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HARMLESS Early Warning System for Advanced Materials

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Advanced Materials (AdMa) play a crucial role for numerous strategies that address global challenges. They are being developed fast, making it increasingly challenging for regulation to keep pace with innovation. Existing frameworks, which are either not designed for AdMa or lack adequate filtering to identify AdMa of high concern, do not (yet) effectively support regulatory preparedness. The HARMLESS Early Warning System (EWS), in contrast, is a practically applicable tool for screening plenty of materials in a reasonable time. It is organized in two tiers, each underpinned by a specific methodology and facilitated by a dedicated online tool. The initial Tier 0 categorizes the materials using the Advanced Materials Earliest Assessment (AMEA) tool. Tier 1 first screens materials asking only 15 questions and is ideal for data-poor materials at early innovation stages. These questions cover issues related to human/ environmental exposure and hazard, sustainability and applicability of existing regulations. In a more elaborated version, experimental testing based on New Approach Methodologies (NAMs) is suggested. As outcome, the user is provided with 1) material-related concerns, 2) prioritization of AdMa and 3) recommendations for (regulatory) follow-up actions. Data from two industrial case studies is presented to demonstrate the applicability of the HARMLESS EWS.

1. Introduction

In the European Union (EU), the European Green Deal was set out in 2019 aiming at a transformation toward a sustainable climate neutral and circular economy.[2] One of the key commitments of the European Green Deal is the movement toward a toxic-free environment. As part of this goal the Chemicals Strategy for Sustainability (CSS) was adopted by the European Commission (EC) in 2020 aiming at (i) a better protection for citizens and the environment and (ii) a promotion of innovation for safe and sustainable chemicals.[3] To this end, the CSS stresses that new chemicals and materials must be inherently safe and sustainable throughout their whole life cycles.

However, the success of the European Green Deal will critically depend on the development of (new) energy- and resource-efficient technologies. Advanced Materials (AdMa)* will play a crucial role in this context as they are important building blocks due to their versatile and often superior properties in comparison to conventional materials (CoMa). A regulatory definition for AdMa does not exist and is also not rational for several reasons.[4] The Organisation for Economic Co-operation and Development (OECD) proposed a working definition (see grey box). AdMa are being developed and used with increasing pace and their demand is expected to further increase

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within the next years.[5] They are applied in nearly every sector covering various fields of application, for example, renewable energy,[6] energy storage/ batteries,[7] building and construction,[8] high performance computers, semiconductors,[9] medicine, agriculture as well as in consumer products.

***Advanced materials – working definition (OECD):**

"AdMa are understood as materials that are rationally designed to have (i) new or enhanced properties, and/or (ii) targeted or enhanced structural features with the objective to achieve specific or improved functional performance. This includes both new emerging manufactured materials, and materials that are manufactured from traditional materials. This also includes materials from innovative manufacturing processes that enable the creation of targeted structures from starting materials, such as bottom-up approaches. It is acknowledged that what are currently considered as AdMa will change with time".[1]

As AdMa are mainly characterized by their advanced material properties and superior performance (compared to CoMa), they comprise a large heterogenous material class that continues to rapidly evolve through innovation. Even though AdMa hold highly promising potential, they may also raise concerns as several of them may indeed pose risks to human health and/or the environment. Problems arise, if these risks are not foreseen or detected in time, which is challenging as this first requires an appropriate methodology that second needs to be adapted continuously as science progresses fast. Highly innovative fields are characterized by a high level of complexity, uncertainty and generally they evolve at high pace such that amending existing regulations is very challenging. This has already been observed for nanomaterials (NMs), where the EU chemicals legislation REACH entered into force in 2007[10] while nano-specific amendments became effective only more than one decade later, in 2020, as a result of intensive discussions involving different stakeholders and regulatory-oriented scientific progress.[10] However, this is even more true for AdMa, which represent a much more heterogenous class of materials that evolve even faster. To address and prevent this discrepancy for the rapidly growing field of AdMa, an appropriate development of concepts, frameworks, methods and tools to support well-informed decision making, is required. Otherwise, innovations would be hampered by a lack of appropriate governance.

To support regulatory implementation of NMs, several risk governance frameworks have been developed. A first comprehensive NM risk governance framework was published by the International Risk Governance Council in 2012 and updated in 2017.[11] Within this framework, a risk pre-assessment is carried out first to "frame the risks". In this stage, initial hints for possible concerns – the so-called "early warnings" – are important to prepare for handling the risks at later stages. Considering AdMa, these materials also can only be sustainable when they are safe and functional (i.e., understood as their performance for the intended application). However, comprehensive data and method development/adaptation often lag behind. Therefore, an essential element of risk governance is the Safe(r) and Sustainable Innovation Approach (SSIA).[12] Within the SSIA two important concepts are combined: (1) the Safe-and-Sustainable-by-Design (SSbD) concept aiming at the innovators[12,13] and (2) the concept of regulatory preparedness (RP) aiming at the regulators.[13] Both demand that during an innovation process safety and sustainability aspects should be addressed as early as possible. However, at the early stages of material development, hazard data is usually incomplete (if at all existing) and will certainly not allow for a (comprehensive) risk assessment. In addition, AdMa are (by definition) different in their material properties compared to CoMa such that in particular at these early stages of innovation, it is not clear if existing data for CoMa can be equally applied for AdMa. Thus, from the regulatory point of view, at these early stages that are characterized by little or no data, only a pre-assessment (or risk framing) will be possible. For this purpose, specific "early warning signals" are derived[14] that allow to identify AdMa raising concerns very early in an innovation process.

The EC Joint Research Centre (JRC) performed a review of the currently existing safe-by-design (SbD) and SSbD frameworks, tools and concepts[15] and developed a SSbD framework based on this.[16] The JRC SSbD framework is a stepwise, hierarchical approach that first addresses safety and in a second step environmental sustainability. Societal and economic sustainability aspects can be included but are still under development. However, the JRC SSbD framework still needs to be operationalized and tailored to the specific needs of each sector, including those of nano- and advanced materials. For such highly innovative fields, it is advantageous to implement the innovation stage-gate model directly in the framework itself as this is a valuable model that schematically depicts the innovation process.

To meet the needs of a safe and sustainable application of AdMa, the OECD Working Party on Manufactured Nanomaterials (OECD WPMN) established two Steering Groups (SG) in 2021: (1) SG Advanced Materials and (2) SG Safer Innovation Approach. One of their tasks is the development of a strategic approach to support RP and SSbD of AdMa and their applications. The SG AdMa was also involved in the refinement of the Early Awareness and Action for AdMa (Early4AdMa), which was originally developed by the National Institute for Public Health and the Environment (RIVM), the German Federal Institute for Risk Assessment (BfR), the Federal Institute for Occupational Safety and Health (BAuA) and the Umweltbundesamt (UBA).[14,17]

Early4AdMa is a pre-regulatory risk governance tool that aims to identify knowledge gaps and possible concerns about safety and sustainability aspects of AdMa. Basically, the system is composed of two tiers. In Tier 1, AdMa are screened for initial concerns and potentially critical AdMa shall be identified by initial expert judgement on human and environmental safety, sustainability, and applicability of regulatory frameworks. Tier 1 ends with a score (green, orange or red) for each AdMa that shall facilitate the decision on proceeding with the detailed assessment in Tier 2 or not. The second tier comprises a more detailed assessment covering four major topics (i.e., safety human health, safety environment, applicability of regulatory frameworks and sustainability). Finally, potential follow-up actions are recommended based on the outcome of Tier 2.

Since its establishment, Early4AdMa was tested using several case studies. In a joint HARMLESS/ OECD SG AdMa workshop organized in November 2022, data obtained in one of the HARMLESS industrial case studies, namely for fiber aerogel mats used for façade insulation, served as an example to compare different AdMa assessment schemes.[18] The feedback on Early4AdMa was that, on the one hand, it was rated to be very useful, since it

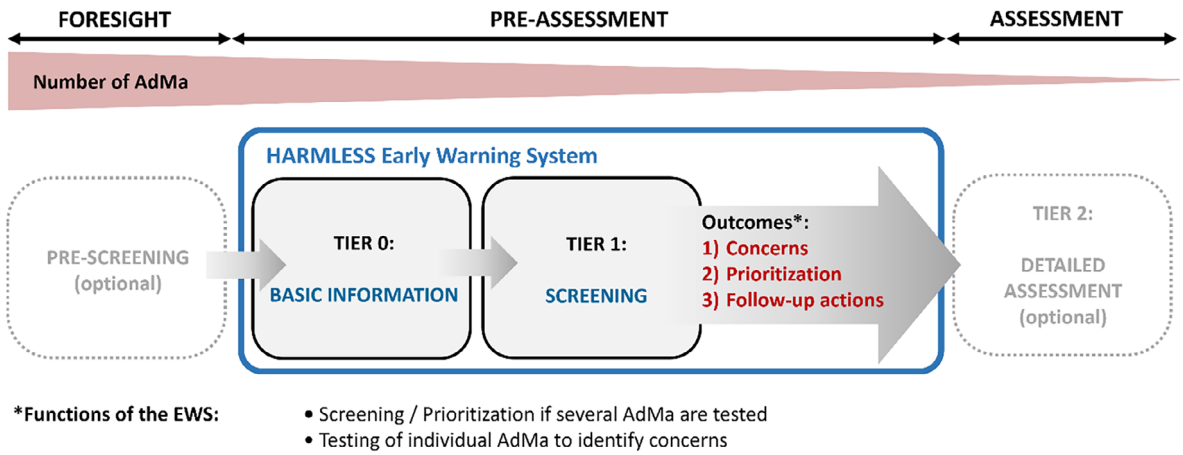

Figure 1. Schematic structure of the HARMLESS EWS and final outcomes. The HARMLESS EWS specifically tackles the pre-assessment phase of the risk governance process. Its design aims for screening and prioritization of AdMa to identify AdMa that raise specific concerns, which then may require a more elaborated assessment and/or specific (regulatory) follow-up actions. Moreover, the HARMLESS EWS can be applied to identify specific concerns for individual AdMa. Pre-screening (foresight) and detailed assessment are not part of the HARMLESS EWS but can be easily added.

considers all relevant topics. On the other hand, it turned out to be very time consuming, since a relatively large amount of detailed data is needed to answer the questions in Tier 2. Furthermore, in the present version of the Early4AdMa expert knowledge is needed for several questions resulting in a limited circle of users. However, apart from the points stated above, the most relevant critical issue in the context of RP is the insufficient filter function of Tier 1. Consequently, for the vast majority of AdMa, the assessment does not stop after Tier 1 such that most AdMa need to be assessed in detail within Tier 2, which is usually difficult and often not even possible as data is lacking. In addition, methods are often lacking, too or they may still require adaptation to meet the specific needs of a particular material class. At the same time, it appears logical that with the increasing pace of AdMa development, it will simply not be possible to assess each material in detail. Therefore, it seems appropriate to improve the screening phase of Early4AdMa as it needs to properly identify AdMa with high concerns. In other words, the "warning" of an early warning system should lead to a prioritization for those materials that require a regulatory follow-up action most urgently.

