user could report the summary of potential issues and follow-up actions is given.

Table 12. Examples of a summarizing table showing the main identified potential issues and suggestions for follow-up actions.

Topic	Summary of potential issues	Suggestions for follow-up actions
Safety assessment – Human health	The material has a morphology that meets the WHO criteria for fibres which represent an inhalation risk.	Conduct (industry/researchers) or support (policy makers/funders) studies to investigate inhalation hazards.
	It is unclear in which form the material is released as a result of abrasion (sanding, drilling) and therefore whether there is a risk of release of particles that may cause inhalation toxicity	Conduct (industry/researchers) or support (policy makers/funders) studies that characterize release and released forms.
	It is unclear under what conditions an active ingredient is released from a carrier and how that impacts toxicokinetics or fate.	Support or conduct research to investigate.
	The fate and toxicokinetic behaviour cannot be investigated because analysis in complex matrices is not feasible.	Support or conduct research to investigate.
Safety assessment - Environment	One component of the material is hazardous to the aquatic environment. Furthermore, the material can dissolve and release toxic components (be it directly, or after individual particles have been release to the environment). Applications of the material suggest the possibility release to the environment during life cycle. Amount and speed of dissolution under realistic conditions is not reported.	Conduct (industry/researchers) or support (policy makers/funders) studies to assess solubility and dissolution rates under environment relevant conditions to allow for an environmental risk assessment and whether the specific form or the multicomponent nature could cause further/additional hazards. Reconsider/substitute use of hazardous component (industry/innovators)
Applicability of regulatory frameworks	The advanced material does not dissolve or disperse well in relevant exposure media for toxicity testing. Results of such toxicity studies therefore do not provide relevant and reliable information.	Conduct research how to design toxicity studies for the type of advanced materials and develop this into guidance.
	There are no standardized approaches for physical-chemical characterization	Support (policy makers/funders) or develop (industry, researchers) suitable (standardised) test methods
Sustainability	Production requires high amounts of energy	Conduct (industry/researchers) or support (policy makers/funders) studies/life cycle assessments to carbon footprint. Design/develop/use a production process with of less energy demand
	There is no data on recyclability of the insulation material, no recycling strategy has been identified	Design effective recyclability and reusability strategy (industry/innovators)