Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2023)34

Unclassified

English - Or. English

7 September 2023

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Advanced Materials Assessment Schemes HARMLESS - OECD Working Party on Manufactured Nanomaterials (WPMN) Workshop Report

Series on the Safety of Manufactured Nanomaterials
No. 107

JT03524808

OECD Environment, Health and Safety Publications
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Paris 2023

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Acknowledgments

1. This workshop report has been prepared by: Blanca Suarez-Merino (TEMAS Solutions GmbH); Nathan Bossa (TEMAS Solutions GmbH); Susan Dekkers (TNO); Anders Baun (DTU); Otmar Schmid (HMGU); Wendel Wohlleben (BASF SE); Andrea Haase (BfR) and Agnes Oomen (RIVM). It summarises the discussions held during the joint HARMLESS-OECD WPMN Advanced Materials Workshop held on the 15th of November 2022.

2. The report was then submitted to the OECD's WPMN Steering Group on Advanced Materials for inputs and subsequently submitted to the Working Party on Manufactured Nanomaterials.

3. HARMLESS provided information on Fibre-aerogel-mats for façade insulation, which served as a case study to compare difference advanced materials assessment schemes. This joint event allowed the exchange of views between HARMLESS experts and those participating at the OECD Working Party on Manufactured Nanomaterials, which was crucial for further refining the OECD pre-regulatory tool for Advanced Materials, Early4Adma [see document ENV/CBC/NANO(2023)13].

The HARMLESS project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 953183

Abstract

4. Advanced Materials could be understood as those purposely designed to have 1) new or enhanced properties, and/or 2) targeted or enhanced structural features with the objective to achieve specific or improved functional performance[1]. As it is the case with nanomaterials, advanced materials have unique properties, which make them attractive, but may also represent a risk to workers, consumers, and the environment. It is therefore of utmost importance to understand if those advanced characteristics challenge traditional risk assessment methods, so that neither safety nor innovation are compromised, and sustainability is weighed in[2]. To move forward in the assessment of currently available assessment schemes and evaluate their applicability as foresight tools to anticipate issues with the safety and sustainability of AdMa, the consortium of the EU-funded HARMLESS project (https://www.harmless-project.eu/) organised an expert's workshop in collaboration with the OECD Steering Group (SG) on AdMa. Within this workshop four recently developed schemes (InnoMat.Life, Arvidsson et al., Early4AdMa, and Kennedy et al.) were reviewed and three of them were tested using data from a selected HARMLESS case study on Aerogels, an already commercially available façade insulation material with advanced properties over conventional thermal insulation materials. During the workshop, experts had the chance to evaluate the different schemes with real data provided by HARMLESS and discuss the pros and cons of each scheme (including data demands, data gaps to fulfil the scheme, ease of use, etc). Results are summarised in this report with the aim to evaluate current foresight schemes regarding their suitability for AdMa and contribute building new and fine-tuning relevant existing schemes to address safety and sustainability issues in AdMa development within the context of product development and regulatory preparedness in a timely manner.

[1] OECD Advanced Materials: Working Description Series on the Safety of Manufactured Nanomaterials No. 104

[2] Fetting, C. (2020). “The European Green Deal”, ESDN Report, December 2020, ESDN Office, Vienna

Introduction

5. There are several examples for progress in materials and advanced materials (AdMa) leading to innovation and speeding up the transformation of conceptual, novel ideas into actual products (e.g., lighter solutions for the transport sector, dent resistant car panels, extra flexibility in sports equipment). AdMa will play a crucial role for reaching several of the UN sustainable development goals and in the implementation of the EU GREEN DEAL goals providing sustainable solutions to current problems regarding energy storage and use, water remediation, and many more.

6. AdMa combine different building blocks, which may be composed of nano or microstructures resulting in complex single or multicomponent materials, which lead to novel and more complex hazard evaluation issues. For example, what triggers toxicity may not accurately be evaluated based on the toxicity driven by the chemistry of their individual components, but on the unique combination of all but in addition may require a consideration of the structure and thereby goes beyond a mere mixture effect. AdMa with structural components having a dimension of less than 100 nm may have unique properties which will require appropriate testing methods due to the nano size (e.g., by considering the new or revised OECD TGs), and hence prediction of toxicities based on micro-size or even bulk materials, following grouping and read-across strategies, cannot be applied without substantiation. This would lead to a situation where testing is performed on a case-by-case basis.

7. Based on the above and considering the high speed at which innovations in AdMa are being developed, the case-by-case evaluation regarding safety and sustainability will not be easily manageable from a cost and time perspective. Moreover, once AdMa is added into a process to produce novel AdMa-enabled products, their characteristics may change, posing novel challenges during production (emissions), use (consumers) and end of life (recycling, incineration, landfilling, etc). Thus, the transformed material should also be considered throughout the entire life cycle of an AdMa containing product. One further layer of complexity regarding safety and sustainability assessment of AdMa is the uncertainty on the suitability of test guidelines for these types of complex materials and lack of available data.

8. Safe and Sustainable by Design (SSbD) strategies have been promoted at the EU level[3] to anticipate issues regarding safety and sustainability at early innovation stages, so actions can be taken in good time and materials/products/processes will be developed in a timely, successful, and cost-efficient manner. Several initiatives (including the EU project HARMLESS[4]) are working toward the development of strategies to address SSbD of AdMa covering the whole innovation process. Likewise, the OECD WPMN has been actively focusing the discussion to materials with potential regulatory gaps (OECD WPMN SG AdMa), as well as developing schemes, which help identifying knowledge gaps and possible concerns in (regulatory) safety and sustainability assessments. Likewise, HARMLESS aims to develop and validate a SSbD framework and Decision Support System (DSS) for real world case studies from industry. HARMLESS organised an expert workshop in collaboration with the OECD WPMN SG of AdMa and

[3] Caldeira et al. Safe and sustainable by design chemicals and materials - Framework for the definition of criteria and evaluation procedure for chemicals and materials, EUR 31100 EN, Publications Office of the European Union, Luxembourg, 2022, ISBN 978-92-76-53280-4, doi:10.2760/404991, JRC128591.

[4] https://www.harmless-project.eu/

Foresight Scheme developers, using one of the HARMLESS AdMa case studies as a test item with the aim to evaluate the applicability of current foresight schemes to anticipate issues with the safety and sustainability of AdMa. Four foresight schemes were selected (InnoMat.Life, Arvidsson *et al.*, Early4AdMa, and Kennedy *et al.*) based on accessibility (open source), relevance (regulatory development/ regulatory perspective), scope (matching the OECD AdMa description, currently focusing on nano as a starting point), and available expertise (partners from HARMLESS and OECD SG). It should be noted that not all these tools have been designed as foresight tools, nevertheless they might be useful for this purpose. The Advanced Material Manifesto 2030 was discussed prior to examining the selected schemes in the group, because it represents a roadmap of innovations that can be expected in the coming decade. In total four schemes were selected and presented (see description below), but the aerogel case study was applied only to three (InnoMat.Life, Arvidsson *et al.* and Early4AdMa).

