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Advanced Materials: Case Study on NanoCarriers - Workshop Report

Working Party on Manufactured Nanomaterials

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SERIES ON THE SAFETY OF MANUFACTURED NANOMATERIALS

NO. 111

Advanced Materials: Case Study on NanoCarriers - Workshop Report

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

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OECD Environment, Health and Safety Publication

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Foreword

The OECD Working Party on Manufactured Nanomaterials (WPMN) is a subsidiary body of the OECD Chemicals and Biotechnology Committee. This programme concentrates on human health and environmental safety and sustainability implications of manufactured nanomaterials (limited mainly to the chemicals sector), and advanced materials[1] and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. It promotes international co-operation on the human health and environmental safety and sustainability of manufactured nanomaterials and advanced materials involving the safety testing and risk assessment of manufactured nanomaterials.

The WPMN plays an important role in developing the guidelines and frameworks that are necessary for the responsible assessment of manufactured nanomaterials and advanced materials, ensuring that advancements in material innovation are accompanied by a thorough understanding of their potential impact and/ or benefits on health and the environment.

This document is published under the responsibility of the Chemicals and Biotechnology Committee of the OECD.

Kindly note the cancelation & replacement done on the 7 March refers exclusively to a style change. The content of the report remains unchanged since its publication on 5 March.

Executive Summary

In the vast evolving field of nanomaterials and advanced materials, the OECD has been playing an important role in standardising the methodologies used for the testing and assessment of chemicals. Since 2006, the Working Party on Manufactured Nanomaterials (WPMN) has been exploring a range of different MNs and identifying the test methods that need to be adapted, or if new tests are needed that respond to the specific characteristics of MNs. The WPMN also has a weather eye on the integration of advanced materials[2] so that overall testing strategies can integrate them and give reliable and useful assessment on their safety. In 2022, the WPMN developed the Safer and Sustainable Innovation Approach (SSIA)[3] which involves integrating cutting-edge approaches on safety with sustainability with a view to prevent potential ecological and safety impacts of emerging materials while fostering innovation.

To learn more on advanced materials, the WPMN initiated a series of discussions on specific materials. The aim was to apply the Early Awareness and Action System for Advanced Materials (Early4AdMa)[4] to identify and describe potential safety, sustainability, and regulatory issues on specific advanced materials at the early stages of their development or use.

This document is the report of the 1st WPMN Workshop on NanoCarriers. NanoCarriers promise benefits for various fields of applications but they also present great diversity in terms of chemical composition, structural features, and applications. The aims of this workshop were to discuss NanoCarriers used in different applications (cosmetic, pharmaceutical, and agriculture) and to use the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa) to identify knowledge gaps and signals of possible concerns, regarding both their safety and/ or sustainability.

1 Nanocarriers: a case study on Advanced Materials

Background

NanoCarriers (nano-scaled structures loaded with an active substance) promise benefits for various fields of applications. First applications were established for medicinal products, applications for other fields are approaching (e.g., pesticides, biocides, cosmetics, food). NanoCarriers, which present great diversity in terms of chemical composition, structural features, and applications, may be viewed as advanced materials (AdMa)[5] . Due to their wide variety a differentiated discussions and dedicated early warning assessment are needed.

The OECD Workshop on NanoCarriers was organised by the German Environment Agency (UBA), the German Federal Institute for Risk Assessment (BfR), and with support of the EU H2020 project ASINA[6]. It was held online on 14 and 15 June 2023. There were 83 participants representing 20 OECD delegations, including Member Countries, as well as observers from South Africa and Thailand, Industry, animal welfare organisations such as ICAPO and invited experts from the EU Projects ASINA and SUNSHINE. The workshop thus benefited from a good mix from governmental representatives, including regulators and policymakers, as well as experts with diverse backgrounds from industry and academia.

The aims of this workshop were to discuss NanoCarriers used in different applications and to use the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa)[7] to identify knowledge gaps and signals of possible concerns, regarding their safety and/ or sustainability. Based on these results, the outcome would be to formulate action needs based on the signals identified due to Early4AdMa system.

The first day was dedicated to set the scene. As such, it included several presentations on Early4AdMa, on NanoCarriers and NanoCarrier synthesis processes in general, on NanoCarriers used in different applications such as pesticides and biocides, cosmetics, and pharmaceuticals, as well as on regulatory challenges and questions. On the second day, participants were divided in three break-out groups, i.e. on i) cellulose encapsulation NanoCarrier for cosmetic use; ii) an polymeric based NanoCarrier type for pesticidal application; and iii) generic liposome based NanoCarrier type for pharmaceutical application and they were invited to fill in the Early4AdMa questions of Tier 2 Step 5 as well as to formulate action needs based on Tier 2 Step 6 of the approach.

This report also includes 2 annexes, presenting the agenda, and the list of participants.

