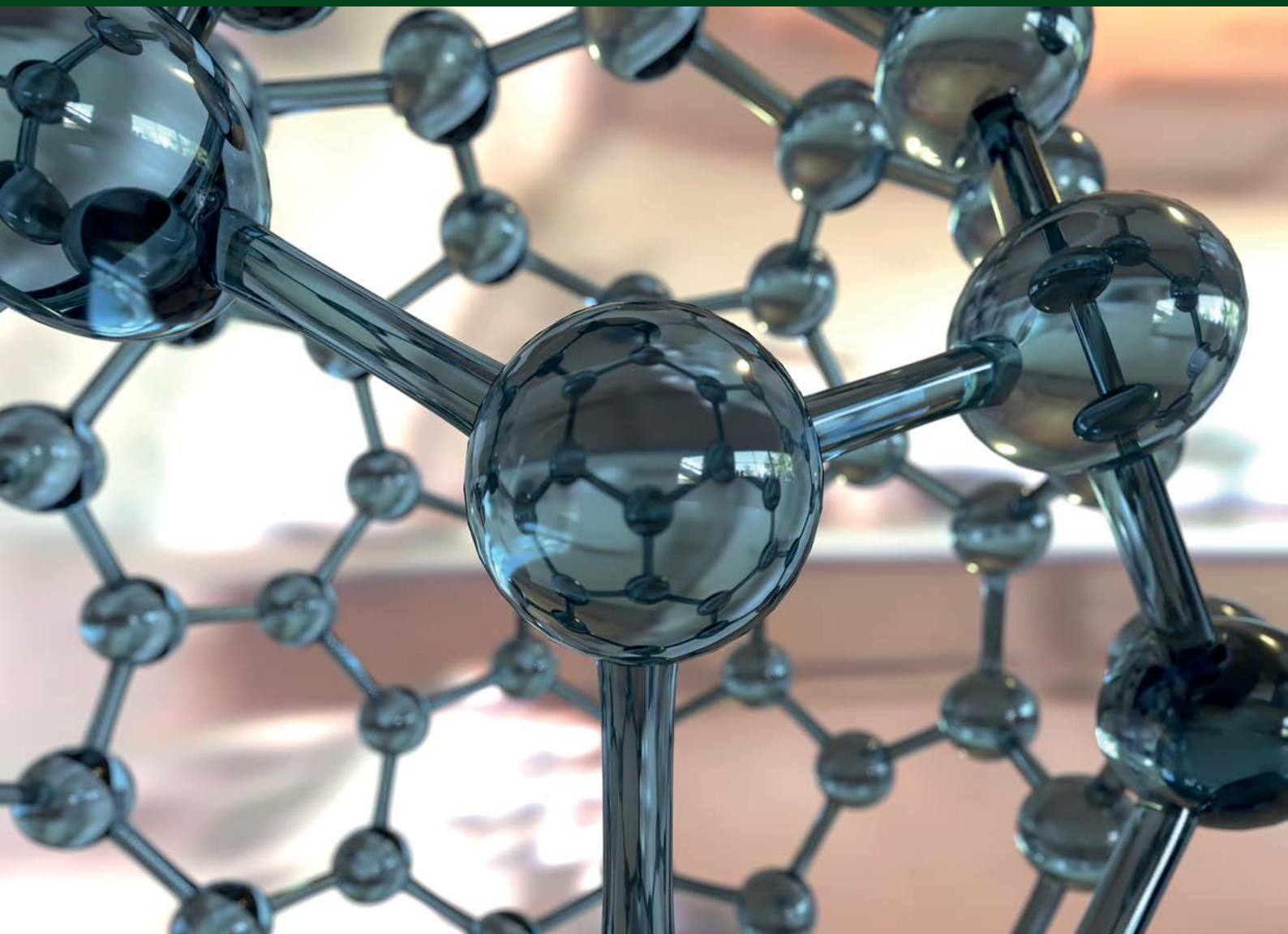
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Towards Safe and Sustainable Advanced (Nano)materials:

A proposal for an early awareness and action system for advanced materials (Early4AdMa)



The Early4AdMa system

It is of utmost importance to develop an anticipatory risk governance approach and to proactively avoid the occurrence of potential unexpected risks of advanced (nano)materials. Addressing safety and sustainability issues early in the innovation chain can support innovation by preventing problems later on. Towards this goal, we propose a novel Early4AdMa system to systematically identify emerging issues of advanced nanomaterials. This system can be applied by regulators, risk assessors, as well as innovators.

Main purpose of this brochure
This brochure of the proposed Early4AdMa system can be regarded as a thought starter, developed by RIVM, BfR, BAuA and UBA. The main purpose of this brochure is to receive input on the structure and content of the proposed Early4AdMa system for advanced nanomaterials. With the input and feedback, we would like to present an improved Early4AdMa system to facilitate discussions at an EU-level and to bring the system to the OECD WPMN Steering Group on advanced (nano)materials.

This brochure does not cover details with regard to which actors should be involved during the different steps of the system and how that can be organised.

Your feedback is needed
We are interested in your feedback on the structure and content of the proposed Early4AdMa system and on the scoring system. With your feedback, the Early4AdMa system can be shaped and improved. Please provide you feedback via: *KIR-nano@rivm.nl*.

The KIR-website provides details about the feedback process.

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Table of Contents

1. Setting the scene

1.1 Introduction: Early awareness, early action

Keeping pace with technological developments is very challenging, particularly with the increase in development of new types of often complex materials. These materials bring opportunities for creating new or improved functionalities. In many cases, such functionalities are created at the nanoscale.

Clearly, innovative materials, often referred to as advanced materials (AdMa), offer many advantages. However, they may also pose potential risks for human health and the environment, or they can create unforeseen sustainability issues. Timely anticipation to such issues can help to address safety and prevent sustainability problems of these materials early on. For example, in some cases the current legislative frameworks – including the adjustments that have been or will be made for nanomaterials – may not be suitable for dealing with all kinds of risks posed by the broad new class of AdMa. For instance, it is not always clear how to deal with the multiple components that AdMa are often comprised of to enable new functionalities. As these components are often structurally highly ordered, classifying these materials as simple "mixtures" may not suffice. Furthermore, it is unclear if a new functionality also entails new risks for human and/or environmental health.