Materials 2030 Roadmap

9. Materials 2030 Roadmap[5]: was developed from the MATERIALS 2030 MANIFESTO: the initiative was triggered to highlight that for Europe to remain competitive and meet citizens' needs for safer and more sustainable advanced materials, Europe needs "a systemic approach to develop the next generation solution-oriented advanced materials which will offer faster, scalable, and efficient responses to the challenges and thus turn them into opportunities for Europe's society, economy, and environment today and in the future". Such a systemic approach will drive cross-sectoral industrial innovation by supporting new applications across all industry sectors. Through selected materials innovation markets sharing system-critical material applications (such as lightweight, carbon capture or advanced surfaces), the Materials 2030 Manifesto exemplifies how advanced materials share much more cross-cutting commonalities across all the different markets they serve than apparent at first sight, notably to address four major materials' challenges: circularity, zero pollution, climate contribution, traceability. The Materials 2030 Manifesto hence is motivated by the lack of sustainability of conventional materials and sets out a vision for "a strong European Materials ecosystem driving the green and digital transition as well as a sustainable inclusive European society through a systemic collaboration of upstream developers, downstream users and citizens and all stakeholders in between" but does not systematically discuss potential negative impacts of AdMa on safety.

InnoMat.Life

10. InnoMat.Life[6]: proposes to categorise materials following the DAMADEI-MatSEEC categories (Design and Materials as a Driver of European Innovation- Materials Science and Engineering Expert Committee), each splitting into three dimensions[7]: • Does the material consist of particles (of any aspect ratio: the original scheme does not differentiate spheroidal, elongated or platelet shape categories. This would be criteria of the ensuing risk screening)? • Is the material nano-enabled? • Are the manufacturing processes or materials considered as "advanced"? (Using the OECD AdMa description, e.g. exceptional properties, specific functionalities and relative novelty against conventional material). It was shown that by this categorization some advanced materials are nano-enabled, but still no nanomaterials by the REACH

[5] MATERIALS 2030 MANIFESTO: Systemic Approach of Advanced Materials for Prosperity – A 2030 Perspective; https://ec.europa.eu/info/sites/default/files/research_and_innovation/research_by_area/documents/advanced-materials-2030-manifesto.pdf Draft, June 2022

[6] http://www.innomatlife.de/index_EN.html

[7] DAMADEI. 2013. Design and Advanced Materials As a Driver of European Innovation.

definition, e.g., the case study of the workshop (aerogels-fibre-mats), whereas some nanomaterials are AdMa, e.g., displays using quantum dots.

Arvidsson *et al.*

11. Arvidsson *et al.*[8]: presents an environmental risk screening method based on two proxy measures: aquatic ecotoxicity and global annual production volumes. In addition to considering current production volumes, it also considers potential future production volumes.

Early4AdMa

12. Early4AdMa[9]: aims to identify knowledge gaps and possible concerns about safety and sustainability aspects of AdMa[10]. 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[11] and the European Chemical Strategy for Sustainability[12]. The system is based on a 2-Tier approach, with the first Tier focusing on screening of novel materials to identify initial issues that may then trigger a more detailed evaluation in the second Tier, considering issues on safety (human health and environment), sustainability as well as regulatory coverage of the evaluated materials.

Kennedy *et al.*

13. Kennedy *et al.*[13]: represents a practitioner-driven definition for AdMa and a practitioner-validated framework for categorizing advanced materials into conceptual categories based on material characteristics and on the feedback from multiple workshops and interviews with practitioners. The definition and categorization framework developed represents a first step in determining if, and when, there is a need for specific ESOH (Environmental, Safety, and Occupational Health) and regulatory screening for an AdMa as well as the type and extent of risk-related information that should be collected or generated for AdMa and AdMa-enabled technologies.

[8] Arvidsson et al. Prospective environmental risk screening of seven advanced materials based on production volumes and aquatic ecotoxicity (2022) NanoImpact, Volume 25, 100941, ISSN 1748-0132, https://doi.org/10.1016/j.nantod.2020.100941

[9] Early4AdMa brochure, https://www.rivm.nl/documenten/Early4AdMa-brochure

[10] Peijnenburg et al. (2021), Identification of emerging safety and sustainability issues of advanced materials: Proposal for a systematic approach. NanoImpact. 23: 100342 https://doi.org/10.1016/j.impact.2021.100342

[11] EC (2019), Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee and the Committee of the Regions - The European Green Deal. Brussels, Belgium: Commission of the European Communities (EC). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52019DC0640

[12] EC (2020), Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee and the Committee of the Regions - Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. Brussels, Belgium: Commission of the European Communities (EC). https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf

[13] Kennedy et all. A Definition and Categorization System for Advanced Materials: The Foundation for Risk-Informed Environmental Health and Safety Testing. Risk Analysis (2019), Vol. 39, No. 8, http://dx.doi.org/10.1111/risa.13304

Methodology

14. HARMLESS organised an expert workshop in collaboration with the OECD WPMN SG of AdMa and Foresight Scheme developers, using one of the HARMLESS AdMa case studies as a test item with the aim to evaluate the applicability of current foresight schemes to anticipate issues regarding the safety and sustainability of AdMa. Four foresight schemes were selected based on accessibility (open source), relevance (regulatory development/ regulatory perspective), scope (matching the OECD AdMa description, currently focusing on nano as a starting point), and available expertise (partners from HARMLESS and OECD SG), namely a) InnoMat.Life, b) Arvidsson *et al.* c) Early4AdMa and d) Kennedy *et al.*, and. These schemes were presented and three of them were selected for detailed evaluation by HARMLESS project partners (Kennedy *et al.* was integrated only selectively). The data requirements for each of the schemes were carefully assessed and collected as much as it was feasibly possible due to time constraints for the aerogels (one of the HARMLESS case studies).

15. Information was collected from the literature (publications and market reports) and through dedicated experiments performed by HARMLESS partners (ecotoxicity in *Daphnia magna* and freshwater algae – *R. subcapitata*). The different Tier levels for each scheme as well as data needs were transformed into excel sheets for ease of data implementation and better visualisation of results, since the selected schemes did not have user-friendly interfaces.