Here, the HARMLESS Early Warning System (EWS) is presented, which has been developed as part of the EU project HARMLESS.[19] It is an easy and practically applicable framework, which is organised in two tiers (Tier 0 and Tier 1), each underpinned with methods and tools. It allows for initial screening to identify AdMa for which substantial concerns exist. The HARMLESS EWS is primarily designed to support RP. Thus, the target groups are risk assessors, regulators and policy makers. Correspondingly, within HARMLESS, a SSbD approach was developed covering the innovator's perspective.[20] It must be emphasized that the HARMLESS EWS was developed in parallel and is aligned with the SSbD approach to foster dialogue between the stakeholders as early as possible during the innovation process. The HARMLESS EWS especially enables the screening of AdMa in early stages of innovation (i.e., before they enter the market or AdMa that just entered the market) to support the pre-assessment phase of risk governance. However, in principle, it can be applied to any material, regardless of the innovation stage. By combining all information that is available (i.e., data on exposure, human and environmental hazards, sustainability, and suitability of existing regulatory frameworks), "warning signals", such as material-related concerns, critical data gaps and specific follow-up actions can be identified in a timely manner. The HARMLESS EWS is designed as a two-tiered standalone tool providing 1) concerns for individual materials, 2) a prioritization for those materials that are critical and 3) recommendations for follow-up actions. At the same time, it can be easily integrated in the existing OECD Early4AdMa.

Figure 1 schematically depicts how the HARMLESS EWS is embedded in the screening process of AdMa. The tool was designed to be applied in the pre-assessment phase. A pre-screening, which could involve different foresight/ horizon scanning techniques/ tools, can precede the HARMLESS EWS. A detailed assessment can be applied following the HARMLESS EWS to assess selected AdMa for which high concerns have been identified to characterize such concerns in a more elaborated manner.

2. Experimental Section

The presented HARMLESS EWS was developed as part of the EU project HARMLESS[19] running from January 2021 until April 2025. The scope of the project is "Advanced high aspect ratio and multicomponent materials: toward comprehensive intelligent testing and Safe-by-Design strategies". Basically, the HARMLESS EWS combines available knowledge in a novel and superior manner compared to existing approaches as described in detail in the following sections. The main sources for the development of the HARMLESS EWS as well as their individual contributions are listed in **Table 1**.

2.1. Data Basis

2.2. Methodology

Next, the methodological approach to the development of the HARMLESS EWS is described.

Table 1. Main sources for the development of the HARMLESS EWS.

Source	Main objectives	Contributions to the HARMLESS EWS
Early Awareness and Action for AdMa (Early4AdMa) system[14,17]	• Pre-regulatory risk governance tool • Aim: to identify concerns for selected AdMa considering human and environmental safety, sustainability, and regulation timely	• Categories for the "warning signals" (Exposure, Hazard, Sustainability, Applicability of regulatory frameworks) • Selection of questions/warning signals
Joint HARMLESS OECD workshop[18]	• Workshop to evaluate four tools (including Early4AdMa) to anticipate safety and sustainability issues on AdMa with data from the HARMLESS case study on aerogels • Aim: to list positive and negative aspects in order to optimize the individual tools	• Feedback for Early4AdMa used in order to optimize the screening tier (Tier 1) of the HARMLESS EWS
Advanced Materials Earliest Assessment (AMEA)[21]	• Approach to fill the gap of inappropriate risk management for AdMa • Design rules and simple assessments are proposed for the Ideation and Business Case Phases of innovation management.	• Adapted as entry point (Tier 0) for the HARMLESS EWS with slight extension
Safe and Sustainable by Design Approach and Decision Support System for Advanced Materials[20]	• Online tool to support decision-making during the design process of innovative products with regard to SSbD and performance. • Support is provided at early innovation stages ((a) Ideation & Business Case Phase and (b) Lab Phase).	• Selection and alignment of questions (warning signals) in Tier 1
Decision Support System for Safe-and-Sustainable-by-Design Advanced Materials – Case study demonstration[22]	• Testing of the Decision Support System (DSS) using data from four different case studies (oxide-perovskites, imogolites, aerogel mats and colloidal silica)	• Improving the DSS and thereby the EWS on several aspects, including rephrasing questions to make them understandable by neophytes and select assessment descriptors suitable for early stages of SSbD
GRACIOUS IATAs[23]	• Integrated Approaches to Testing and Assessment (IATAs) build a framework to conclude on the toxicity of chemicals in a specific regulatory scenario or decision context. • During the GRACIOUS project several nano-specific IATAs have been developed aiming to support grouping and read-across of NMs.	• Elaborated version of Tier 1 (NAM-based assessment for categories A (Exposure) and B (Hazard)) • Tiered testing strategies and selection of NAMs
NAMS4NANO review on NAMs for NMs[24]	• Review of existing NAMs with potential use for risk assessment of NMs in the food and feed sector. • Overview of nano-specific NAM-frameworks and individual NAMs.	• Elaborated version of Tier 1 (NAM-based assessment for categories A (Exposure) and B (Hazard)) • Selection of NAMs

2.2.1. Joint HARMLESS OECD Workshop

HARMLESS organised an expert workshop in collaboration with the OECD WPMN SG AdMa involving the developers of the Foresight Schemes to jointly discuss the HARMLESS case study on fiber aerogel mats (held online on 15 November 2022). This workshop had three main objectives: 1) to evaluate three currently available schemes as foresight tools to anticipate safety and sustainability issues on AdMa with data from a HARMLESS case study on aerogels, 2) to list pros & cons, and 3) to provide suggestions for optimized use of these foresight schemes. During the workshop the four foresight schemes (a) InnoMat.Life,[25] b) Arvidsson et al.,[26] c) Early4AdMa,[14,17] and d) Kennedy et al.)[27] were presented.

The outcome of the workshop has been published by the OECD.[18] The following conclusions were drawn:

1) The InnoMat.Life approach was regarded as a useful tool for early stages while the more data demanding Early4AdMa was found better located further down the innovation process.
2) Low-tier schemes (such as Arvidsson et al.[26] and InnoMat.Life)[25] may be integrated into Early4AdMa as earlier steps.
3) The attendants highlighted that Early4AdMa may be used by regulators for identification of knowledge gaps and possible concerns. Availability of requested data was one main issue expected to be driving the future use of these schemes.
4) Early4AdMa was considered very complex, lacked guidance and contained some unprecise questions.
5) Early4AdMa requires experts from different disciplines (chemists, toxicologists, sustainability experts). Furthermore, it was acknowledged that a second layer of analysis may be required for successful application of Early4AdMa, to take into account correct weighting of results and potential biased answers since several experts were required to fill the scheme.

The outcome of this workshop was the basis for the selection of questions/warning signals of the HARMLESS EWS.

2.2.2. Advanced Materials Earliest Assessment

In line with the outcome of the HARMLESS OECD workshop, the HARMLESS consortium developed an "Advanced Materials Earliest Assessment (AMEA)" approach.[21] AMEA is an extension of the InnoMat.Life approach[25] by integrating input from HARMLESS. Initially, AMEA was developed to propose assessment steps and guidance for design rules for the early stages

of an innovation process (e.g., Ideation, Business Case and Lab Phases). It provides a structured approach to exploit the available knowledge at each phase, starting from the intended product, application and global region, using also the known sustainability benefits and challenges of the CoMa in the same application, which often constitute the motivation for AdMa development.

In AMEA, materials are categorized in three dimensions, which have relevant implications for the later risk assessment.

The three dimensions are:

1) Does the material consist of particles?
2) Is the material nano-enabled?
3) Is the manufacturing process or the material itself considered as "advanced"?

The online tool representing the AMEA concept[28] displays the resulting cube in the 3D space, and prioritizes recommendations for testing and assessment.

2.2.3. Safe-and-Sustainable-by-Design Approach and Decision Support System

The SSIA that is followed within the HARMLESS project comprises three main elements, that is, (1) the SSbD approach, (2) tools for innovators (Warning flags, design Advice & Screening Priorities (WASP) and Alternative SSbD inspector (ASDI)) and (3) the HARMLESS EWS presented here. The tools for innovators (WASP and ASDI) were developed to support the user with decision-making during the design process of innovative materials[20] and were tested using data from four different case studies.[22] Basically, these tools focus on (a) the Ideation & Business Case Phase and (b) the Lab Phase, both located at early stages within the innovation process. For each of the phases, individual tools are applied that are tailored to the needs for the respective innovation stage. AMEA,[21,28] WASP,[29] ASDI and the simple version of the HARMLESS EWS are currently included in the Decision Support System (DSS).[20,30] The HARMLESS SSbD and the HARMLESS EWS were developed in parallel and the 15 simple questions that the HARMLESS EWS considers in the screening phase (Tier 1) are aligned as much as possible with WASP to obtain warning signals in a coherent manner.

2.3. Tools

2.3.1. GRACIOUS IATAs and Tiered Testing Strategies

Integrated Approaches to Testing and Assessment (IATAs) are being developed to combine different sources of information (existing and newly generated data) in a reasonable manner to tackle risk assessment with a minimum amount of new testing.[31] Basically, within an IATA, versatile data on a chemical or a group of chemicals (i.e., physicochemical properties, in silico models, grouping and read-across approaches, in vitro methods, in vivo tests and human data) are evaluated, weighed and integrated to obtain an overall assessment while minimizing the need for new experimental tests, in particular for in vivo studies.[32] IATAs are typically structured as decision trees that consist of various decision nodes that each ask for a specific piece of information, which may be answered based on existing data or by means of specific methods often based on New Approach Methodologies (NAMs) and tools (e.g., computational).