A systematic early warning system towards identifying potential human and environmental risks of AdMa can help to gain a better understanding on the safety and sustainability aspects that deserve more attention and at what point in time [1]. This approach supports regulatory preparedness by giving policymakers, decision makers and regulators the opportunity to anticipate on material innovations. In addition, it allows examining whether the development of new materials is in line with other policy goals, such as the European Green Deal [2] and the European Chemical Strategy for Sustainability [3] where safe-and-sustainable-by-design, circularity and life-cycle approaches (including recyclability) play an important role. In this way, tailored actions that support the safe and sustainable development, production, use and end-of-life treatment of specific AdMa can be suggested.

Here we propose and early awareness and action (Early4AdMa) system to identify, describe and prioritise warnings related to safety and sustainability in the field of advanced materials. The system includes a description of relevant potential follow-up actions that can inform decision makers, policy makers and regulators, in order to allow initiation of timely actions towards avoiding or reducing safety and/or sustainability issues. Thus, such a systematic approach can be an important tool in an anticipatory European risk governance approach. The Early4AdMa system aims for proactive avoidance of potential and unexpected risks and sustainability issues of advanced materials, whilst not hindering innovation. The system is intended to be used in Europe, since potential actions are related to European legislation. This does not preclude that (elements of) the approach can be beneficial outside of Europe.

1.2 Current developments in the field of advanced materials

The European Union's new growth strategy, the European Green Deal [2], has set the EU on an urgent course to become a sustainable, climate neutral and circular economy by 2050. This includes the goal of better protecting human health and the environment as part of an overarching ambitious approach to tackle pollution from all sources. The Green Deal defines the Commission's commitment to tackling climate change and environment related challenges. It sets ambitious goals like a zero-pollution approach for a toxic-free environment, outlined in the EU's chemicals strategy for sustainability [3] that is part of the Green Deal. Major investments in cutting-edge research and innovation are put into place to achieve these transformative objectives, accompanied by the new research Framework Programme Horizon Europe [4] that is based on modern innovation principles.

The development of advanced materials is thought to be critical in reaching some of the transitions and goals of the European Green Deal [3]. Advanced materials are central to the design of a range of innovative technologies and products that include systems engineering, energy harvesting, energy storage, and biomedicine [3]. They play an increasingly important role, e.g. in innovative solar and battery technologies, in lighter and stronger construction materials as well as for water filtration and environmental remediation. New classes of materials are currently at the edge of technological development. These classes include metamaterials, specifically engineered materials designed to have material properties beyond those of the individual components. Another class are active or intelligent materials that are at the boundary between materials and devices, e.g. new biomedical soft materials which can autonomously perform sensor functions. A recent report commissioned by the German Environment Agency identified eight clusters of advanced materials [5], ranging from (DNA-based) biopolymers [6] to advanced alloys comprising two or more constituents [5]. In the Netherlands advanced materials have been categorized according to their main area of application [7].

Novel materials with intricate structures can, however, impose new risks during their life cycle, e.g. exhibiting hitherto unobserved fate/toxicokinetic behaviour, (eco) toxicity profiles of the material or of released (nano-sized) building blocks. Innovation processes would benefit from a timely identification of potential implications for human and environmental health risks and other sustainability issues, from early stages of innovation onwards and including the whole life cycle [8]. Towards this goal, sustainable use of raw materials, and sustainable production, manufacture, use and recycling of the novel materials should be considered. To keep up with the pace of innovation foreseen within the European Green Deal, it is therefore essential that appropriate risk governance is put into place. Such risk governance should be capable of coping with the potential new risks and sustainability issues. To this end, national and international 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 innovations [9]. Important lessons have been learned recently in the nanotechnology domain. These have shown that a lack of such a balance can result in a situation of continued uncertainty amongst innovators and other stakeholders, both about the safety of materials, products and production processes, and about how to comply with legislation. The lack of a synchronized approach has led to risk governance that is increasingly lagging behind innovation, as is exemplified for nanomaterials [8, 10].

With the objective of a climate-neutral, toxic free environment and a circular economy, a new era in technological innovation has started. One that may thrive by the development of (amongst others) the AdMa, also termed materials for tomorrow, smart (nano)materials, or next-generation materials. In this brochure we will use the term 'advanced (nano)materials'. AdMa in general have in common that they are at the forefront of innovation with relatively little knowledge available on their potential adverse effects for human and the environment, as explained below.

The present brochure and system focus on advanced nanomaterials that consist or contain nanomaterials or have a nanostructure. This is for two reasons. Firstly, many innovations and AdMa are enabled by nanotechnology, and secondly, the expert knowledge is advanced enough to allow for the establishment of a science-based early warning system. The application area of the system is currently thus limited to advanced nanomaterials, allowing for a scientifically focused assessment. In the future, the system can be adapted for other types of AdMa.

It is of utmost importance to develop an anticipatory risk governance approach and to proactively avoid the occurrence of potential unexpected risks of these AdMa. Addressing safety and sustainability issues early in the innovation chain can support innovation by preventing problems later on. Towards this goal, we propose a novel system to systematically identify emerging issues of advanced nanomaterials. This system can be applied by both regulators, risk assessors, as well as innovators.

What are Advanced Materials (AdMa)?

New developments in material science use many different terms for the innovations, e.g. advanced materials (AdMa), materials for tomorrow, smart (nano)materials, or next-generation materials. Although the terms may not be fully synonymous, these materials have in common that they are at the forefront of innovation with relatively little knowledge available on their potential adverse effects for humans or environment. AdMa can be considered to be rationally designed through the precise control of their composition and internal or external structure in order to fulfil new functional requirements [11]. In this brochure we will use the term 'advanced material' to indicate them. **Furthermore, we presently focus on AdMa consisting or containing nanomaterials or having a nanostructure.**

1.3 Aim of brochure

The main purpose of this brochure is to receive input on the structure and content of the proposed Early4AdMa system for advanced nanomaterials. With the input and feedback, we would like to present an improved Early4AdMa system to facilitate discussions at an EU-level and to bring the system to the OECD WPMN Steering Group on AdMa.