16. A preparatory meeting was held with HARMLESS project partners and key representatives from the OECD SG of AdMa, who had either played a role in foresight scheme development or were deeply involved in safety and sustainability considerations of AdMa. The workshop itself was held online on 15 November 2022 with experts from the OECD (foresight framework developers, regulators) as well as key participants from the EU projects SUNSHINE and DIAGONAL, NMBP16 sister projects of HARMLESS that are also engaged in developing SSbD solutions for AdMa and AdMa-enabled products. Participants were provided with pre-read material to supporting information on the selected schemes, those included a tutorial on the use of the Arvidsson tool for the selected aerogel case study, and the following documents; Kennedy et al. Risk Analysis, Vol. 39, No. 8, 2019, BMBF-Projekt InnoMat.Life EXCERPT from Deliverable 1.7 (chapter 4.2: Categorisation of Advanced Materials), a brochure about Early4AdMa entitled “Towards Safe and Sustainable Advanced (Nano)materials: A proposal for an early awareness and action system for advanced materials (Early4AdMa)”, the peer-reviewed paper presenting the Arvidsson et al. scheme (Arvidsson et al. NanoImpact 25 (2022) 100393), tutorial excel sheets summarizing how Early4AdMa, InnoMat.Life and Kennedy et al. can be applied to the aerogel case study. Upon signing up for the workshop a questionnaire had to be filled out by all participants to evaluate the degree of pre-workshop knowledge on each of the schemes among participants. During the workshop, attendants were divided into two break out groups. Break out group 1 dealt with the: a) InnoMat.Life and b) Early4AdMa schemes (this group was briefly introduced to the c) Kennedy et al. scheme too without considering aerogel data), and a second, break out group covered the d) Arvidsson et al. scheme and the b) Early4AdMa scheme. For the purpose of this workshop, HARMLESS had asked to focus the assessment on a single application (façade insulation), because only then all schemes could be compared. This restriction would also match the industrial need to make decisions about further development of a certain AdMa for a certain market need.

17. The lead authors of each of the four schemes a)-c) participated in the respective sessions as experts. Since Early4AdMa is more complex than any of the other schemes it was decided that both groups

will go through this particular scheme. Due to time constraints each respective excel sheets weas prefilled with HARMLESS produced data or data retrieved from the literature, so attendants could directly visualise the demands per scheme in the workshop breakout groups.

18. Feedback regarding pros and cons per scheme from attendants during the breakout sessions was collected by pre-assigned note-takers or by attendants (in an online document). At a final plenary session, the moderator of each breakout session presented an overview of the feedback and discussion points from both sessions.

Results

19. A total of 52 experts joined the workshop, which included large industry (7%), NGOs (2%), policy makers (15%), regulators (18%), scientific community (49%), SMEs (7%) and others (2%) which did not indicate their background. Prior to the workshop, stakeholders were requested to provide their knowledge level on the different schemes. As can be seen in Figure 1, participants were most familiar with the Materials 2030 Manifesto/Roadmap and the Early4AdMa scheme (ca. 50% had significant prior knowledge), while ca. 80% of the participants had very little experience with the other schemes. After a brief introduction on the scope and format of this workshop, the two parallel breakout sessions started with tutorials on the different schemes using the HARMLESS case study as an example followed by a discussion guided by two main questions:

- What is the greatest asset of the scheme (what are the pros)?
- How could the scheme be improved (what are the cons)?

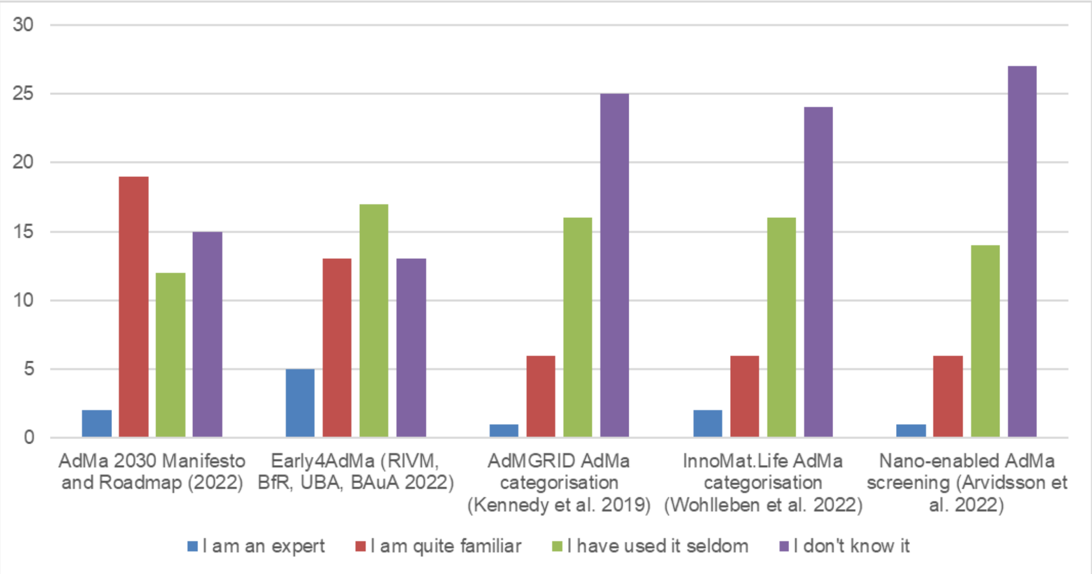

Figure 1: Prior knowledge of the workshop attendants with respect to the four different schemes and the Advanced Materials Manifesto, addressed in this workshop. The Y axes represents number of participants whereas the X axis represents the degree of knowledge of participants per scheme as indicated by the coloured legend.

Case study description

20. The case study is an already marketed (TRL 9) Fibre-aerogel-mat for façade thermal insulation that enables to reduce the thickness of insulating layers by a factor 3 in comparison to conventional materials. The material is one of many layers of the façade and is used whenever higher performance of insulation (i.e., even lower thermal conductivity than conventional insulation) is needed, e.g., due to constraints of space. The material is a silica-aerogel synthesized inside a glass fibre mat consisting of a dry fiber blanket impregnated with a solution of silica, catalyst and dopant following a sol-gel process. The resulting glass fibers are aged and undergo a supercritical heat drying process. The silica creates a nano porous feature within the glass fiber materials and the nano porosity is key in the advanced materials property. The aerogel mats are optimized to have as high a porosity as possible with pores that should be so small that the air molecules can barely move. This means that the inherent air cannot transfer heat, a phenomenon named Knudsen effect after the Danish physicist Martin Knudsen. Realistic aerogel panels which are multi-component materials using a glass fiber mat as mechanical support have been studied by SEM microscopy and are shown in Figure 2. The case is actively investigated in HARMLESS, and both original data and literature data were provided in pre-reads.