In the EU-funded Horizon 2020 project GRACIOUS, several nano-specific IATAs have been developed aiming to support grouping and read-across of NMs.[23,33–37] Basically, all GRACIOUS IATAs were designed in a modular structure considering physico-chemical properties ("What they are?"), toxicokinetics ("Where they go?") and related adverse outcomes ("What they do?"). For each decision node, a tiered testing strategy is provided.

To support the elaborated version of Tier 1 within the HARMLESS EWS, the tiered GRACIOUS IATAs were used and adopted as needed. In detail, the HARMLESS EWS suggests to use NAM-data first to enable a decision on specific questions being related to human hazard (Table 4B). For the HARMLESS EWS, five descriptors from the GRACIOUS IATAs were identified that can be assigned to certain warning signals (see Table 4 column "Endpoints for elaborated version" for assignment). The five descriptors are: (1) dissolution, (2) reactivity, (3) inflammation, (4) genotoxicity and (5) cytotoxicity. In Table S1, Supporting Information the tiered testing strategies for each of these five descriptors are summarized.

Table 2. List of CB tools that are integrated within the HARMLESS EWS.

Control banding tool	Integration within the HARMLESS EWS
Stoffenmanager Nano[42]	• Human hazard assessment for the material • Occupational exposure assessment (part of LICARA nanoSCAN)[43,44]
NanoRiskCat[40]	• Consumer exposure assessment (part of LICARA nanoSCAN)[43,44]
Precautionary Matrix[41]	• General population exposure assessment (part of LICARA nanoSCAN)[43,44]

2.3.2. Control Banding Tools

For chemicals, several control banding (CB) tools exist that have emerged as a pragmatic approach to ensure occupational safety, despite the fact that much data are missing. A few of the CB tools have also been adjusted for the needs of NMs.[38–42] Although they do not cover benefits and societal values of materials, they can provide useful information regarding different exposure scenarios. Thus, for the elaborated version of the HARMLESS EWS several CB tools are mentioned in the guidance part (see **Table 2**).

2.3.3. NAM Assays Applied in the HARMLESS Case Studies

The HARMLESS EWS was tested using (NAM) data from two HARMLESS case studies (Perovskite Model Catalysts and Fiber Aerogel Mats). A list of NAM assays, that have been performed as part of the HARMLESS project, is provided in **Table 3**.

It should be noted that Table 3 provides an overview on those NAMs that have been applied in the selected HARMLESS case studies, which may serve as a reasonable starting point in the HARMLESS EWS. However, a much more comprehensive overview on the currently available NAMs for NMs with a

Table 3. List of NAM assays applied in the HARMLESS case studies on Oxide-perovskites and Fiber Aerogel Mats.[22]

NAM assay	Case study
Reactivity	
FRAS assay	Aerogel; Oxide-perovskites
EPR assay	Oxide-perovskites
Oxidative stress – carbonylation	Oxide-perovskites
DCFDA	Oxide-perovskites
8-OHG (nucleic acid oxidative stress)	Aerogel; Oxide-perovskites
Cytotoxicity	
Cytotoxicity – WST-1/LDH assay	Oxide-perovskites
CellTiter-glo (cell viability)	Aerogel; Oxide-perovskites
DAPI (cell number)	Aerogel; Oxide-perovskites
Caspase 3/7 (apoptosis)	Aerogel; Oxide-perovskites
Membrane integrity (Blue Dextran)	Oxide-perovskites
Cytostasis (CBPI)	Oxide-perovskites
Genotoxicity	
Genotoxicity (Micronucleus assay)	Oxide-perovskites
Gamma-H2AX (DNA damage)	Aerogel; Oxide-perovskites
Dynamic dissolution via Continuous flow system in lung simulant conditions	Aerogel; Oxide-perovskites
Inflammation	
Pro-inflammatory markers (ELISA – IL-6, IL-8, IL-1B)	Oxide-perovskites
Calculations	
In silico calculation	Aerogel; Oxide-perovskites
Unsupervised ML	Aerogel; Oxide-perovskites

particular focus on those that show potential to be applied for risk assessment has been recently provided by the EFSA NAMs4NANO project.[24] Even though this review specifically focuses on risk assessment of NMs in the food and feed sector, it considers all three major human exposure routes: oral, inhalative and dermal. Importantly, it also provides a working definition for NAMs. Last but not least, even though NAMs are applied here in a pre-regulatory assessment, they ideally should be validated or at least otherwise proven to be scientifically valid. The most challenging question is how to demonstrate that a NAM that is not yet validated is scientifically valid. Several projects have dealt with that question.[45–47] Currently, two major approaches that are conceptually very similar are discussed and tested in project-internal case studies, namely beta-testing in the Partnership for the Assessment of Risks from Chemicals (PARC)[48] and qualification as proposed by the EFSA NAMs4NANO project.[49]

2.3.4. Sustainable Development Goals

At the global level, the Sustainable Development Goals (SDGs) have been established by the United Nations in 2015.[50,51] The SDGs are political objectives aiming at worldwide sustainable development on economic, social and ecological levels. In total, 17 SDGs comprising 169 sub-goals have been formulated with a duration until 2030. Innovative materials, that are characterized by new properties, can show positive or negative impacts on SDGs. In this context, especially eight SDGs might be affected, which are "Good Health & Well-being" (SDG 3), "Clean Water and Sanitation" (SDG 6), "Affordable and Clean Energy" (SDG 7), "Industry, Innovation and Infrastructure" (SDG 9), "Sustainable Cities and Communities" (SDG 11), "Responsible Consumption and Production" (SDG 12), "Climate Action" (SDG 13) and "Life below Water" (SDG 14). Within the HARMLESS EWS the named SDGs constitute the sustainability screening.

3. Results and Discussion

3.1. The HARMLESS EWS

The HARMLESS EWS has been primarily developed to support risk assessors, regulators and policy makers for decision-making for AdMa, which are very heterogenous and rapidly evolving. However, since regulatory follow-up actions are not tied to a certain stage of the material, it was decided that the HARMLESS EWS shall be applicable at any stage of innovation. This is in contrast to the tools for innovators included in the DSS that was developed in parallel, which addresses the pre-market phase only. The DSS tools were especially designed according to the Cooper stage-gate model considering three innovation stages ((1) Ideation & Business Case Phase, (2) Lab Phase and (3) Pilot Phase).[20] Nevertheless, in its current version, the HARMLESS EWS is expected to be most beneficial for materials in early stages of an innovation process (before or shortly after market-entry) and thus not (yet) falling within existing regulatory frameworks.

The HARMLESS EWS has been developed as a framework, which is organised in two tiers. First (Tier 0) materials are initially categorized, mainly to determine how to best enter/ proceed in Tier 1. In detail, within Tier 0 basic information for the material is collected, whereas the actual screening (including the "warning") takes place in the consecutive Tier 1 (**Figure 2**). For easier application, Tier 1 is further split in two versions. The first version (simple version) asks 15 questions to assess the warning signals regarding hazard, exposure, sustainability and regulatory applicability. The second version (elaborated version) can be applied in two manners, first to follow-up "flagged questions" as obtained in the simple version by experimental NAM-based testing. However, it is equally possible to directly jump to the elaborated version following Tier 0 if the material is not data-scarce (i.e., for a material that already is on the market for some time). Please note that the designations as "Tier 0" and "Tier 1" were deliberately chosen to allow for an easier integration into the existing OECD Early4AdMa. This integration is graphically implied in Figure 1 (with Tier 2 being the detailed assessment in Early4AdMa) and is further discussed below.

3.1.1. Tier 0: Basic Information (based on AMEA)

Within Tier 0, basic information is collected/ evaluated with the aim to initially categorize the material. The overall intention is to decide whether (a) the material is within the scope of the HARMLESS EWS and (b) how to best proceed in Tier 1 (choice of Route A: "exposure first" or Route B: "hazard first"). Three questions ((1)-(3)) were adopted from AMEA,[21] whereas a fourth question related to the material's category was added (Figure 2, Tier 0,