The proposed Early4AdMa system can be regarded as a thought starter. Discussions and cocreation are needed to shape and improve the system. The here described system includes various approaches proposed by RIVM, BfR, BAuA and UBA. It combines the early warning system by BfR, named NESSI (Novelty, Exposure, Severity, Scope, Immediacy) [11], and the more detailed early warning system by RIVM.

Furthermore, within the Early4AdMa system, questions are raised that helps the user to systematically consider aspects relevant to identify materials of concerns to safety or sustainability. The Early4AdMa system can serve as a tool in an anticipatory risk governance approach, aiming to identify and avoid the occurrence of potential risks and sustainability issues of advanced nano.

This brochure does not cover details with regard to which actors should be involved during the different steps of the system and how that can be organised.

In Chapter 2, the Early4AdMa system is presented and described. In Chapter 3, the scoring and detailed questions (Tier 2, step 5) are presented in more detail as they are considered the main feature of Tier 2.

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2. Proposed early awareness and action system for advanced materials

The goal of this early awareness system is the early identification of potential human health, environmental and sustainability issues to support the Safe-and-Sustainable by Design (SSbD) development, production, use, and end-of-life treatment of AdMa. The current early awareness and action system helps to assess different warnings in a systematic manner. In addition, the system will support the identification of gaps and pitfalls of regulatory frameworks.

It is important to fully exploit the innovation potential of AdMa and at the same time to warrant that potential health, safety and sustainability issues are identified and handled in an early stage of development.

Below, the information on the aim and structure of the Early4AdMa system is provided. This is followed by an overview of the system and explanation on the two tiers and different steps therein.

2.1 Aims and structure of the Early4AdMa system

The aims of the presented system are:

I. to identify potential safety and sustainability issues of AdMa
II. to gather relevant information for such an identified warning to allow timely informed decision-making on AdMa through the assessment of those issues that may lead to risks or sustainability issues
III. to systematically compare warnings to allow prioritisation
IV. to propose tailored follow-up actions

Structure (Figure 1): The early warning system by BfR (NESSI; Novelty, Exposure, Severity, Scope, Immediacy) is integrated as the first screening Tier of the system. It is complemented with screening considerations on sustainability and the applicability of regulatory frameworks. In Tier 2, detailed sets of questions allow for more in-depth consideration of the warnings identified in Tier 1. The detailed questions and their answers can be used to compare the findings on safety and sustainability issues for different AdMa, to develop and prioritise warnings, and to develop proposals for tailored follow-up actions (Figure 1). The proposed system merges some aspects from the International Risk Governance Centre (IRGC) Guidelines for Emerging Risk Governance [12] with some aspects from the EU Environmental Foresight System Final Report of the 2018-2019 Annual Cycle [13].

*Figure 1. The different Tiers making up the **Early4AdMa system.***

2.2 The Early4AdMa system

The aims of the system (see section 2.1) translate in an Early4AdMa methodology that consists of the following steps (Figure 2):

Tier 1:

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

Tier 2:

4. Collect additional information
5. Scoring by experts
   - Application and Market-entry stage
   - Safety assessment - Human Health
   - Safety assessment – Environment
   - Applicability of Regulatory Frameworks
   - Sustainability
6. Assessment of warning and prioritisation between warnings
7. Early warning and proposal for follow-up action: outcomes are defined and communicated to decision makers, policy makers and regulators
8. Reflection and evaluation: evaluation and monitoring of the impact of the warning and the action(s) taken

The steps are described in more detail below.

Early4AdMa system: Steps to identify, describe, prioritise and respond to warnings in the field of advanced nanomaterials (AdMa)