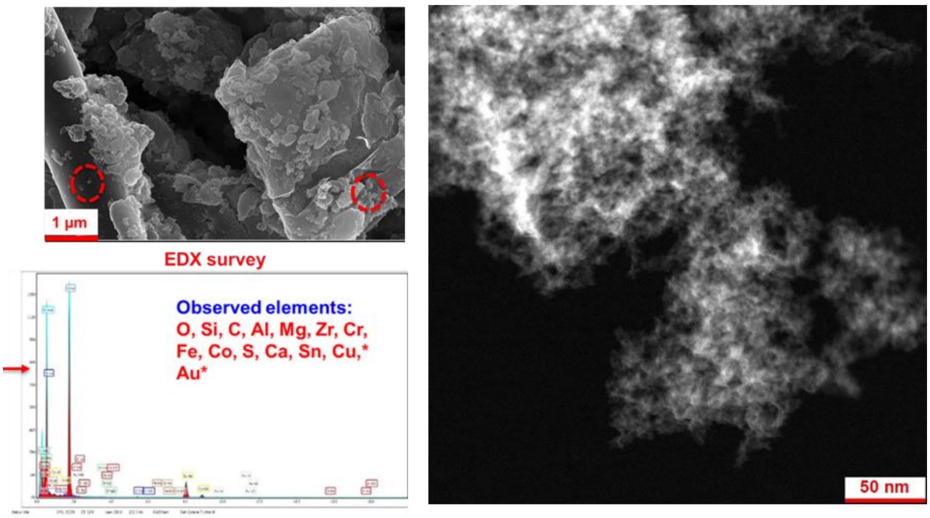

Figure 2: Scanning electron microscopy (SEM) pictures produced from aerogel panels. Left (silica-based aerogel structure) and corresponding elemental (EDX) analysis focusing on the area highlighted by red circles. Right (zoomed-in image of the aerogel structure).

Feedback collected from the InnoMat.Life scheme

21. The InnoMat.Life scheme was presented by Wendel Wohlleben (BASF). The presentation included a tutorial on how to address the corresponding data demands from this scheme using the HARMLESS case study on aerogels (Figure 3). The scheme allowed the categorization of the material as an AdMa highlighting physico-chemical properties of concern (presence of fibres). The scheme is also flexible enough to accommodate relevant definitions regarding nanomaterials depending on the regulatory framework and geographical location of the user. Data to fill this scheme with the required level of detail was readily available from the AdMa developers since it is based on physico-chemical characteristics of the material.

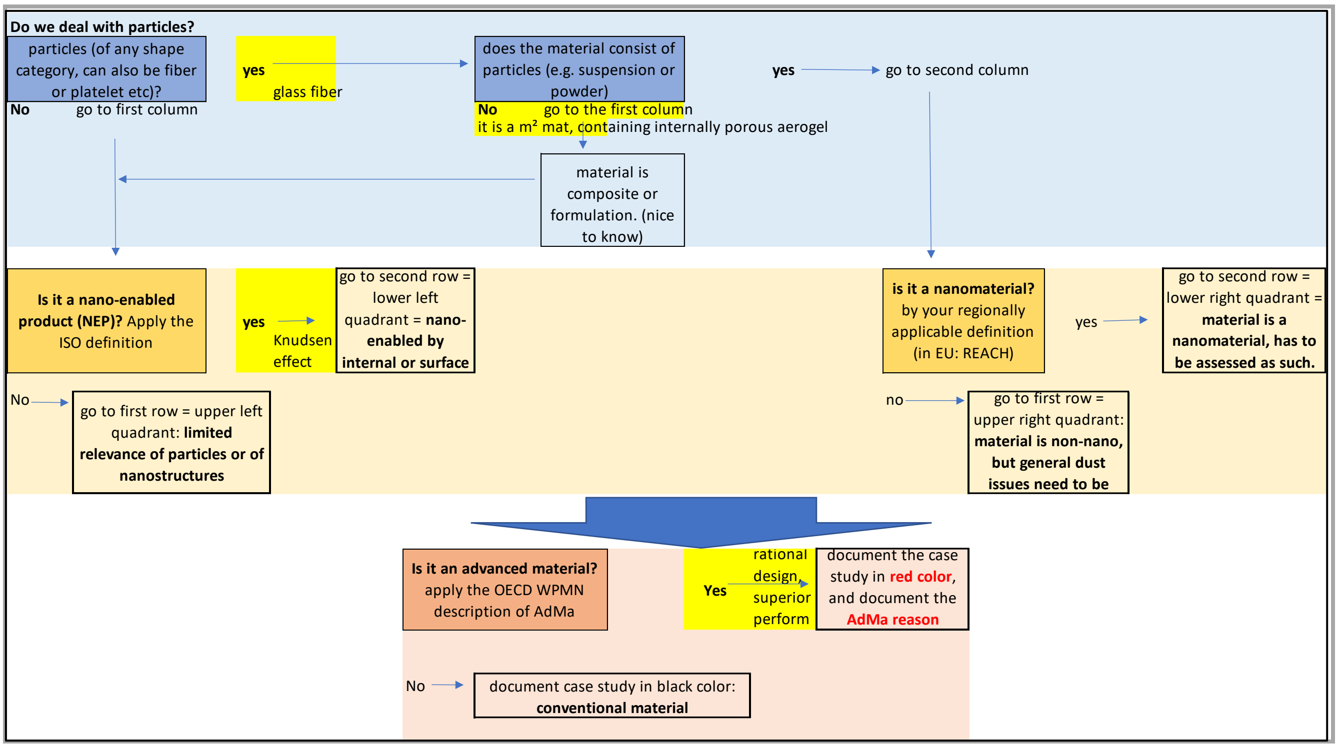

Figure 3: Information needs and flowchart of InnoMat.Life using the HARMLESS case study on aerogels as an example. Input derived from the case study is highlighted in yellow

22. The attendants welcomed the flexibility of the scheme regarding regulatory definitions of nanomaterials and hence it's adaptability to AdMa (not all AdMa can be considered nanomaterials) as well as the early distinction between advanced *vs* conventional materials. The scheme is compatible with the new recommendation of a definition for nanomaterials as published by the European Commission[14], which includes only solid particles now. This definition is still to be implemented by different regulations. Attendants indicated that some materials of concern will be overlooked by the scheme (e.g., asbestos, not being novel), however, it was important to highlight that the purpose of this scheme is to identify unknown and unregulated materials which currently may not be seen on the regulatory radar, for which hazardous conventional materials serve as benchmark. Thus, InnoMat.Life is not a risk screening tool but a tool facilitating screening of novel materials, anticipating use scenarios, also introducing functionality to further elucidate if the material is novel enough to be categorized as "advanced". Attendants missed a module on the evaluation of release, which is also linked to risk assessment and highly relevant to identify harmful materials to humans and environment. The case study was a good example, with some measurable nano porous fragments released during the simulated application onto a façade by professionals. Another attendant highlighted the importance of unconventional use, as it may be the case in third world countries. This extra input may greatly improve the widespread use of the tool and better fulfil the foresight role of these type of schemes, but the uncertainty in guessing unconventional uses was also mentioned. In contrast, the tool developers considered the typical use (intended or not) of the comparable conventional material as a guiding principle to reduce the uncertainty in the assessment of the AdMa. Based on the collected feedback an analysis of the pros and cons of InnoMat.Life was produced as shown in Figure 4.