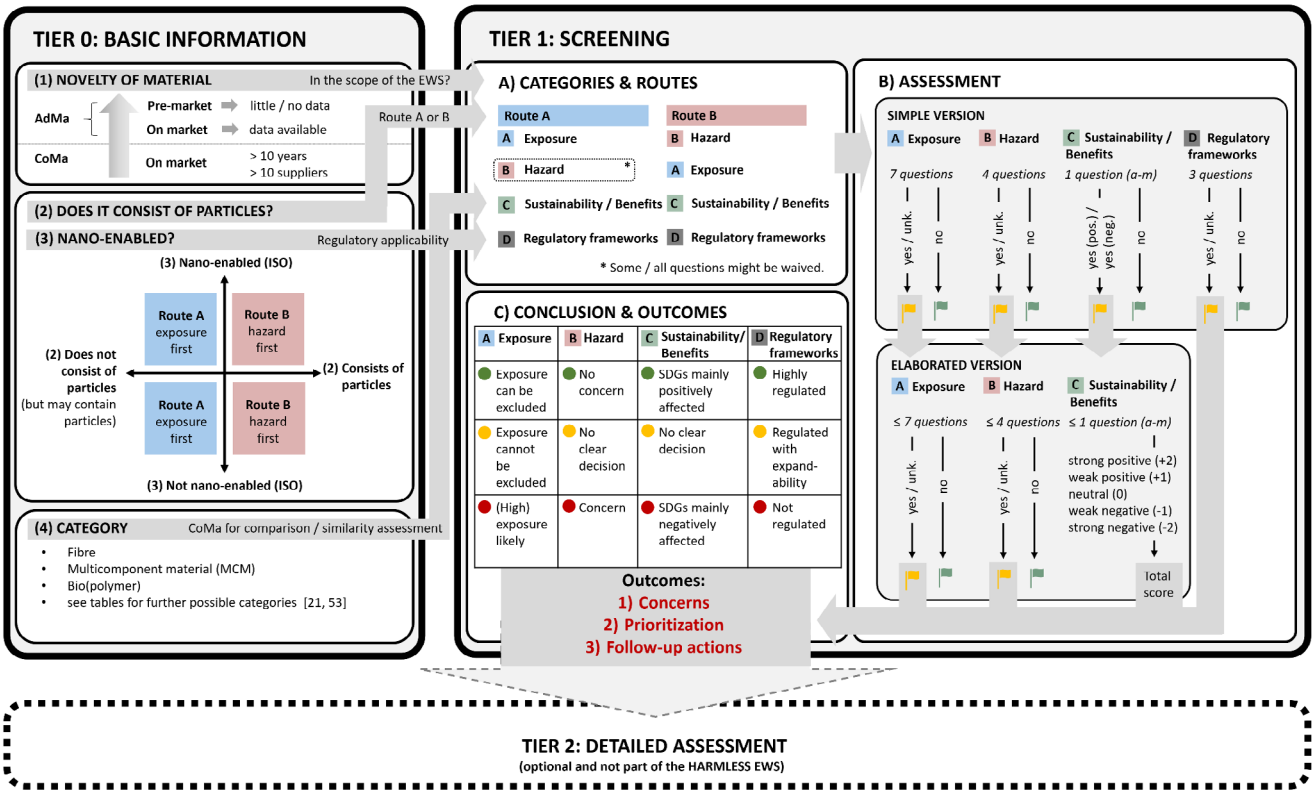

Figure 2. Overview of the HARMLESS EWS and its two tiers. Tier 0 is based on AMEA[21] and asks four questions in order to initially categorize the material. Moreover, the outcomes of Tier 0 define how to proceed in Tier 1. The assessment in Tier 1 starts with a simple version by answering a maximum of 15 questions in four categories (A (Exposure), B (Hazard), C (Sustainability/Benefits), D (Applicability of regulatory frameworks)). Respective arrows show possible answers for each category. Depending on the answer, each question is assigned with a "yellow flag" (representing a warning) or a "green flag". For questions with "yellow flags" in categories A, B and C, a subsequent elaborated assessment is performed by reviewing data (including NAM data) in order to support or refute identified concerns. A conclusion for the material is drawn by assigning a color to each of the four individual categories (red, yellow or green) and combine these to an outcome combination. The outcome combinations (see Figure 3 for details) serve as a prioritization list for ensuing (regulatory) follow-up actions.

question (4)). In Figure 2, the individual impact of each question in Tier 0 to the subsequent Tier 1 is shown by grey arrows.

In step (1), the novelty of the concerning material is categorized. Here, the following distinction is proposed:[21] a material is considered (a) a CoMa if it is on the market for more than a decade and if it can be obtained from several (> 10) suppliers in similar quality in ton scale, (b) AdMa, which have been on the market for a short time (< 10 years) and (c) an AdMa, if it is still under development and not yet commercially available or only recently entered the market and is not yet available from several suppliers or in ton scale. Since the HARMLESS EWS focusses on AdMa, this first aspect of Tier 0 defines whether the material is in the scope of the HARMLESS EWS or not.

In the next step, two questions are asked: (2) Does the material consist of particles? and (3) Is the material nano-enabled? Both aspects are schematically depicted within a 2D coordinate system resulting in four quadrants. Depending on the answer to question (2), the subsequent assessment in Tier 1 starts with the exposure-related questions (Route A) or with the hazard-related ones (Route B). On the one hand, if the AdMa consists of particles, is has to be taken into account, that these particles may be inhaled or taken up via other routes into the body. Consequently, the hazard signals are assessed first in Tier 1 (Route B). On the other hand, for an AdMa not consisting of particles, it is more relevant to assess exposure first in order to determine if particles, critical fibers or other harmful substances can be released (Route A). The distinction between Route A and Route B allows for a streamlined assessment by taking a risk-based prioritization, as supported also for simplified SSbD by recent guidance.[52] To be more precise, if Route A is followed and exposure can be excluded, then most of the hazard-related questions might be waived (Figure 2, Tier 1, A) CATEGORIES & ROUTES, dashed frame). This option is highly beneficial in cases where no or only limited hazard data exist and thus presents a clear advantage over tools that first require hazard data.

The answer to question (3) Is the material nano-enabled? has a direct impact on category D (Applicability of regulatory frameworks) in Tier 1. It defines which regulatory definition could be applied, that is, (a) the revised EU recommendation for NMs for materials that consist of particles or (b) the ISO term "nano-enabled" that also comprises materials with internal nanoporosity or nanostructured surfaces.[21]

In the last step of Tier 0, a category for the AdMa is defined, for example, a fiber or a multicomponent material (MCM) besides others (tables with further possible categories can be found elsewhere).[21,53] This offers several advantages. First, it allows to

identify a conventional material of the same material category, which can then be used for comparison/similarity assessment. This also allows to decide if the assessed AdMa behaves superior with regard to SSbD aspects, where also the functionality for an intended application needs to be addressed. Furthermore, this is of particular interest to answer questions in category C (Sustainability/Benefits) of Tier 1 as it makes most sense to compare materials within a similar context. Finally, the categorization of AdMa is also relevant for selecting appropriate NAMs for experimental testing. It should be kept in mind that most NAMs have been developed/ adapted for NMs only and even though they still might be a reasonable starting point for other AdMa, they still may require further optimization and adaptation.

3.1.2. Tier 1: Screening

The overall intention of Tier 1 is to screen a variety of AdMa aiming to identify those that are critical. Thus, Tier 1 finally results in a prioritization, listing AdMa in descending order of importance with respect to RP. This is based on material-specific concerns. Furthermore, recommendations for possible (regulatory) follow-up actions are also provided as an outcome.

Basically, the assessment in Tier 1 is divided into two versions: (1) a simple version (qualitative screening for all categories A-D) and (2) an elaborated version (screening based on (NAM) data (for categories A and B) or rather based on sustainability-related data (for category C)) (Figure 2). The simple version aims at identifying initial concerns or data gaps, which are further assessed – and either supported or refuted – within the subsequent elaborated version. The idea behind a two-step assessment is to lay the focus on those descriptors that raise any concern. Especially, if only little data is available for the assessed material, it is not possible to deeply analyze each particular question. Therefore, it makes sense to perform a quick initial evaluation of the material first (simple version), that possibly allows for the exclusion of some questions. If initial concerns are raised, they are further evaluated during the subsequent elaborated version.

Simple Version: The simple version of the assessment serves as an initial qualitative screening to get a first overview on the material's properties and to possibly identify concerns or data gaps. For category D (Applicability of regulatory frameworks), only the simple version exists, since it does not seem reasonable to underline the corresponding questions with additional data. On the contrary, for categories A (Exposure), B (Hazard) and C (Sustainability/Benefits), two options exist, depending on the amount of appropriate data (e.g., NAM data and information on sustainability-related benefits or drawbacks). On the one hand, if such data is not available, the assessment starts with the simple version. On the other hand, for materials with available data, the simple version for one or more questions may be skipped, and the elaborated version is accessed, directly. Thus, the simple version of Tier 1 serves as a bridge, which is built for cases, where adequate data is not available.

Starting with the simple version, the user is quickly guided through a maximum of 15 questions, which are listed in **Table 4** for categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks) and Table S2, Supporting Information for category C (Sustainability/Benefits). The user is asked to answer these questions without an in-depth search for data. Most questions in categories A, B and D can be answered with "yes", "no" or "unknown (unk.)" (exception: Q13). For sustainability-related questions (category C), a 3-point scale is applied with three possible answers: "no, no impact", "yes, a positive impact" and "yes, a negative impact". In Figure 2 (Tier 1; B) Assessment) a summary of all possible answers is given with the respective arrows for each category. Each answer directly corresponds to a "yellow flag" (representing a "warning signal") or a "green flag" (no concern), which is assigned to each question. For categories A, B and C, those questions that are assigned with a "yellow flag" are further considered in the subsequent elaborated version. The aim of the elaborated version is to support or refute the initially identified concerns by means of more detailed considerations.

Warning Signals: The goal of the 15 questions is to reveal warning signals of the material in question. They are divided into four categories ((A) Exposure, (B) Hazard, (C) Sustainability/Benefits and (D) Applicability of regulatory frameworks). In Table 4, the questions for categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks) are listed and supplemented by explanations and endpoints for the elaborated version. For category C (Sustainability/Benefits), the respective questions 12a-m are listed in Dekkers et al.[20] and Table S2, Supporting Information. To realize a broad application spectrum of the HARMLESS EWS, the questions cover three perspectives, that is, (1) consumer, (2) occupational and (3) environmental safety. The questions for (A), (B), and (C) are aligned with the WASP tool in the DSS which identifies early warning flags and provides design and SSbD assessment advice to innovators in the Ideation and Business Case Phase.[20] The alignment between both systems underscores the importance that regulators and innovators think about the same questions in the context of RP and SSbD, respectively. This in turn clarifies that an extensive exchange between both parties is crucial in order to push forward safe and sustainable innovations ("trusted environment"). Despite the synergies between the HARMLESS EWS and the WASP, both tools fundamentally differ in their scope, that is, the intention of the EWS is to support regulators, whereas the WASP focusses on the innovator's perspective. The difference between the two systems is most obvious by category D (Applicability of regulatory frameworks), which is only included in the HARMLESS EWS. The final evaluation process is also different for both tools yielding different outcomes and recommendations from each system.

Depending on the outcome in Tier 0 the user either starts with the exposure-related warning signals (Route A) or the hazard-related ones (Route B). In cases following Route A, some or even all hazard-related questions might be waived, if exposure can be excluded. In order to support the user, explanations are also listed in Table 4 for each question. However, especially at very early stages of an innovation process relevant information to answer these questions might be missing or difficult to find. As further support, a separate guidance document is currently in preparation.