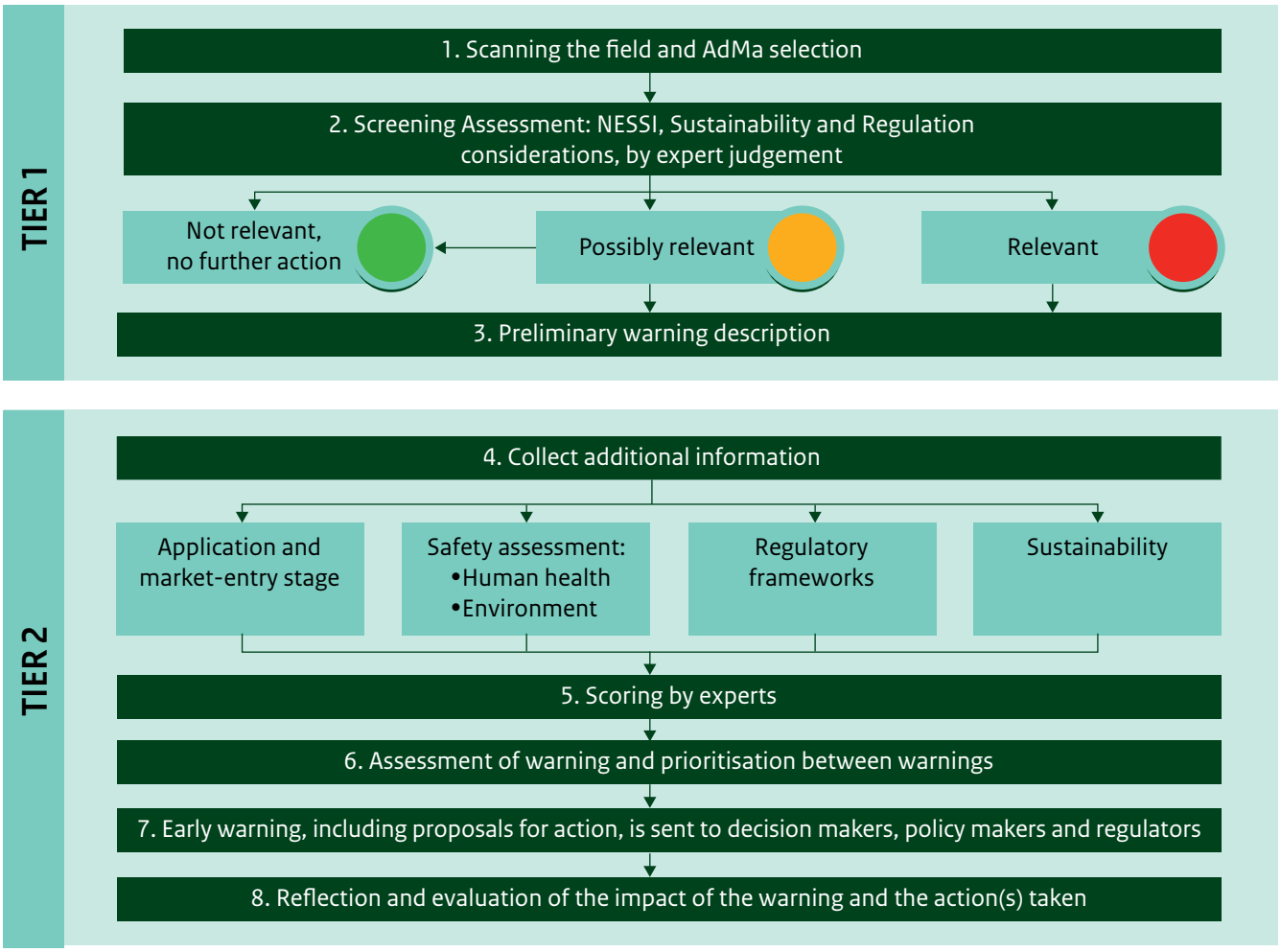

Figure 2. Proposed early awareness and action system (Early4AdMa) for early detection and priority setting of potential safety and sustainability concerns of advanced materials in support of successful, safe and sustainable innovation.

2.3 Step 1: Scanning the field and AdMa selection

This initial step consists of two activities:

Activity 1: Scan the field involves a general inventory of the latest developments within the broad field of AdMa and innovative technologies. Actions to obtain an indication of the latest advancements in nanotechnology and/or material science could involve periodic scanning of the scientific literature, news sites, websites, electronic databases and stakeholder networks. Additional sources of information include for instance: the Advanced Materials Journal, workshops such as e.g. The German Environment Agency Thematic Conferences on Advanced Materials (Dec. 2019, June 2020, Sept. 2020, June 2021), and the Safe and sustainable smart materials workshop (Sept. 2020). Other relevant sources include the European Technology Platform for Advanced Engineering Materials and Technologies (EuMaT). It is to be noted that this list of sources is not exhaustive and needs to be updated on a regular basis.

Activity 2: Based on the field scan, a type or *a group of AdMa* is selected for further consideration, along with some relevant information. Such a (group of) AdMa can be:

A. A broad group in which multiple materials and/or combinations of materials fit, i.e. the group of metal-carbon hybrids or antibacterial AdMa.
B. Small, specific group of materials. This will have a more specific description such as antibacterial AdMa 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.
C. A single AdMa.

As a broader group encompasses a variety of materials, more alerts may be triggered (see step 5, section 2.7). In this case, a higher expert score might be seen, in comparison with a specific group of materials being assessed. In such cases it might be useful to perform the follow-up assessments with sub-groups only. An important aspect of the expert judgement is therefore to define which AdMa should be considered that go through steps 2 to 8 of the Early4AdMa system. Finetuning is possible by specifying some conclusions for sub-groups of AdMa within the broader description.

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

The second step consists of an early assessment of the selected (group/sub-group of) AdMa by using the NESSI approach, complemented by an initial screening on potential sustainability issues and early considerations whether expected/anticipated concerns are covered by current regulation. The various items under NESSI as well as items of sustainability and regulatory coverage are scored by experts. The overall NESSI score addresses whether there may be emerging human health or environmental risks that would require further timely attention. Together with the results on sustainability and whether current regulations are expected to cover concerns, a decision needs to be made to either 1) take no further action regarding this (group/sub-group of) AdMa, or 2) escalate to more detailed assessment of the warning in Tier 2.

For AdMa, **NESSI** comprises an assessment of the following items [11]:

- 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 AdMa 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.

Scoring in NESSI

Each item is given a score between 1 to 5. The scores are added up to a total "NESSI" score ranging from 5 to 25.

The resulting assessment results in a classification of the issue in one of three categories based on the NESSI score, represented by a traffic light. A green light (NESSI score 5-9) concludes the issue is an irrelevant warning, while a red light (NESSI score 16-25) shows an issue where a potential concern is expected. A yellow light (NESSI score 10-15) represents a situation where there is a possible relevant early warning regarding a human or environmental risk.

Sustainability: Comprises all further factors that may indicate issues related to sustainability, e.g. resource use (critical raw materials), environmental footprint, and poor recyclability/reusability to support circular economy during manufacturing, production, transport, use and end-of-life.

Considerations on applicability of regulation: Comprises an initial screening whether or not the material or product is covered in current EU chemical legislation, and whether or not any potential concerns can be assessed based on the information that is to be provided in a regulatory dossier.

Decision making at the end of TIER 1

At the end of Tier 1 (Figure 2), a decision is needed whether to progress to Tier 2. Three different scenarios can be distinguished:

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

B. Possible relevant preliminary warning (orange in Figure 2):
- NESSI score between 10-15 (yellow light), or
- NESSI score between 5-9 (green light) and possible sustainability issues

Expert judgement is needed to decide whether to escalate to Tier 2.

Some considerations for potential follow-up activities:

For instance, if the yellow NESSI score can clearly be attributed to specific items further assessments of these specific topics only under Tier 2 may be considered. This may then result in a clear green or red to decision.