[14] https://ec.europa.eu/environment/chemicals/nanotech/pdf/C_2022_3689_1_EN_ACT_part1_v6.pdf

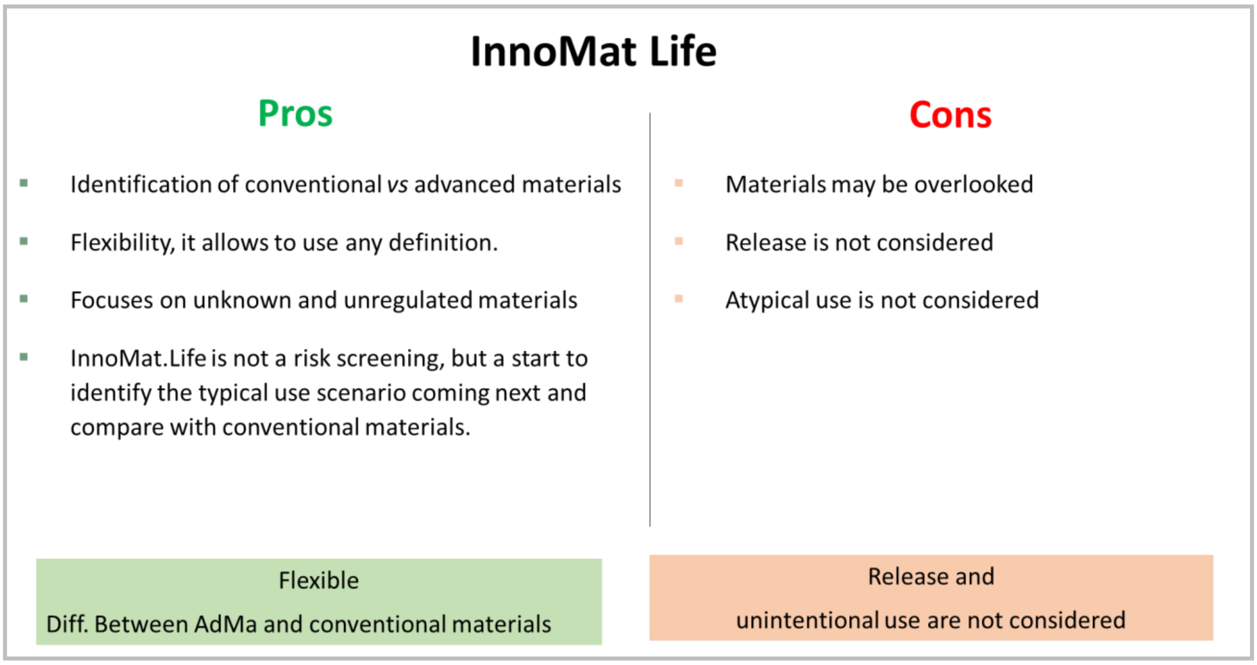

Figure 4: Analysis of the pros and cons of the InnoMat.Life scheme based on the feedback collected at the HARMLESS OECD workshop.

Feedback collected from Arvidsson et al.

23. A tutorial was provided by Anders Baun (DTU) on the use of this scheme with particular attention to the HARMLESS aerogel case study (Figure 5). The attendants acknowledged the simplicity of the tool, as well as its intuitive graphics, its guiding questions and availability of an OECD test guidelines to address data demands.

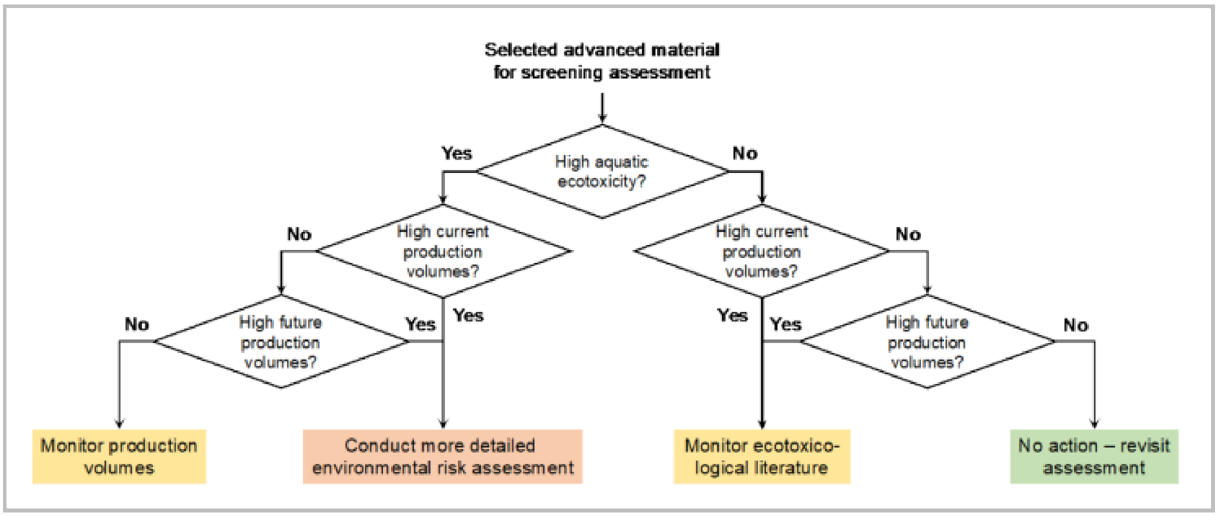

Figure 5: Decision tree for categorizing materials according to recommended actions depending on the outcome of the proxy measure risk screening approach by Arvidsson et al.

24. The ecotoxicity endpoints to be used in this scheme are addressed in a simple way, and it can already be anticipated that data will be available for the selected ecotoxicity tests for existing substances and materials. These results will most often be obtained by OECD test guidelines thus regulatory adequacy of the data is ensured as long as the methods used are applicable to the AdMa investigated. However, it is also anticipated that the required ecotoxicity data and information on the global production volume will not be (readily) available for newly developed AdMa. While estimated production volumes may be available in market reports these are only commercially available and often at a relatively high cost. The ecotoxicity results can of course be generated but will require that a new data set is generated for each new AdMa. Other weak points highlighted by the attendants were that it was difficult to deal with cut off values at the borderline between “high” and “low”, that the scheme does not take into account “no data” situations, and that it only addresses aquatic toxicity. There was also a discussion on uncertainties of the outcome either due to incidental data gaps or the lack of applicability of existing assessment tools (e.g., OECD TGs) for various AdMa. It was mentioned that the scheme may not be useful for situations where materials are poorly wettable and release to the aquatic environment is unlikely. It was also acknowledged that, by developing a scheme on the global scale, regional and local issues may be overlooked. Furthermore, it was not clear how to relate the outcome for a pristine/single material to the final product on the market. As the tool was originally developed for risk screening of existing nanomaterials guiding the question on why and when to act, appear too general to serve directly for SSbD purposes. Participants also provided input on how to improve the scheme including a) introduce a simple similarity assessment for those materials close to a low/high threshold (adding the GRACIOUS IATAs[15] may be an option), b) provide background information on how thresholds are derived, c) since it is a screening scheme, perhaps threshold values could be lowered, d) include dissolution in water as a proxy for cases when aquatic toxicity is unlikely, e) introduce weighting factors to account for toxicity of other species, f) introduce an environmental impact assessment direction, e.g. account for leaching effects which may depend on the used media. Based on the collected feedback a pros and cons analysis was produced as shown in Figure 6.