The contents of the four categories A, B, C and D are briefly summarized in the following:

A Exposure (7 questions): Exposure-related questions cover human and environmental aspects (Table 4; B). Moreover, the three perspectives (occupational, consumer, environment) are

Table 4. Overview of the warning signals for categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks). The respective questions for category C (Sustainability/Benefits) are listed in Table S2, Supporting Information. Endpoints for the elaborated version of Tier 1 are printed in bold type, supplemented by guidance (recommended methods, tools or approaches). "GRACIOUS" refers to guidance given by the GRACIOUS project.[54]

A EXPOSURE		
Possible answers: yes, no, unknown		
Question	Explanation	Endpoints for elaborated version and recommended methods/tools/approaches
1. Does the material itself or its production, manufacturing, use or end of life generate inhalable dust or aerosols?	Is it possible that the material or product becomes airborne or that it releases airborne dust or aerosols (particles or liquid droplets in air or another gas, such as produced by pressurized spray cans for paint or deodorant) or volatile compounds (e.g., solvents from paints or glues)?	GRACIOUS: **Particle size** (what they are), **Surface area** (what they are), **Composition** (what they are), **Dissolution** (inhalation IATA),[33] **Reactivity** (inhalation IATA)[33] OTHER (exposure): **Dustiness, Respirable fraction**
2. Is exposure to consumers or the general population expected?	Is it expected that the material will: (a) be used in a consumer product (e.g., sunscreen), or (b) be released in such a way that consumers or the general population will be exposed (e.g., pesticide residues on food products)?	GRACIOUS: **Particle size** (what they are), **Surface area** (what they are), **Composition** (what they are), **Dissolution** (inhalation IATA),[33] **Reactivity** (inhalation IATA),[33] **Hydrophobicity** (dermal IATA)[34] OTHER (exposure): **Dustiness, Respirable fraction, Expected amount (or %) of material to which the consumers could be exposed** ***GUIDANCE***: *Possible tools/approaches*: *a) NanoRiskCat*[40] *for consumer exposure (part of LICARA nanoSCAN)*[43,44] *b) Precautionary Matrix*[41] *for general population exposure (part of LICARA nanoSCAN)*[43,44] *c) Three step release assessment strategy for AdMa (Wohlleben* et al. *(reviewed recently))*[55]
3. Is occupational exposure expected via inhalation?	Note that if protective equipment is used, occupational exposure will be reduced, but should still be considered likely. Consider potential occupational exposure during the following life cycle stages: • Production: Exposure during synthesis of the material • Manufacturing: Exposure during manufacturing of a nano-enabled product • Use (professional): Exposure during professional use of the product • End-of-Life: Exposure of workers in waste treatment or recycling.	For each stage: **Dustiness, Respirable fraction, Type of release, Composition of released material, Mass percentage of release** ***GUIDANCE***: *Possible tools/approaches*: *a) Stoffenmanager Nano*[42] *for occupational exposure (part of LICARA nanoSCAN)*[43,44] *b) Three step release assessment strategy for AdMa (Wohlleben* et al. *(reviewed recently))*[55]
4. Is there more than one form of expected human exposure (i.e., different chemical composition and/or particle size)?	The form of the expected human exposure may be different depending on when and how the exposure takes place (e.g., the release of SiO_2 powder during manufacturing of paint is different from the dust generated during sanding of a painted surface). Humans can be exposed to the pristine material or to a transformed form of the material. The exposure can be to the material embedded in a matrix or formulation or to free particles. Especially differences in chemical composition and particle size may lead to differences in human health risks.	For each form: GRACIOUS: **Particle size** (what they are), **Surface area** (what they are), **Composition** (what they are), **Dissolution** (inhalation IATA,[33] oral IATA[35] and dermal IATA),[34] **Reactivity** (inhalation IATA,[33] oral IATA[35] and dermal IATA),[34] **Hydrophobicity** (dermal IATA)[34] OTHER (exposure): **Dustiness** (inhalation), **Respirable fraction** (inhalation) ***GUIDANCE***: *Possible approach*: *Three step release assessment strategy for AdMa (Wohlleben* et al. *(reviewed recently))*[55]

(*Continued*)

Table 4. (Continued)

A EXPOSURE		
Possible answers: yes, no, unknown		
Question	Explanation	Endpoints for elaborated version and recommended methods/tools/approaches
5. Is wide-dispersive use foreseen, based on the sector, product and final application in which the material is intended to be used?	Consider the industrial sector of the product or final application in which your material is intended to be used. Is wide-dispersive use foreseen? For example, if the final application is for specific industrial use only (B2B), it probably does not have a wide-dispersive use. If the final application is a commonly used consumer product (B2C), it probably has a wide-dispersive use. If wide-dispersive use is foreseen, it is an indication that several sectors are affected and thus, several regulatory legislations may apply (see Q13).	Consider adding additional descriptors such as in vitro toxicity testing or higher tiered NAMs of GRACIOUS IATAs: **Genotoxicity, Inflammation, in vitro reactivity, Cytotoxicity, Membrane integrity** etc. GRACIOUS aquatic systems IATA[56]: **Dissolution, Dispersion stability, Chemical transformation** If available: **Toxicity to algae, daphnia, fish cell lines**
6. Could you enter the tonnage assumed to calculate the Expected Commercial Value (ECV)? If you don't know, is large scale production of your material expected?	In decision-making in the development of new products, the Expected Commercial Value (ECV) often plays an important role. The tonnage used to calculate the ECV gives an indication of how widespread the new product is expected to be used, which greatly influences the magnitude of impact the new product may have on the various SSbD aspects. Also, the higher the tonnage level, the larger the expected investment needed for regulatory testing. *Here "high tonnage" is understood as > 1 t (in line with REACH tonnage bands).*	Consider adding additional descriptors such as in vitro toxicity testing or higher tiered NAMs of GRACIOUS IATAs: **Genotoxicity, Inflammation, in vitro reactivity, Cytotoxicity, Membrane integrity** etc. GRACIOUS aquatic systems IATA[56]: **Dissolution, Dispersion stability, Chemical transformation** If available: **Toxicity to algae, daphnia, fish cell lines**
7. Is there (direct) exposure for any environmental compartment expected?	Consider the industrial sector of the product or final application in which your material is intended to be used. For many industrial sectors, the general hotspots of environmental exposure are known.	GRACIOUS aquatic systems IATA[56]: **Dissolution, Dispersion stability, Chemical transformation** ***GUIDANCE***: *Possible approaches*: *a) OECD GD 29 – Guidance Document on Transformation/Dissolution of Metals and Metal Compounds in Aqueous Media combined with detailed testing guidance in Di Battista* et al.[57] *b) Three step release assessment strategy for AdMa (Wohlleben* et al. *(reviewed recently))*[55]
B HAZARD		
Possible answers: yes, no, unknown		
Question	**Explanation**	**Endpoints for elaborated version and recommended methods/tools/approaches**
8a. Is the material expected to be persistent?	Materials with low solubility in physiologically relevant media are expected to be persistent in the human body and/or environment. They are expected to have a low clearance rate from the body which may lead to accumulation within the body and possibly also within the food chain (bioaccumulation). Persistency greatly depends on chemical composition (e.g., carbonous materials are generally very persistent).	**Dissolution** (in relevant media) (GRACIOUS inhalation IATA,[33] oral IATA,[35] dermal IATA,[34] aquatic systems IATA)[56]; see Table S1, Supporting Information for tiered testing strategy including NAMs)
8b. (If answer to 8a is yes:) **Is the material foreseen to contain or consist of fibers with a critical morphology (rigid, persistent, aspect ratio > 3), especially fibers with a length > 5 µm and diameter < 3 µm?**	If the material contains or consists of biopersistent long, rigid fibers (with a length > 5 µm and a diameter < 3 µm), this may raise a concern for asbestos-like behavior. If it is not possible to assess the precise length, diameter, biopersistence and rigidity this question may be answered with yes if the material contains or consists of fibers that are expected to be biopersistent based on the chemical composition (e.g., carbon-based fibers) and they are not expected to be flexible or short.	**Fiber length and diameter** (GRACIOUS HARN IATA)[36] **Dissolution** (in relevant media) (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs)

(*Continued*)

Table 4. (Continued)

A EXPOSURE		
Possible answers: yes, no, unknown		
Question	Explanation	Endpoints for elaborated version and recommended methods/tools/approaches
9. Is the material expected to show high/enhanced reactivity?	If a material contains metals or metal oxide nanoparticles, it may be reactive due to the tendency of metals to lose electrons and due to the ability of metals and metal oxides to form Reactive Oxygen Species (ROS). The ability of metals and metal oxides to create ROS is, amongst other things, correlated with the band gap energy. Some molecular structures are also expected to have an increased reactivity (e.g., if they contain one or more weak bonds or bonds that have an unequal distribution of electrons between the two atoms, or if the molecular structure of organic compounds creates a resonance, inductive or steric effect).	**Reactivity** ((a) in silico NAMs (e.g., electronegativity), (b) in chemico NAMs (e.g., acellular ROS) or (c) in vitro NAMs (e.g., cellular carbonylation), if available (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs))
10. Is the material a multicomponent material?	Multicomponent materials are materials consisting of two or more chemical components, including composites and co-polymers. If the material is multicomponent, the transformation of the material throughout its life cycle becomes more important and the risks of the potentially newly formed species and their release should be taken into account.	**Dissolution of transformed material (including leaching of metal ions)** (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs) **Reactivity of transformed material** ((a) in silico NAMs (e.g., electronegativity), (b) in chemico NAMs (e.g., acellular ROS) or (c) in vitro NAMs (e.g., cellular carbonylation), if available (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs))
11. Is the material and/or its chemical components expected to be hazardous for the human health or environment? **(if no information, specify chemical components and use Substance Information System (SIS) to check for human and environmental hazard band and/or classification)**	a) First, look for available information indicating if your material is hazardous (e.g., H-phrases on MSDS, (self)classification according to CLP). b) Second, specify the chemical components (including elemental composition) of the material (including coating and surface modification) and use SIS to identify if these chemical components are classified as hazardous (i.e., GHS/CLP classification, specific H-phrases and H-bands). If the material contains chemical components or elements with specific hazardous properties, it can be expected that the material has similar hazardous properties.	**Quantity (w/w %) of hazardous components in the material or of the hazardous material in the final application**. **1) Human hazard** **Initial toxicity screening endpoints** (overview given in NAMS4NANO review on NAMs for NMs):[24] **Genotoxicity** (GRACIOUS genotoxicity IATA[37]; see Table S1, Supporting Information for tiered testing strategy including NAMs) **Inflammation** (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs) **Cytotoxicity/cell viability** (GRACIOUS oral IATA[35]; see Table S1, Supporting Information for tiered testing strategy including NAMs) **Reactivity/oxidative stress** ((a) in silico NAMs (e.g., electronegativity), (b) in chemico NAMs (e.g., oxidative damage) or (c) in vitro NAMs, if available (GRACIOUS inhalation IATA[33]; see Table S1, Supporting Information for tiered testing strategy including NAMs)) **Barrier integrity** **2) Environmental hazard** **Dissolution** **Dispersion stability** (OECD GD 318 for the testing of dissolution and dispersion stability of NMs and the use of the data for further environmental testing and assessment strategies)[58]