Furthermore, if this AdMa is not covered by existing legislation, the orange would turn into red, demanding for an in-depth evaluation.

C. Relevant preliminary warning (red in Figure 2):
- NESSI score between 16-25 (red light), or
- NESSI score between 10-15 (yellow light) and possible sustainability issues, or
- clear sustainability issues, or
- current chemical legislation does not adequately cover the AdMa.

The preliminary warning escalates to Tier 2, which comprises a detailed follow-up assessment.

2.5 Step 3: Preliminary warning description

When a preliminary warning with a potential concern has been identified, the third step is to produce a warning description that addresses each of the topics of the scoring system (i.e. NESSI, Sustainability, Regulatory frameworks).

The preliminary warning description represents the finalisation and reporting of Tier 1.

2.6 Step 4: Collect additional information

With step 4, Tier 2 of Early4AdMa is entered. Dependent on the preliminary warning description and available information in Tier 1, additional information needs to be gathered for the detailed assessment of AdMa in step 5 (section 2.7). In this step 4, information will be collected on the five major topics relevant for the assessment of AdMa: application and market entry-stage, safety assessment for human health, safety assessment for the environment, applicability of regulatory frameworks, and sustainability aspects. Specifically, information needed to answer the questions for the assessment has to be collected (see step 5 in section 2.7 and details in Chapter 3).

2.7 Step 5: Scoring by experts

In this step, each preliminary warning of Tier 1 is assessed in more detail. In this assessment, the selected (group of) AdMa is evaluated using a detailed scoring system that addresses the major topics relevant for the assessment of AdMa. The scoring of each of the five major topics is based on specific questions and should be performed by an interdisciplinary group of experts. Expertise of the group should cover the areas of market potential and use, material science, physico-chemical properties, ecotoxicity, environmental fate, human toxicity, exposure assessment, risk assessment, regulatory frameworks and sustainability.

Each topic is broken down into sub-topics (see Table 1) with each sub-topic having multiple questions. Each question may receive a score ranging between 0 and 9 (score dependent on the question) where a higher score is indicative of a clear issue. Through this scoring range, a distinction can be made between clearer and weaker indications on e.g. whether health or environmental risks or sustainability issues are expected, or whether this is unknown or uncertain. The outcomes of the scoring of the questions are combined in a final score. This final score may be used for prioritisation of the warning by comparison to other warnings, as described in the next step.

Particularly in the early stages of product development, data on materials safety is scarce or even virtually lacking, which leads to higher uncertainty. It is also important to identify those cases of low or medium risk that have a high uncertainty. Such cases could develop into high-risk cases when more information becomes available. To identify such cases, the scoring system includes an uncertainty assessment. Details of the scoring, the detailed set of questions per topic and the uncertainty assessment are explained in Chapter 3 (Early4AdMa scoring system).

Table 1. An overview of major topics and sub-topics that are part of step 5, scoring by experts.

Topic	Sub-topic
Application and market-entry stage	• On market or close to market • Scale of application
Safety assessment for human health	• Physico-chemical properties • Hazard • Kinetics • Exposure
Safety assessment for the environment	• Physico-chemical properties • Hazard • Fate • Exposure
Applicability of regulatory frameworks	• Identification of the adequacy of relevant regulatory frameworks, including applicability assessment of underlying test methods and assessment strategies
Sustainability	• Raw materials and resources • Manufacturing, production, transport and use • End-of life (recyclability and reusability)

2.8 Step 6: Assessment of warning and prioritisation between warnings

The scoring by experts helps to identify areas of concern with respect to one or a group/sub-group of AdMa. Based on this assessment, sense-making can be performed. If a score of one or more topics is relatively high, an early warning will be described. Potential critical issues for each relevant topic can be identified by considering the score per topic and/or subtopic. An exception is a case where a relatively high score is identified only on the topic 'application and market-entry', while no or low concerns are identified on the other topics, i.e. safety for human health or the environment, applicability of regulatory frameworks, and sustainability.

The scoring of different warnings can be compared to guide prioritisation between warnings.

2.9 Step 7: Early warning and proposal for follow-up action

Based on the results of step 5 and 6 (sections 2.7 and 2.8), potential follow-up actions will be described. The early warning, together with a proposal for follow-up actions, will be communicated to decision makers, policy makers and regulators to inform them about the potential risks and to provide recommendations about actions. Potential follow-up actions are given in Table 2.

Table 2. General overview of the potential follow-up actions in relation to each major topic. Note: *This is not an exhaustive list.*

Topic	Potential actions
Application and market entry stage	• Obtain more information on how close the material/product is to the market, the potential scale of application, and whether the material/product has a significant societal or economic benefit. For example, by industry consultations or investigating trends in patents and publicly funded research projects. • Gather detailed information of (anticipated) applications. For example, by industry consultations.
Safety assessment (human health and environment)	• Reduce uncertainties by generating additional (safety) data. • Consider substitution of materials of concern and/or regulatory action • Encourage development of suitable (standardised) test methods and improve assessment strategies. • Develop guidance and best practices.
Applicability of regulatory frameworks	• Share knowledge with the involved Agencies, Ministries, Authorities and Committees (e.g. EC, EMA, ECHA, EFSA, SCCS, SCHEER*) to allow timely consideration whether/which current regulatory frameworks need adaptations. • Define guidance, and best practices. • 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, circular economy, substitution. • Facilitate interaction between relevant stakeholders. • Regularly monitor developments of innovations.

* *EC, European Commission; EMA, European Medicines Agency; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; SCCS, Scientific Committee on Consumer Safety; SCHEER, Scientific Committee on Health, Environment and Emerging Risks.*

Important issues related to Safe-and-Sustainable by Design (SSbD) are not included separately in the scoring system of step 5 (section 2.7, Chapter 3), as safety and sustainability aspects are already covered by the questions. However, in case an AdMa is not yet on the market and still in development, SSbD-related issues should be addressed in the early warning at this step 7 to allow the development of appropriate proposals for actions on this topic. The following questions about SSbD could be of help in the description of the early warning and related follow-up actions:

- Has the developer or innovator paid attention to safe-by-design during the innovation process?
- Is attention (being) paid to limit the energy consumption and/or the impact on global warming potential (greenhouse gas emission) over the life cycle, and is this documented? This includes processes such as the extraction of raw materials, production, use, and recycling.
- Is attention (being) paid to limit the use of resources (e.g. raw material, water, land) over the entire life cycle?
- Is reusability or recycling possible or are recycling options foreseen and where needed facilitated?