[15] Stone et al. A Framework for Grouping and Read-Across for nanomaterials – Supporting innovation and risk assessment (2020) nanotoday volume 35 100941

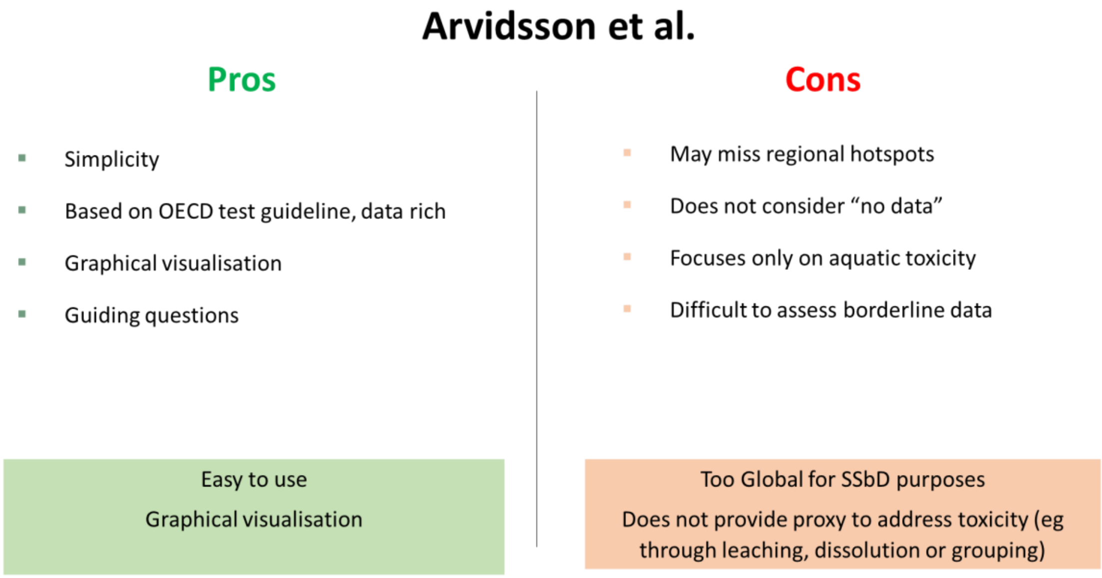

Figure 6 Analysis of the pros and cons of the Arvidsson et al scheme based on the feedback collected at the HARMLESS OECD workshop.

Feedback collected from the Early4AdMa scheme

25. The Early4AdMa scheme was presented by Agnes Oomen (RIVM) and Andrea Haase (BfR), and data needs of the scheme were met by filling out an Early4AdMa excel tool with several tabs to address different Tiers and questions per Tier (Figure 7). The Early4AdMa was the only tool that was designed as a comprehensive early warning scheme. It is a very complex approach, which is why more time was allocated during the workshop to discuss it. Hence, the feedback on this scheme is also more detailed compared to feedback for the others. Due to time constraints the workshop organisers decided to focus on Tier2 question 2 (Safety Assessment Human Health), Tier2 question 3 (Safety Assessment Environment) and Tier2 question 5 (Sustainability), which means that the final assessment and follow up actions covered under Tier2 Steps 6 and 7 could not be addressed. The Early4AdMa scheme takes the users through two different Tiers, the first one serves as screening to assess if there is a need for a more detailed analysis within the Tier2.

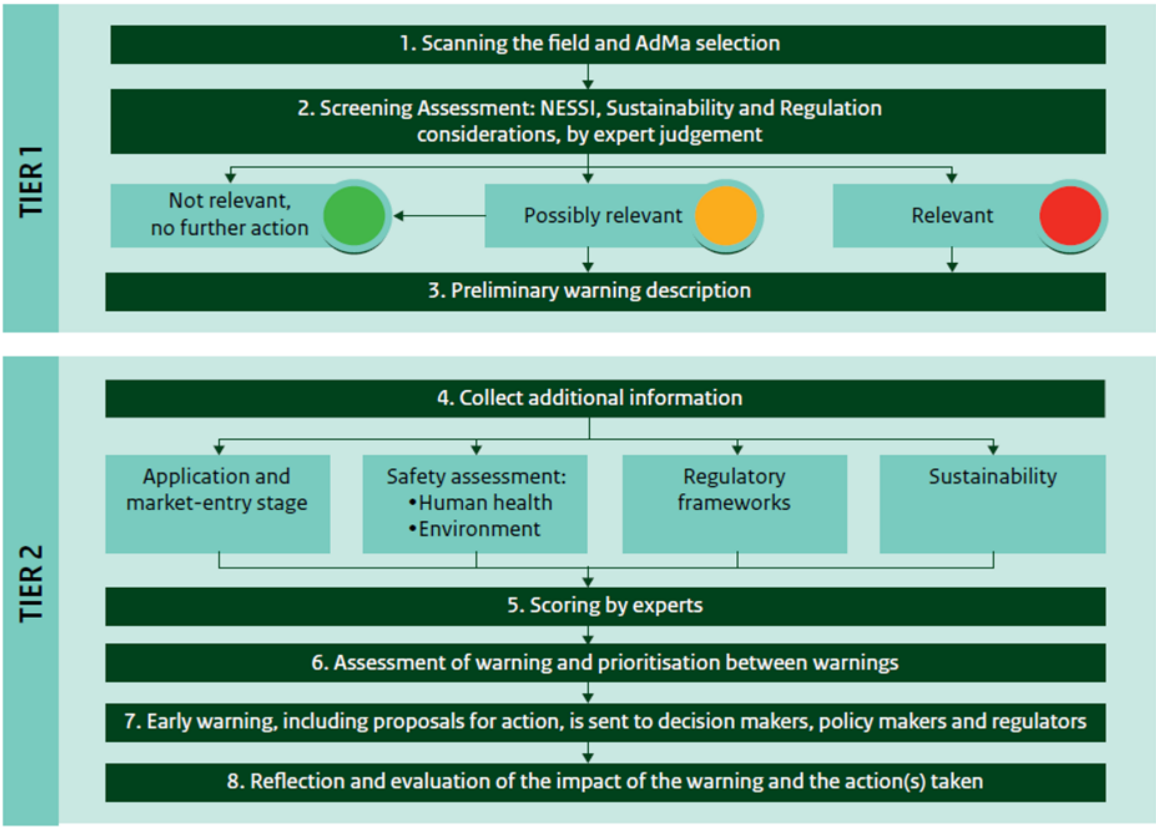

Figure 7: Proposed Early4AdMa system for early detection and priority setting of warnings on safety and sustainability issues of advanced nanomaterials in support of successful innovation

26. Albeit two Tier levels are available it is anticipated that in most cases users will end up in Tier2 due to scarcity of data required for completion of Tier 1. For the same reason, some Tier2 questions were difficult to answer. In addition, it should be noted that the Early4AdMa was developed for advanced nanomaterials, taking into account lessons learnt from nanomaterials and expanding these to cover also AdMa. Thus, for the HARMLESS aerogel case study, which was not a nanomaterial, some questions were difficult to answer, also due to lack of guidance provided by the tool. A few questions also were not being precise enough. The scheme was praised for being flexible enough to accommodate new questions. Based on the collected feedback a pros and cons analysis was produced as shown in Figure 8.