(*Continued*)

Table 4. (Continued)

A EXPOSURE		
Possible answers: yes, no, unknown		
Question	Explanation	Endpoints for elaborated version and recommended methods/tools/approaches
D APPLICABILITY OF REGULATORY FRAMEWORKS		
Possible answers: yes, no, unknown (exception: Q13: selection of proposals)		
Question	**Explanation**	
13. For which application is the material used and consequently, which legislation(s) need(s) to be considered?	Several legislations may apply, especially, if a wide-dispersive use of the material is foreseen (see Q5).	
	REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (EC) 1907/2006[10]
	CLP	Classification, Labelling and Packaging of Chemicals (EC) 1272/2008[59]
	Occupational	OSH directives: 2019/1831,[60] 2017/164/EU,[61] 2009/161/EU,[62] 2006/15/EC,[63] 2000/39/EC[64] – indicative occupational exposure limit values 2009/148/EC[65] – exposure to asbestos at work 2004/37/EC[66] – carcinogens, mutagens or reprotoxic substances at work 98/24/EC[67] – risks related to chemical agents at work 91/322/EEC[68] – indicative limit values
	Biocides	Biocidal Products Ordinance (EC) 528/2012[69]
	Plant protection products	(EC) 1107/2009[70]
	Cosmetics	EU Cosmetics Regulation (EC) 1223/2009[71]
	Novel Foods	Novel Foods Regulation (EU) 2015/2283[72]
	Food contact materials	(EC) 1935/2004,[73] (EU) 10/2011[74]
	Food	Food Additives Ordinance (EC) 1333/2008[75]
	Feed additives	(EC) 1334/2003[76]
	Medicinal or veterinary products	Medical Device Regulation (EU) 2017/745[77]
	Veterinary medicinal products	Veterinary Medicinal Products Regulation (EU) 2019/6[78]
	...	
14. Is the legislation applicable for this category of AdMa or for a similar/ comparable AdMa?	In the scope of current chemical legislation(s)? Definition (ISO ongoing work AdMa) Are there guidance documents available? (OECD Guidelines for the Testing of Chemicals, Section 4, OECD Guidance Documents...)	
15. Are there methods available/adopted?	Are there methods/SOPs available which could be adopted? Consider the AMEA recommendation to provide at least controls for absence of assay interference when testing AdMa with existing methods/SOPs[21].	

taken into account with a focus on the inhalation route of exposure and a potential wide-dispersive use.

B Hazard (4 questions): The warning signals for the hazard aspects cover very basic aspects concerning the morphology, composition and the physico-chemical behavior of the material (Table 4; B; questions 8–10). In addition, it is asked for hazardous properties (human and environment) of the material (Table 4; B; question 11).

C Sustainability/Benefits (1 question (a-m)): In category C, the user is asked to focus on aspects related to sustainability/benefits (Table S2, Supporting Information). The related warning signals are based on the 17 SDGs, which aim at worldwide sustainable development on economic, social and ecological levels.[50,51] For the HARMLESS EWS, the 13 most relevant targets originating from eight SDGs are separately asked for. Furthermore, potential synergies and trade-offs between affected SDGs are taken into account by the applied 3-point and 5-point scales in the simple and elaborated versions.

For RP, positive impacts (benefits) are of higher interest than negative impacts (drawbacks). This is due to the fact that benefits may lead to a faster entrance to the market and thus, a faster regulatory follow-up action may become necessary.

D Applicability of Regulatory Frameworks (3 questions): Finally, the HARMLESS EWS comprises a category related to regulatory aspects, which is essential in order to support RP. First, it is asked for which application the material is used and which

legislation needs to be considered. Second, the user is asked to check if the legislation is applicable for this category of AdMa or for a similar/ comparable AdMa. Finally, it is screened if methods are available or could be adopted for the material of interest.

Conclusion After Simple Version: During the simple version of the assessment a maximum of 15 questions in four categories are answered. The actual number of questions might be lower if Route A is followed and questions are waived (see Figure 2 and section 3.1.1. for details). For a conclusion after the simple version, each of the questions is assigned with a "yellow flag" or a "green flag". Depending on the category (A-D), this is realized in two ways. First, for categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks) questions that were either answered with "yes" or "unknown" are assigned with a "yellow flag". Questions that were answered with "no" are assigned with a "green flag". Second, for category C (Sustainability/Benefits) a 3-point scale is applied during the simple version of the assessment. Questions answered with "no, no impact" are assigned with a "green flag" whereas questions answered with either "yes, a positive impact" or "yes, a negative impact" are assigned with a "yellow flag".

For category D (Applicability of regulatory frameworks), the assessment stops after the simple version (Figure 2B) Assessment). Within the subsequent elaborated version, only those questions from categories A (Exposure), B (Hazard) or C (Sustainability/Benefits) are considered that either raised any concern or that could not be answered during the simple version and thus, were assigned with a "yellow flag".

The objective of the subsequent elaborated version is to either support or refute concerns raised in categories A (Exposure) and B (Hazard) by integrating (NAM) data. In the case of category C (Sustainability/Benefits), the elaborated version represents a further graduated system that allows to distinguish between strong and weak impacts on the different sustainability aspects. The detailed procedure is explained in the subsequent section "Elaborated version".

Elaborated Version: As explained before, within the elaborated version of the assessment in the HARMLESS EWS, only those questions from categories A (Exposure), B (Hazard) and C (Sustainability/Benefits) are considered that were assigned with a "yellow flag" during the simple version (Figure 2). However, in general, one can also directly jump to the elaborated version for data-rich materials. This is currently abeing worked out by the HARMLESS consortium and will be described in more detail in a guidance document at the end of the project. Here, the elaborated version aims at drawing final conclusions on flagged aspects. In analogy to the simple version, which is aligned with the WASP tool for innovators, the elaborated version is aligned with the ASDI tool for innovators.[20]

In case of categories A (Exposure) and B (Hazard), for each question, associated endpoints are listed in Table 4 (right column). These are used to obtain the information needed to answer the related question. Each endpoint in turn can be approached by several methods and tools. Within the HARMLESS EWS, the focus for the methods is on NAMs since data based on in vivo tests are not available for most AdMa in early stages. The recommended NAMs in Table 4 are mainly based on NAM selection for the HARMLESS case studies (Table 3), findings from previous projects (especially GRACIOUS)[33,35,37] and extended by additional NAMs that have been identified within the NAMs4NANO review on NAMs for NMs.[24] It is important to mention that the suggested NAMs have been primarily developed for NMs. Thus, the transferability to an AdMa under investigation needs to be examined carefully by the user. Furthermore, it must be emphasized that the methods listed in Table 4 are only suggestions and that the final choice of an appropriate method is up to the user.

For category C (Sustainability/Benefits), the elaborated version represents a possibility to evaluate positive and negative impacts on different SDG targets in a more graduated way compared to the simple version. The applied 5-point scale is based on the Portfolio Sustainability Assessment v2.0 published by the World Business Council for Sustainable Development (WBCSD)[79] and explained in detail in Dekkers et al.[20] Herein, the impact on a certain SDG target can be rated in the following way: strong positive impact (+2), weak positive impact (+1), neutral (0), weak negative impact (−1) or strong negative impact (−2). The assigned values in brackets are summed up to obtain a total score which is used for the final outcome of category C (Sustainability/Benefits) (see also Figure 2; Tier 1; B) Assessment).

Conclusions and Outcomes: In order to support RP, the outcomes of the HARMLESS EWS provide answers to the following three questions: (1) Which concerns are connected to the material? (2) What is the priority for a (regulatory) follow-up action? and (3) What kind of (regulatory) follow-up actions are recommended?

For RP, it would be disadvantageous if outcomes for different categories could outweigh each other. For instance, a scoring system that counterbalances benefits and hazards would possibly overlook the need for (regulatory) follow-up actions. Thus, an approach was developed, that considers all four categories equally and independently. First, the colors green, yellow and red, representing severity/priority, are assigned to each of the four categories. For categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks) the resulting colors are directly connected to the numbers of "yellow flags" and "green flags" allocated during the simple and elaborated versions of the assessment (**Figure 3**). The exact criteria for color assignments as well as recommendations for each color in each category are depicted in Figure 3.

For categories A (Exposure), B (Hazard) and D (Applicability of regulatory frameworks), the priority for (regulatory) follow-up actions increase from "green" over "yellow" to "red" (see colored arrows in Figure 3). On the contrary, for category C (Sustainability/Benefits) the priority for RP increases in two directions. On the one hand, materials that are highly sustainable ("green" in Figure 3) might lead to faster market-entries and thus may require intensified research and dialogues with industry and other stakeholders. On the other hand, such dialogues are also recommended for materials with low sustainability – however, in this case with the aim to find other materials using SSbD principles.

By comparing the combinations of colors for different materials, a prioritization list is obtained. In this way, the materials with the highest concern(s) can finally be filtered out from the increasing amount of AdMa and (regulatory) follow-up actions may be chosen, for example, a detailed assessment (e.g., Early4AdMa Tier 2).