2.10 Step 8. Reflection and evaluation

Where relevant and with input from step 6 (section 2.8), follow-up actions related to identified warnings can be taken by the appropriate actors (step 7, section 2.9). The actions are subsequently expected to have an impact. Therefore, it is important that, after some time, experts reflect and evaluate on:

- the warning identification (steps 1 to 6),
- the actual action(s) taken, and
- the impact of the actions.

This reflection step 8 helps 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.

3. Early4AdMa scoring system (details on step 5)

As part of step 5 of the early awareness system for AdMa (section 2.7), each preliminary warning of Tier 1 (steps 1 to 4) is systematically assessed by a group of different experts using a set of questions related to the following topics:

- Application and Market-entry stage
- Safety assessment
  - Human Health
  - Environment
- Applicability of Regulatory Frameworks
- Sustainability

The sets of questions per topic are further organised in sub-topics, which are presented on the following pages. Each question leads to a score. Through these questions and scores, the different warnings are assessed in a similar and systematic manner, allowing for the comparison and prioritisation of different warnings. The topics and sub-topics that show high scores for a warning also provide starting points for defining potential follow-up actions (step 7, section 2.9).

The scoring procedure. Scoring is performed in a conservative way: the questions refer to specific information that may not be available, and therefore, an indication – in contrast to clear evidence – is sufficient to attribute the maximum score. When no information is available or information on a specific property is unknown, a default score of 1 is applied. This score of '1' may also be applied in case of 'maybe', in case the indications are too weak to justify giving the maximum score of 3, 6 or 9. The overall score per topic is then calculated by dividing the total score given by the maximum score possible, resulting in a value between 0 and 1. This relative score allows for the comparison between topics and between warnings. See Appendix for an example of how the scores are calculated.

To increase the robustness of the scoring, it is recommended that a larger pool of experts performs the scoring. By averaging the score of the different experts, a more balanced view is obtained. The pool of experts should include experts from different backgrounds and fields and with different levels of expertise on AdMa. The perspective of the expert is important as some questions use qualitative terms like 'low', 'large' and 'high'. Indicating clear quantitative thresholds rather than these qualitative terms is not yet feasible.

Dealing with uncertainty. When no information is available, a score of 1 is given. Thus, cases with no or little information (and so a high level of uncertainty) receive a relatively low final score. Such cases may develop into cases of low risk or high risk once further information becomes available.
For the interpretation of the scores, it is important to be able to differentiate cases of low potential risk and low uncertainty from cases of low or medium risk that have a high uncertainty. To address this uncertainty issue, two additional scores are calculated based on the score given by the expert reviewer: *a potential minimum score and a potential maximum score*. The minimum score is calculated by giving a score of '0' to all questions that received a score of '1' from the expert due to uncertainty. The potential maximum is calculated by giving the maximum score of a particular question to these questions. The potential minimum and maximum score thus represent the potential risk band-width of a particular case. If a digital scoring system is used, the minimum and maximum scores can be automatically calculated based on the scoring of the expert. Thus, the experts only need to give a single score per question.
A detailed example of how the uncertainty assessment is done can be found in Appendix.

3.1 Topic: Application and Market-entry stage

The first topic relates to application and market-entry stage. It provides insight in whether the application is already on the market or an indication on the time to market, and whether the (anticipated) scale of application is large.

Table 3. Application and Market-entry stage Higher scores indicate that the application is already on the market or near to market and large-scale application is occurring or foreseen.

Descriptor	Question[a]	Answer *(score)*			Comment/ clarification
		Yes (9,6 or 3)	***No (0)***	***? (1)***	
Scale of application *(max. 12 points)*	Is (one of) the (intended) application(s) of the AdMa for use at large (e.g. used by many consumers, at high amounts), medium scale or limited scale? *Score: yes, large scale=9, yes, medium scale=6, limited scale=3, unknown=1, no=0*				
	Is use of the AdMa in more than one application foreseen? *Score: yes=3, unknown/possibly=1, no=0*				
On market or close to market *(max. 12 points)*	Is the AdMa already on the market, in pilot production and demonstration, or 'beyond concept of validation'? *Yes, on the market: score=9* *Possibly on the market: score=6* *Yes, in pilot production and demonstration (TRL[b]>6): score =6* *Possibly in pilot production and demonstration (TRL>6): score =3* *Yes, beyond concept validation: score=3* *Possibly beyond concept validation: score=1* *Unknown: score=1* *No=0*				
	Is there more than one indication on the development of the AdMa (multiple publications, patents, information from developers) *Score: yes=3, unknown/possibly=1, no=0*				
	Total marks (max. 24)				
	Total relative score (=total marks/24)				

[a] If for a certain AdMa more than one application is foreseen, provide the score for the application that is closest to the market and has a considerable or high (anticipated) scale of application. Niche applications that are already on or close to the market are then not taken into consideration.

[b] TRL: Technology Readiness Level [14].

3.2 Topic: Safety assessment - Human Health

Safety assessment - Human Health provides insight in whether human health safety issues need further attention. Issues specific for AdMa are included. These comprise issues relevant from the chemical composition (e.g. whether substances of concern are present), as well 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.