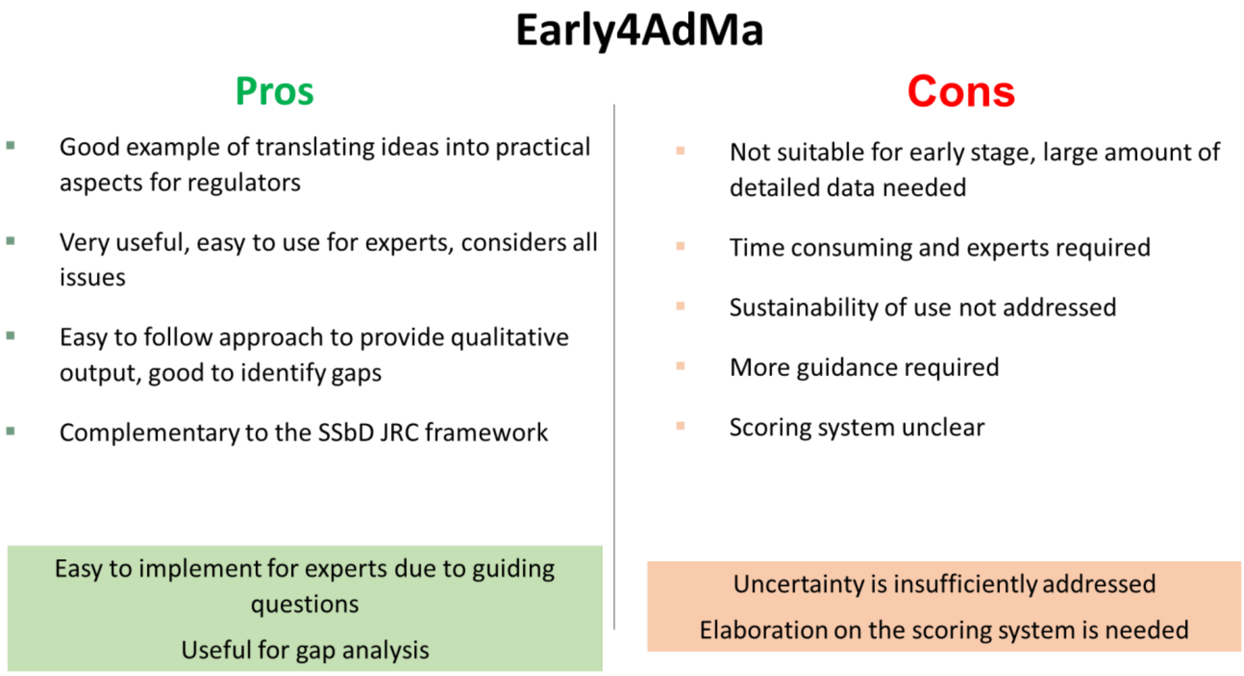

Figure 8: Analysis of the PROs and CONs of the Early4AdMa scheme based on the feedback collected at the HARMLESS OECD workshop.

General remarks regarding the use of Early4AdMa

27. The Early4AdMa was well received by the attendants with a policy/regulatory/scientific background. They praised the scheme due to its guided questions, which represents a good example of translating scientific concepts into practice. Since the scheme proposes a tiered approach with guided questions it was perceived by some participants as easy to use, providing a qualitative output which will help identify knowledge gaps. The Early4AdMa can be used, for example, by regulators as a preparatory exercise for gap finding prior to the implementation of the SSbD framework[3]. Although the case study focused on a single application, the discussion shortly mentioned if questions can even be answered if all potential applications are considered.

28. Issues which should be further improved focus mainly on sustainability and the information demands that are very high (bearing in mind the scheme is developed for novel materials or even during innovation), and hence many questions are likely to be left unanswered, bringing high uncertainty. Because a score ‘1’ is given when the answer to a question is unknown, this uncertainty is not directly visible to the user, but incorporated in the overall score. Also, for the case study of the workshop, which is still relatively novel, but TRL9 with full-scale industrial production, the answer to many questions was unknown. In addition, sustainability benefits during the use phase was not considered, which will bias the results of the overall sustainability scores. This was particularly highlighted by the HARMLESS aerogel test case, which leads to large energy savings during the use phase (on residential houses in the specified case, but also on industrial pipes etc in other cases). It was not possible to include this aspect in the Early4AdMa sustainability assessment. Furthermore, the scoring is also unclear and should be harmonised among different questions. The reasoning behind having a score “1” for an unknown answer should be provided and reconsidered. Sometimes it is difficult to understand if the product or the AdMa itself are to be addressed. In the case of the Aerogel even the release fragments might need consideration. In addition, several participants indicated that there are a lot of questions to address, and many questions are quite information extensive. This raised the question if all questions need to be addressed and if it would be

possible to guide the user to data sources in a practical guidance or data check list. Input is also based on expertise and no uniform rating can be expected by different experts, so a correction for this should also be included, as well to weight results, for example, with the implementation of a multicomponent decision criteria analysis to evaluate the final results. The amount of time required to fulfil this scheme was considered in the range of days, and together with the need of several experts to put the information together, this complicates the implementation of Early4AdMa by industry (in particular SMEs). Tier 1 questions were seen as of little added value, since most AdMa cases will lead to Tier 2 questions. As a conclusion it was indicated that, even though if this scheme was developed for early product development phases, the amount of data directs the scheme to more advanced innovation stages. Sustainability is considered, which was seen as a positive step, however more focus should be brought into the potential benefits the developed materials bring in. Uncertainties should be reconsidered, to make sure that the scheme can provide red flags for data poor cases. Attendants also acknowledged that there is a need to add some guidance into how to fulfil data generation and interpretation with respect to some of the toxicological endpoints, and the various endpoints should be individually addressed.

29. The scheme was developed as an early warning system, yet data demands make it more suitable for later development phases or materials already on the market, as shown by the present workshop on a TRL 9 case study. Users acknowledge difficulty in addressing some of the questions, in particular those regarding sustainability. General guidance, guidelines or references will be welcomed to alleviate this effort. The development of a visualisation tool to evaluate the results will also be welcomed by users. Other suggestions for improvement were to integrate the GRACIOUS IATAs[15] into the scheme to facilitate grouping at a later phase, to use a team of experts when applying the scheme, to include the possibility to enter comments on how experts assign a score, inclusion of social impacts, define the applicability domain and end users of the scheme. The final users of this tool should be identified.