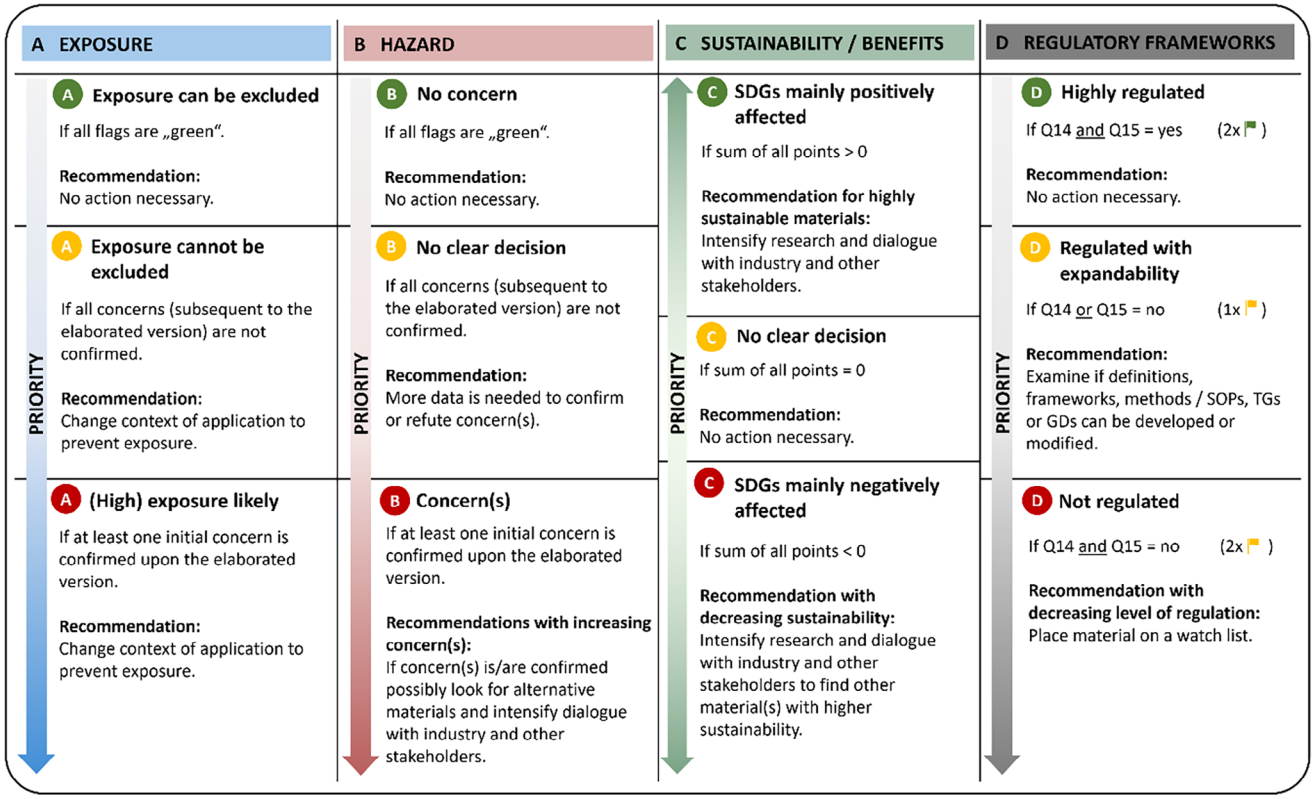

Figure 3. Outcomes of different categories, prioritization and recommended (regulatory) follow-up actions. For each of the four categories (A (Exposure), B (Hazard), C (Sustainability/Benefits), D (Applicability of regulatory frameworks)) a color according to a traffic light system (green, yellow, red) is assigned, which is connected to a recommendation for (regulatory) follow-up actions. The criteria for color assignment are listed and directly correlate with the numbers of "yellow flags" and "green flags" obtained from the simple and elaborated versions of the assessment. Increasing priorities for (regulatory) follow-up actions are indicated by colored arrows.

Following the final outcome, it is recommended to start an expert dialogue to discuss concerns, clarify uncertainties and plan possible follow-up actions.

3.2. Exemplification by Case Studies

3.2.1. The Aerogel Case Study

As a first application, the HARMLESS EWS was tested on a silica based inorganic aerogel mat which is already on the market (Technology Readiness Level (TRL) 9). The material is used for façade thermal insulation and enables to reduce the thickness of insulating layers by a factor 3 in comparison to CoMa, due to their reduced thermal conductivity (twofold lower than benchmark).

The AdMa is basically composed of a silica-aerogel with nano porosity inside a glass fiber mat. A detailed description of the SSbD development including exposure scenarios and hazard assessment was recently published by Di Battista et al.[80] The key feature of the AdMa is that the nano pores are small enough that air molecules inside the pores can barely move and thus, cannot transfer heat (Knudsen effect).

In **Figure** 4A, the results of Tier 0 and Tier 1 for the aerogel case study are summarized (see also Excel sheet SIa for detailed explanations). During Tier 0, the aerogel mats are categorized as AdMa, that do not consist of particles but are nano-enabled by ISO definition. For comparison, conventional stone wools are taken into account. Since the material does not consist of particles, Tier 1 starts with the exposure-related questions (Q1 – Q7; Route A).

The results of Tier 1 are explained in the following for each of the four categories A-D:

A (Exposure) (Q1 – Q7): During Tier 1, several exposure-related concerns are raised: (1) significant occupational exposure is expected during installation due to released dust (Q1, Q3); (2), different types of handling (sanding compared to sawing) can result in different forms of human exposure (Q4); (3) wide-dispersive use is foreseen (Q5); (4) high tonnages (50 t) are expected (Q6) and (5) environmental exposure is unknown for life-cycle stages other than the use period of the material (Q7). Most of the exposure-related concerns raised during the simple version could be supported during the elaborated version of Tier 1 resulting in five definite "yellow flags". The only exception is the unknown environmental exposure which could neither be supported nor refuted during the elaborated version.

As exposure is likely for the reasons above, none of the questions in subsequent category B (Hazard) could be waived.

B (Hazard) (Q8 – Q11): For the hazard-related aspects, two concerns are raised: (1) the respective aerogels are multicomponent materials (Q10) and (2) two of the main components (SiO_2

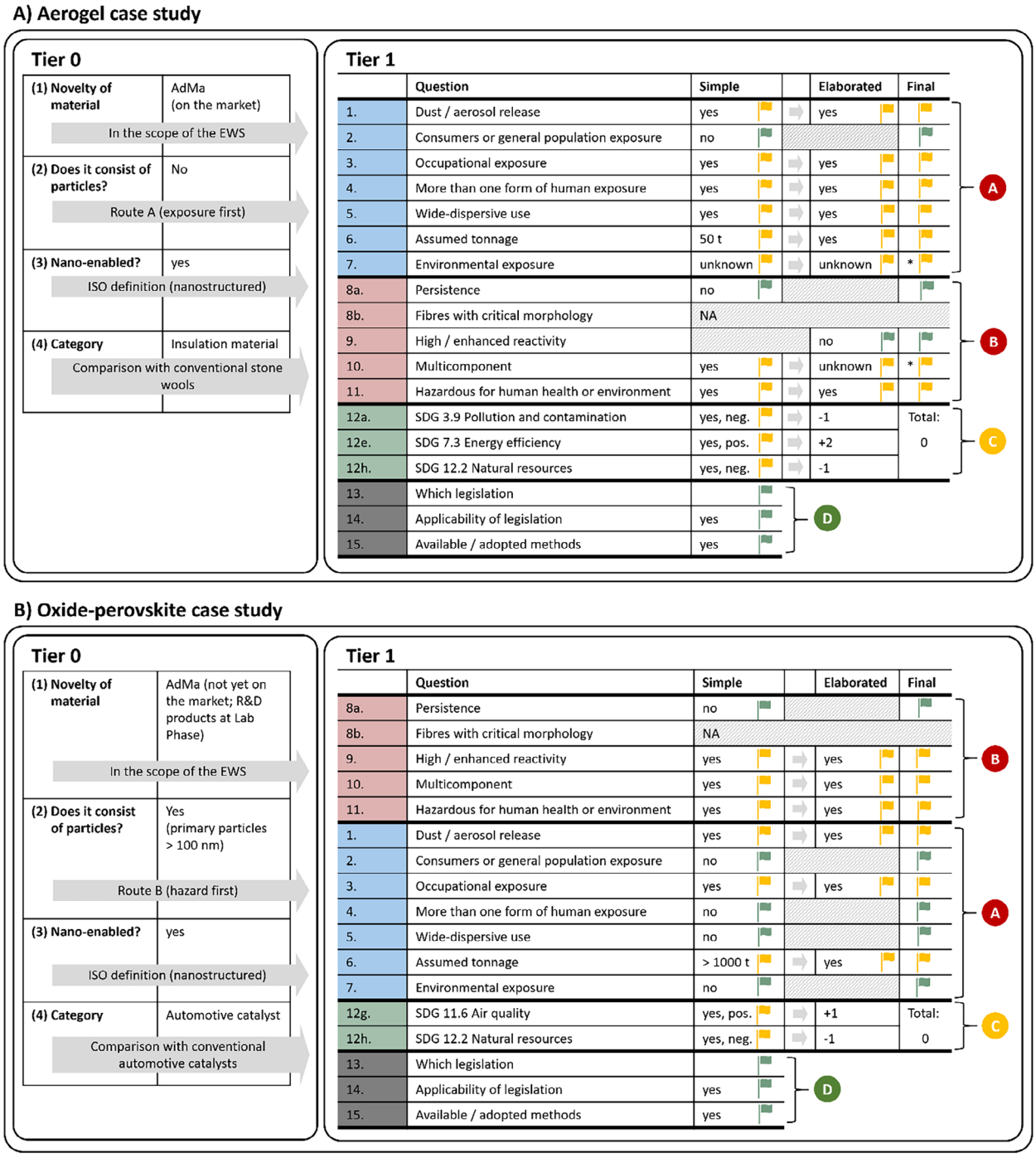

Figure 4. Results for the A) aerogel case study and the B) oxide-perovskite case study. Results for Tier 0 include the impacts on the ensuing Tier 1 (grey arrows). For Tier 1 the results for the simple and elaborated versions are summarized by "green flags" and "yellow flags". Initial concerns that could neither be confirmed nor refuted during the elaborated version are highlighted by *. The final outcomes for categories A-D are obtained according to the traffic light system depicted in Figure 3.

and silanamine) may cause damage to organs through prolonged or repeated exposure (according to the classifications provided by companies to ECHA in REACH registrations for SiO_2 or rather to the harmonized classification and labelling for silanamine) (Q11). If the material is multicomponent, questions regarding the dissolution and the reactivity of the transformed material follow in the elaborated version of Tier 1. However, for the transformation of the aerogels, no data is available and thus, this concern could neither be supported nor refuted. On the contrary, the concern about hazardous substances (Q11) was supported in

the elaborated version since the amounts of SiO_2 (25–40%) and silanamine (5–20%) within the aerogels are known.