Table 4. Safety assessment - Human Health. Higher scores indicate that there are indications for human health issues. *Unless indicated differently, score refers to: yes=3, no=0, unknown/possibly=1. An indication for a specific physicochemical property, hazard, (toxico)kinetic behaviour or exposure is sufficient to attribute the maximum score. Unknown (=?) can also be interpreted as 'maybe' in case the indications are weak.*

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		Yes (3 or 6)	***No (0)***	***? (1)***	
Physico-chemical properties *(max. 15 points)*	Is there an indication of new or enhanced properties (e.g. electric, electromagnetic) related to the nano/multicomponent/ advanced character of the material?				
	Is there an indication of persistency due to low dissolution or degradation rate in any physiologically relevant media?				
	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 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.				
Hazard *(max. 15 points)*	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s) • Related to the new or improved functionality. For instance, because the material is active/stimulus responsive[c]. • Due to combination of materials. For instance, if the different components enhance each other's effects or events leading to toxic effects. • Based on information from similar AdMa. *(score: yes=6, unknown=1, no=0)*				

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		***Yes* (*3 or 6*)**	***No* (*0*)**	***?* (*1*)**	
Hazard *(max. 15 points)*	Is (one of) the (constituent) chemical(s) itself a substance, material or constituent classified under CLPc, relating to human health hazards?				
	Is there an indication of carcinogenicity/ genotoxicity/mutagenicity of the material?				
	Is there an indication of toxicity (e.g. immunotoxicity, sensitising properties, lung toxicity, endocrine toxicity) of the material?				
Kinetics *(max. 15 points)*	Is there an indication of change in kinetic profile compared to the conventional material(s)?				
	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?				
	Is there an indication that a multicomponent material can be taken up and distributed in a way different from that of the individual components of the material?				
Exposure *(max. 15 points)*	Are consumers likely to be exposed to the AdMa, or released substances/particles thereof?				
	Are workers likely to be exposed to the AdMa or released substances/particles thereof in an occupational setting, including during the end-of-life or recycling process?				
	Are the AdMa 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 marks (max. 60)				
	Total relative score (=total marks/60)				

[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.

[b] Reference to the Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008) [15]. Only substances on this list that relate to human health hazards are considered.

[c] Active nanomaterials respond to a stimulus, i.e. pH, temperature, light. In contrast, passive materials are 'stable during their use' [16].

3.3 Topic: Safety assessment - Environment

Safety assessment - Environment provides insight in whether environmental safety issues need further attention. Issues specific for AdMa are included comprising both issues relevant from the chemical composition, e.g. whether substances of concern are present, as well 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.

Table 5. Safety assessment - Environment. *Higher scores indicate that there are indications for issues related to the environment. Unless indicated differently, score refers to: yes=3, no=0, unknown/possibly=1. An indication for a specific physico-chemical property, hazard, (toxico)kinetic behaviour or exposure is sufficient to attribute the maximum score. Unknown (=?) can also be interpreted as 'maybe' in case the indications are weak.*

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		***Yes* (*3 or 6*)**	***No* (*0*)**	***?* (*1*)**	
Physico-chemical properties *(max. 15 points)*	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 in any environmentally or physiologically relevant media?				
	Is there an indication of reactivity? E.g. due to surface area, type of chemical, surface treatment, light absorbance.				
	Is there an indication of release of toxic ions or molecules?				
	Is there an indication that the attachment of the AdMa to natural organic matter (NOM) is different from that of the conventional material(s)?				
Hazard *(max. 15 points)*	Is there an indication of another hazard or increased toxicity as compared to the conventional material(s)? • Related to the new or improved functionality. For instance, because the material is active/stimulus responsive[c]. • Due to combination of materials. For instance, if the different components enhance each other's effects or events leading to toxic effects. • Based on information from similar AdMa *(score: yes=6, unknown=1, no=0)*				

Descriptor	Question[a]	Answer *(score)*			Comment/ clarification
		Yes (3 or 6)	***No (0)***	***? (1)***	
Hazard *(max. 15 points)*	Does (one of) the (constituent) chemical(s) itself fall in one of the following categories? • substance, material or constituent classified under CLP[b], relating to environmental hazards • PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) • or very high persistence in combination with mobility in water and/or potential for long-range transport.				
	Is there an indication of short- or long-term toxicity (incl. reproduction toxicity, antimicrobial activity) of (one of) the (constituent) chemical(s)?				
	Is there an indication of endocrine disruption?				
Fate *(max. 15 points)*	Is there an indication that fate of multi-component material differs from that of the individual components of the material?				
	Is there an indication of accumulation/ persistence in the environment (of the AdMa or released substances/particles)?				
	Is there an indication of potential of high mobility across environmental compartments (of the AdMa or released substances/particles)?				
	Is there an indication of uptake by animals or plants (of the AdMa or released substances/ particles)?				
	Is there an indication of uptake of incorporated active ingredients or chemicals associated with the AdMa by animals or plants?				

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		***Yes* (*3 or 6*)**	***No* (*0*)**	***?* (*1*)**	
Exposure/ environmental release *(max. 15 points)*	Is it likely that the AdMa will be used in high volumes, in many products and/or by the wide population?				
	Is direct exposure of biota in one or more environmental compartments likely?				
	Is weathering/leaching of the AdMa itself or of released substances/particles to one or more environmental compartments likely?				
	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 marks (max. 72)				
	Total relative score (=total marks/72)				

[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. Specific materials for which only niche applications are foreseen may be disregarded, if applicable.

[b] Reference to the Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008) [15]. Only substances on this list that relate to the environment are considered.

[c] Active nanomaterials respond to a stimulus, i.e. pH, temperature, light. In contrast, passive materials are 'stable during their use' [16].

3.4 Topic: Applicability of Regulatory Frameworks

The questions related to Regulatory Frameworks provide insight in whether the current regulatory frameworks are expected to address the AdMa adequately and potential risks are addressed accordingly.

Table 6. Applicability of Regulatory Frameworks. Higher scores indicate that the risks are not likely to be considered by current regulations.