Remarks based on specific Early4AdMa questions raising issues during preparation of pre-reads and discussion in the break-out groups:

- T2 Topic Safety Assessment Human
    - ***Is there an indication of new or enhanced properties (e.g., electric, electromagnetic) related to the nano/multicomponent/advanced character of the material?*** This question is answered based on scores from 0-6, with 1 indicating unknown. Following the HARMLESS case study on aerogels, the answer will be 6 since the Knudsen effect of nano porous structure is linked to the functionality of the material, however a similar question under Tier2 (T2) Topic Safety Assessment Environmental complements the question has an extra sentence “that may have an impact on risk” and here the answer is “0”, bringing inconsistency between Human assessment and environmental assessment.
    - ***Is there an indication of persistency due to low dissolution or degradation in any environmentally or physiologically relevant media?*** To answer this question HARMLESS partners had to perform a dedicated test following ISO/TR19057-2017, so it indicates materials developers did not have this test on their data portfolio, hence it is already interesting to understand the costs that this experiment implies. A reference to what is considered “low” should also be added.
    - ***Is there an indication of another hazard or increased toxicity as compared to the conventional material(s)?*** (Score: yes=6, unknown=1, no=0) Multiple choice one of which indicates “Due to combination of materials. For instance, if the different components enhance each other’s effects or events leading to toxic effects”. This question was difficult to address having in mind the HARMLESS test case on aerogels. An idea would be that the developers of the scheme provide guidance on how to address this question.
    - ***Is there an indication of carcinogenicity/genotoxicity/mutagenicity of the material?*** This question should be followed by a guidance on which methods to use with AdMa, supporting

industry with the implementation of Early4AdMa. Methods must not incur costs or delays that are incompatible with screenings during industrial R&D, if AdMa are to be assessed at "early" development phases.

- ***Is there an indication of toxicity (e.g., immunotoxicity, sensitising properties, lung toxicity, endocrine toxicity) of the material?*** It was difficult to address this question with just one score since data may be available for one endpoint but not for others.
- ***Kinetics.*** A series of questions on kinetics lack a detailed guidance or guidelines on how to address those endpoints and hence were complicated to answer using the HARMLESS aerogel case study and it can be anticipated that industry may fail to address those if no further guidance is provided.

- T2 Topic Safety Assessment Environment:

30. Some questions overlapped with the questions previously addressed in human safety assessment (as was already indicated above).

- ***Is there an indication that fate of the multi-component material differs from that of the individual components of the material?*** Regarding the HARMLESS aerogel case study, the score for this question is yes, since the final fate of the individual materials is different to that of the final, advanced material enabled product. Our answer then to this question provides a negative result, however, since the silica in the final product is embedded into the final matrix, exposure is expected to be lower than when it is freely available and hence, the answer to this question will provide an unnecessary bad score.
- ***Is it likely that the AdMa will be used in high volumes, in many products and/or by the wide population?*** While answering this question we identified an inconsistency with a similar question found under human safety assessment "*Are the AdMa used or likely to be used in many products and/or by a wide population*".

- T2 Topic Sustainability:
  - ***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. This question was hard to address with the HARMLESS aerogel case study and users may need to direct to LCA on similar manufacturing and production processes, transport and uses. See LCA for similar production process, https://doi.org/10.1016/j.supflu.2018.09.003.

- ***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). This question was difficult to address. HARMLESS partners have used the Sol-gel manufacturing process, as an example (patent WO2016193877A1). This is an example of data from related conventional technologies being used due to analogy/similarity.
- ***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. In our opinion this question should be rephrased as "is there a potential to recycle"? The reasoning of the pre-read was not contested, if an emerging technology is "emerging" it is unlikely that there is a recycling system in place.

Conclusions

31. The HARMLESS OECD 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 and 2) to list pros & cons, and 3) to provide suggestions for optimized use of these foresight schemes.

32. The feedback gathered in this workshop allowed for the positioning of each scheme along the innovation process, with schemes such as InnoMat.Life representing an early categorisation scheme and more data demanding schemes such as Early4AdMa are situated further down the innovation process. Low-tier schemes such as Arvidsson *et al.* and InnoMat.Life may be integrated as earlier steps in the more complex Early4AdMa scheme and may guide safety and sustainability assessment by better definition of conventional material and industry segment as point of comparison, as this is especially needed for SSbD decisions in industry.

33. The attendants also highlighted that Early4AdMa may be used by regulators for identification of knowledge gaps and possible concerns prior to the implementation of the European Commission's Safe and Sustainable by Design Framework. Availability of requested data was one main issue expected to be driving the future use of these schemes. For the case study performed here, the required data for InnoMat.Life was more readily available as compared to the Arvidsson and Early4AdMa schemes. In addition, the Early4AdMa scheme lacked guidance and contained some unprecise questions.

34. The level of expertise required per scheme was also assessed. Early4AdMa requires experts from different disciplines (chemists, toxicologists, sustainability experts). During the session it was also acknowledged that a second layer of analysis may be required for Early4AdMa, to take into account correct weighting of results and potential biased answers since several experts were required to fill the scheme.

35. Some missing elements were identified by the attendants, which included unintended use and thus not considered material release from aerogel insulation mats. Moreover, a global scheme such as Arvidsson et al. may fail to detect regional hotspots. Each of the schemes could be modified to remove deficiencies.

36. This workshop represents the first practical evaluation of the applicability of foresight schemes to a high-TRL industrial case study. The results of the workshop can be used to improve each of these schemes, so they can become more useful tools to guide safe and sustainable AdMa development.

Annex 1. Workshop Participants

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	EU
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Annex 2. Agenda

15th November 2022
13:00h - 17:00h CET

OECD
BETTER POLICIES FOR BETTER LIVES

HARMLESS/OECD SG AdMa Workshop

13:00 - 13:15 **Introduction to workshop**
Otmar SCHMID, HARMLESS Coordinator, Helmholtz Zentrum München

13:15 - 13:45 **Materials 2030 Roadmap presentation**
Lars MONTELIUS, Lund University

13:45 - 14:00 **Introduction to case study**
Wendel WOHLLEBEN, BASF SE

14:00 - 15:30 **Parallel break-out sessions for the different assessment concepts**

Breakout 1 „InnoMat.Life & Early4AdMa" moderated by Blanca SUAREZ, TEMAS Solutions GmbH
Breakout 2 „Early4AdMa & Arvidsson" moderated by Susan DEKKERS, TNO

Experts in the breakout rooms:

> InnoMat.Life: Wendel WOHLLEBEN, BASF SE
> Arvidsson et al.: Anders BAUN, DTU
> Early4AdMa: Andrea HAASE, BfR, & Agnes OOMEN, OECD WPMN SG AdMa
> Expert contribution by US-ERDC (CPSC project) is being prepared with Alan KENNEDY and team

15:30 - 16:00 *Coffee Break*

16:00 - 17:00 **Plenary session**
Discussion: Strength & opportunities for integration
Wrap-up
moderated by Blanca SUAREZ, TEMAS Solutions GmbH, and Rapporteurs

HARMLESS project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 953183.