C (Sustainability/Benefits) (Q12a-m): Out of the 13 SDG targets listed in Table S2, Supporting Information for category C (Sustainability/Benefits), three have been identified to be either negatively (SDG 3.9 "Pollution and contamination" and SDG 12.2 "Natural resources") or positively affected (SDG 7.3 "Energy efficiency") during the simple version.

According to the 5-point scale in the elaborated version, the impact on SDG 7.3 has been rated as being strong (+2) since the aerogel mats show high insulation capacities.

The negative impacts on SDG 3.9 and 12.2 have been scored both as weak (−1), resulting in a total score of "0".

D (Applicability of regulatory frameworks) (Q13 – Q15): Finally, from the regulatory point of view, the aerogels are already highly regulated (Q13 – Q15) with occupational/OSH directives that are applicable to mitigate occupational exposure. Additionally, the GRACIOUS framework has been adopted for aerogels[81] showing that nanosafety concepts can be applied to concerns of AdMa that contain or release nanostructures.

3.2.2. The Oxide-Perovskite Case Study

Perovskite-type oxides have attracted attention as promising three-way automotive catalysts due to their enhanced oxygen storage capacity and their ability to remove CO, hydrocarbons and NOx from the car exhaust.[82] Basically, oxide-perovskites can be present in versatile stoichiometries and crystal structures. In the present case study, six oxide-perovskites of structure type $AB_{0.8}O_3^{-\delta}$ (A: La; B: Co and Ni, doped with Pt and Pd) have been investigated. Although they comprise nano-structured materials, they are not considered as NMs since their primary particle sizes exceed 100 nm (in accordance with the REACH definition).[10] Currently, the oxide-perovskites are R&D products at the Lab Phase of the stage-gate model and thus, not on the market.

In Figure 4B, the results of Tier 0 and Tier 1 for the oxide-perovskite case study are summarized (see also Excel sheet SIb for detailed explanations). According to Tier 0, oxide-perovskites are categorized as AdMa, that consist of particles which are nano-enabled by ISO definition. Additionally, conventional automotive catalysts are identified as the appropriate CoMa used for comparison.

In the case of the oxide-perovskites, Tier 1 of the HARMLESS EWS starts with the hazard-related questions (Q8a – Q11; Route B) since the material consists of particles before being manufactured into catalysts.

The results of Tier 1 are explained in the following for each of the four categories A-D:

B (Hazard) (Q8 – Q11): During Tier 1 several warning signals were raised: (1) the material is highly reactive due to its catalytic activity (Q9); (2) oxide-perovskites are multicomponent materials (Q10) and (3) some of the components are hazardous metals, that is, (a) nickel, which is classified to be skin sensitizing and suspected to be carcinogenic and (b) cobalt, which is classified to be carcinogenic, toxic to reproduction, skin sensitizing, respiratory sensitizing and suspected to be mutagenic (Q11). All three yellow flags were supported during the elaborated version of Tier 1 by using appropriate data sources (see Excel sheet SIb for detailed information).

A (Exposure) (Q1 – Q7): For exposure three yellow flags were raised: (1) the oxide-perovskites are in powder form and thus may form respirable dust (Q1); (2) this leads to likely occupational exposure during production of the oxide-perovskites and manufacturing of the heterogeneous catalyst (Q3) and (3) the assumed tonnage is > 1000 t (Q6). All initial warning signals could be supported during the elaborated version.

C (Sustainability/Benefits) (Q12a-m): Two SDG targets were found to be either negatively (SDG 12.2 "Natural resources") or positively affected (11.6 "Air quality"). During the elaborated version these aspects have been scored by "−1" and "+1", respectively, resulting in a total score of "0".

D (Applicability of Regulatory Frameworks) (Q13 – Q15): For the oxide-perovskites existing occupational/OSH directives are applicable (Q13, Q14) and the ONORM EN 17199-4:2019 gives guidance for the dustiness of bulk materials containing nanoobjects or particles in the sub-micrometer range (Q15). Thus, the oxide-perovskites are already highly regulated.

3.2.3. Comparison of the HARMLESS EWS Applied to Both Case Studies

The HARMLESS EWS was tested using data from the aerogel and the oxide-perovskite case studies.

In Figure 4, the results of both cases are briefly summarized. Additionally, exhaustive tables with comments and considered data on each question can be found in the SI (Excel sheets SIa and SIb).

Basically, both materials are in the scope of the HARMLESS EWS, as they are AdMa by definition (aerogels are already on the market and oxide-perovskites are R&D products at Lab Phase). Moreover, both are nano-enabled materials and can be compared to CoMa used for the same applications. However, since oxide-perovskites consist of particles and aerogels do not, different routes were followed in Tier 1.

The final outcomes for both materials are obtained according to Figure 3 and depicted in Figure 4 on the right. Both materials are assigned with A (Exposure) = red, B (Hazard) = red, C (Sustainability/Benefits) = yellow and D (Applicability of regulatory frameworks) = green.

Consequently, both materials get the same priority from the perspective of RP. Recommendations for possible (regulatory) follow-up actions in each category are directly connected to the final outcomes (see Figure 3).

During Tier 1, two types of concerns have been identified: (1) supported concerns and (2) concerns that could neither be supported nor refuted during the elaborated version (highlighted with * in Figure 4). The latter ones have only been identified for the aerogels (Q7 and Q11), whereas for the oxide-perovskites all initial concerns have been confirmed. As depicted in Figure 1, a detailed assessment (not part of the HARMLESS EWS) might optionally follow as Tier 2 (e.g., Early4AdMa Tier 2) – especially for those concerns that could not be confirmed by running Tier 1 of the HARMLESS EWS.

4. Conclusion

AdMa play a critical and enabling role in the development of energy- and resource-efficient technologies that will decide on the success of EU and worldwide sustainability goals. Hence, they are already applied in many different sectors such as renewable energy, energy storage, building and construction, high-performance computing, advanced therapies and superior consumer products. Hence, AdMa comprise very heterogenous material classes with many different types of AdMa that share little or no commonalities – overall they are mainly characterized by their specific material properties and a superior performance (compared to CoMa). From a regulator's point of view, it will be impossible to assess each single material type in this highly innovative field of AdMa where new materials are evolving fast. Therefore, efficient screening and prioritization approaches are needed that allow for a proper identification of those AdMa that raise high concerns based on well-founded scientific principles.

This is precisely the unique selling point of the herein presented HARMLESS EWS, which is a simple and practicable tool on its own that has been established by combining existing knowledge in a novel and superior manner. It is organised in two tiers (Tier 0: Basic information; Tier 1: Screening), each underpinned with specific methods/ tools and facilitated by a dedicated online tool.[29] Tier 1 consists of two versions. The simple version relies on a maximum of 15 questions in four different categories (A (Exposure), B (Hazard), C (Sustainability/Benefits) and D (Applicability of regulatory frameworks)). The elaborated version of Tier 1 is suggesting NAM-based testing, where the NAMs as applied in the HARMLESS case studies may be a reasonable starting point also for other AdMa. As a final outcome, the user is provided with (i) material-related concerns, (ii) prioritized AdMa (for a more elaborated assessment) and (iii) (initial) recommendations for (regulatory) follow-up actions. The most important improvement is a proper "filter function", which truly enables a prioritization list of AdMa to identify those that need highest regard from a regulatory point of view. This is the most valuable advancement compared to other existing tools. The currently available version of the OECD Early4AdMa puts the major focus on Tier 2, which is a very detailed assessment.[14] However, the authors already emphasize that in future versions of Early4AdMa, Tier 1, which is the screening phase, may need to be further improved.[14] In the current Early4AdMa version the screening tier (Tier 1) is considered to be optional.[14] However, we are convinced that within a "functional" warning system the screening tier needs to be mandatory as only then a proper filter function can be ensured. This will significantly reduce the number of AdMa that actually require an elaborated assessment and/or (regulatory) follow-up actions.

Therefore, the HARMLESS EWS is presented here as a novel, easy and functional stand-alone tool that facilitates the screening phase and that moreover can be integrated easily into the existing Early4AdMa. Although the HARMLESS EWS already provides the user with material-related concerns, a more detailed assessment, for example, by applying Tier 2 of the Early4AdMa or other elaborated tools for assessment, can be beneficial for such cases to substantiate the concerns.

Importantly, the HARMLESS EWS has already been successfully tested using data from two HARMLESS case studies (aerogels and oxide-perovskites). In both cases exposure- and hazard-related concerns were identified that require subsequent regulatory follow-up actions. Additionally, for categories C (Sustainability/Benefits) and D (Applicability of regulatory frameworks) no follow-up actions are necessary neither for the aerogels nor for the oxide-perovskites due to a final score of "0". To finally prioritize one of the materials it seems to be reasonable to carry out an expert dialogue.

Since the development of the HARMLESS EWS was closely linked to the WASP tool of the SSbD-DSS,[20] which share an online tool for innovators and regulators, it furthermore supports an efficient communication between regulators and innovators. Such a dialogue is an essential element of the trusted environment concept of the OECD SSIA and is therefore essential for RP and SSbD to work together.[12]

Further advancements of the HARMLESS EWS will focus on a better integration of NAM data. Currently, during the elaborated version, the user is encouraged to use available NAM data to support or refute initial concerns. However, the weighing of evidence following the weight of evidence concept is not specified in detail. This results in uncertainty on how contradictory NAM data for one endpoint shall be treated. Moreover, the consortium currently also works on the integration of more complex NAM data such as data received from high-throughput screening (HTS) and/ or multi-omics approaches. A scoring system for different NAMs is also still under development. Finally, the integration of CB tools is foreseen in a more simplistic manner to merge hazard- and exposure-related issues into a combined safety-related evaluation, which appears reasonable following a risk-based approach. In addition, we also aim at an appropriate visualization of the final outcome (e.g., via heat maps), which will be of high importance to provide the users with a clear and easy understandable presentation of the results.

Overall, we believe that the herein presented HARMLESS EWS is an important step forward and will be a major contribution to tackle the complex challenge of proper risk governance of AdMa. Therefore, the next step is to present these results to the OECD and to lay the basis for a wider scientific discussion.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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advanced materials, early warning system, regulatory preparedness, risk assessment, safe-and sustainable-by-design, sustainability

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