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		***Yes* (*0 or 3*)**	***No* (*0,3 or 9*)**	***?* (*1*)**	
Applicability Regulatory Frameworks *(max. 12 points)*	Does the material(s) or application(s) fall within the scope of one or several current chemical legislation(s)? *(score: yes=0, borderline situation for different frameworks=3, unknown=1, no=9).*				
	If the material(s) or application(s) falls within the scope of relevant (regional) legislation, do the information requirements cover the potential exposure/release, kinetic/ fate and hazard issues (section 3.2 and 3.3) for the AdMa? *(score: no=3, unknown=1, yes=0)*				
	Are the existing test methods and assessment strategies (e.g. guidance) considered applicable for the AdMa? *(score: no=3, unknown=1, yes=0)*				
	Total marks (max. 12)				
	Total relative score (=total marks/12)				

[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 AdMa may be disregarded.

3.5 Topic: Sustainability

The questions related to sustainability provide insight in whether the material is/can be sustainably used.

In the questions below, the following sustainability aspects are taken into consideration: critical raw materials (see footnote b to the list of questions on sustainability), hazard, environmental impact, and recyclability/reusability to support circular economy. The use of hazardous or persistent substances or materials are problematic for achieving a circular economy. These are therefore not only addressed under the 'safety' related questions (section 3.2 and 3.3), but also under sustainability.

Social aspects with regard to sustainability are not explicitly included. In a limited way, social aspects are included in the list of critical raw materials, because this list takes into account demographic considerations. Social aspects might be included more explicitly in the future.

Table 7. Sustainability. Higher scores indicate that there are indications for issues related to sustainability.

Descriptor	Question[a]	Answer *(score)*			Comment/ clarification
		Yes (0 or 6)	*To a limited extent (3) or unknown (1)*	*No (0 or 6)*	
Raw Materials and Resources *(max. 30 points)*	Are critical raw materials[b] used? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Are the raw materials used classified as hazardous or persistent (CLP)? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	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)? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Can the raw materials be recycled? *(score: no=6, to a limited extent =3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
	Is the recycling process efficient? (i.e. is volume and quality of recycling product sufficient for a circular economyc?) *(score: no=6, to a limited extent =3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
Manufacturing production, transport and use *(max. 30 points)*	Does the process of manufacturing, production, transport, use and/or consumption require high energy or land consumption and/or have an impact on global warming potential (emission of greenhouse gases)? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Is there a high amount of waste in the process of manufacturing and production? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Is the waste generated during manufacturing, production, transport and use recyclable or reusable? *(score: no=6, to a limited extent =3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
	Does the waste generated during manufacturing, production, transport and use contain persistent or hazardous substances (CLP)? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				

Descriptor	Question[a]	Answer (*score*)			Comment/ clarification
		Yes (0 or 6)	***To a limited extent (3) or unknown (1)***	***No (0 or 6)***	
Manufacturing production, transport and use *(max. 30 points)*	Do the processes of manufacturing and production use a high volume of solvents or water? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
End-of life (Recyclability and reusability) *(max. 30 points)*	Is there an efficient system in place to recycle the products/AdMa? Or is there a concept or plan to recycle the material/recover the individual materials? *(score: no=6, to a limited extent=3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
	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)? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Is it possible to re-use (most of) the materials in the same or another function? *(score: no=6, to a limited extent =3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
	Are different components used that are integrated, which might make recycling technically difficult? *(score: yes=6, to a limited extent =3, unknown=1, no=0)*				
	Is the application of the AdMa durable[d], e.g. long-term functionality, or reparable? *(score: no=6, to a limited extent =3, unknown=1, yes=0)* *Please note a 'no' leads to the highest score.*				
	Total marks (max. 90)				
	Total relative score (=total marks/90)				

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

[b] For instance, is raw material included in the EU list of Critical raw materials (europa.eu)?

[c] For instance, in batteries, the most generous reports suggest that currently 50% of Li-ion batteries reaching the end of their life are recycled. The problem of recovery of essential materials such as lithium is that the recovery is often too low to be suitable for reusability [17].

[d] Durable indicates that there is long-term functionality.

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Appendix: Calculation of score and assessment of uncertainties

Calculation of the scores. The table below gives an example of how the scoring by an expert is done. In this illustrative example, only the scores for the first of the five topics is shown (i.e. Application and market-entry stage). In the table, the 'Maximum score' column shows the maximum score that each question may receive. The column in blue (i.e. 'Expert score') shows the score given by the expert. The 'Potential minimum score' and the 'Potential maximum scores' are determined based on the 'Maximum score' and the 'Expert score'. The minimum score is calculated by giving a score of '0' to all questions that received a score of '1' related to uncertainty from the expert. The potential maximum is calculated by giving the maximum score of a particular question to these questions. In the example, the last two questions received an expert score of '1', which means that it is unknown whether these issues apply to the selected AdMa. In the 'Potential minimum score' column, these questions thus receive a score of '0' whereas in the 'Potential maximum score' column the maximum score of the respective question is given ('9' and '3'). For all 'Expert scores' other than '1', the potential minimum and maximum score are the same as the score given by the expert (see for an example the first two questions). The final scores for the topic are calculated by dividing the total scores of the 'Expert score' (in this example 11), 'Potential minimum score' (9) and 'Potential maximum score' (21), respectively, by the total 'Maximum score' (24). The potential minimum and maximum score represent the potential risk bandwidth of a particular case based on which the certainty of the derived expert score can be evaluated.

The calculation of these potential minimum and maximum score can be done automatically if an digital scoring system is used.

Application and market-entry stage					
Subtopic	***Question***	***Maximum score***	***Expert score***	***Potential minimum score***	***Potential maximum score***
Scale of application	Is (one of) the (intended) application(s) of the AdMa for use at large (e.g. used by many consumers, at high amounts), medium scale or limited scale?	9	9	9	9
	Is use of the AdMa in more than one application foreseen?	3	0	0	0
On market or close to market	Is the AdMa already on the market, in pilot production and demonstration, or 'beyond concept of validation'?	9	1	0	9
	Is there more than one indication on the development of the AdMa (multiple publications, patents, information from developers) ?	3	1	0	3
	Total	24	11	9	21
	Final score (total relative score)		**0.46**	**0.38**	**0.88**

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