Notes

[1] Read more about Advanced Materials and the WPMN: OECD (2022) Advanced Materials: Working Description. Series on the Safety of Manufactured Nanomaterials. No. 104. [ENV/CBC/MONO(2022)29]

[2] See also: ENV/CBC/MONO(2022)29

[3] Read more about the WPMN Safer and Sustainable Innovation Approach:

Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products. Series on the Safety of Manufactured Nanomaterials. No. 96. [ENV/JM/MONO(2020)36/REV1]

Sustainability and Safe and Sustainable by Design: Working Description for the Safer (and Sustainable) Innovation Approach. Series on the Safety of Manufactured Nanomaterials. No. 105. [ENV/CBC/MONO(2022)30]

[4] Read more about the Early4AdMa: Early Awareness and Action System for Advanced Materials (Early4AdMa): Pre-regulatory and anticipatory risk governance tool to Advanced Materials

[5] OECD (2022), Advanced Materials: Working Description, Series on the Safety of Manufactured Nanomaterials No. 104, [ENV/CBC/MONO(2022)29]

[6] EU Horizon 2020 funded project "Anticipating Safety Issues at the Design Stage of Nano Product Development" (ASINA) https://www.asina-project.eu/

[7] OECD (2023), Early awareness and action system for advanced materials (Early4AdMa) Pre-regulatory Strategic Approach to Advanced Materials, Series on the Testing and Assessment of Manufactured Nanomaterials No. 108, https://www.oecd.org/chemicalsafety/safer-and-sustainable-innovation-approach/early-awareness-and-action-system-for-advanced-materials-pre-regulatory-anticipatory-risk-governance-tool.pdf

2 NanoCarriers: setting the scene.

The first day was dedicated to set the scene. As such, seven presentations were made as summarised below.

The Early4AdMa system: background and notes on use

Elmer Swart (National Institute for Public Health and the Environment (RIVM), Netherlands) presented the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa).

The Early4AdMa system assists in systematically identifying potential human health, environmental, sustainability and/ or regulatory issues of advanced materials. Specifically, the Early4AdMa system aims to:

identify and describe potential safety, sustainability, and regulatory issues of advanced materials in a systematic manner and identify potential follow-up actions (for example need for a Test Guideline or guidance to be developed),

support regulatory preparedness[1] by giving policymakers, decision makers and regulators the opportunity to early anticipate material innovations and,

provide a tool for anticipatory risk governance to facilitate innovation and safe and sustainable development of advanced materials.

The Early4AdMa system consists of two tiers. **Tier 1** is "***Broad screening assessment (optional)***" to scan the field and identify the potential issues, and **Tier 2** is "***Detailed screening assessment***" to focus on the assessment, by questions on Safety, Regulatory frameworks, and Sustainability while a context description refers to market entry stage, benefit of application, social-economical aspects, and anticipated manifestation forms (during a life cycle) of the investigated AdMa.

In **Step 5 of Tier 2**, a more detailed assessment is performed. The assessment is divided into four major topics:

1) safety assessment for human health,
2) safety assessment for the environment,
3) applicability of regulatory frameworks, and
4) sustainability.

Each topic is broken down into sub-topics with each sub-topic having multiple questions. Each question can be answered by '***Yes***', '***No'***, '***Don't know***', and '***Not applicable'***. The questions are phrased so that a 'Yes' always indicates a potential issue.

This final outcome of the system can be documented in a report that should highlight the focus of the assessment, a summary of the detailed assessment conducted in step 5 as well as a proposal for potential follow-up actions. The outcomes of the assessment in step 5 can be graphically shown in, for example, donut charts.

The Early4AdMa system is an expert assessment-based system. Notes on the aim, scope and limitations of the system are available in the main document published by the OECD.

Results of a research on types and applications of NanoCarriers

Dr. Bernd Giese (University of Natural Resources and Life Sciences (BOKU), Austria) presented the results of research on the types and applications of NanoCarriers.

In his presentation, he explained that NanoCarrier is a heterogeneous, dynamic technology field. The application is mainly in medicine, but also in agriculture, cosmetics, food, food supplements, household products, textiles, and electronics/electrical engineering since the 1980s. The term “NanoCarrier” has only appeared in the scientific literature since the beginning of the 2000s.

NanoCarriers can be made of various materials including natural structures and a size range of up to 1000nm[2]. They can have a broad range of functionalities from the simple carrier and encapsulation function to the protection from degradation of the active ingredient. Carriers might influence the behaviour of the active ingredient and can have possible effects on the rate of release, its bioavailability, the transformation of the active ingredient and its degradation or mobility.

Dr. Giese explained that a keyword search performed on Web of Science, further filtered, and classified based on expert knowledge, resulted in a total of 132 types of NanoCarrier identified for categorization. The greatest structural diversity was found for carriers made of organic materials. Precise design of structure at the molecular level enables advanced functionalities (e.g. DNA origami). Many NanoCarriers are being considered for more than one area of application and more are currently under development.

Overview of NanoCarrier Synthesis

Dr. Duangporn Polpanich (NANOTEC, Thailand) presented an overview of NanoCarrier synthesis.

NanoCarriers are colloidal nanosystems loaded with active agents (drugs or any macromolecules), which allow the molecules to selectively accumulate at the target site. They can be classified into three types: lipid-based NanoCarrier, inorganic nanoparticles, and polymeric nanoparticles.

Several manufacturing methods and a comparison of their respective advantages and limitations on lipid-based NanoCarrier (low energy methods[3], high energy methods[4], ultrasonication[5] and novel technology) and polymeric nanoparticles (solvent evaporation method and nanoprecipitation method[6]) were presented.

NanoCarrier in cosmetic: SSbD strategies for stabilising and delivering active ingredients

Dr. Anna Luisa Costa (CNR-ISTEC, Italy) presented research on “Cellulose Encapsulated Silver Nanoparticles for Cosmetic Use” performed within the EU funded project ASINA. In her presentation, she highlighted the link between the design variable and the performance attribute as the key issue facing safe by design (SbD).

The synthesis design space of Ag-based nanoforms proposed as aquasome carrier in cosmetics was explored. KDFs (key design factors) were linked to KPIs (key performance indicators), addressing SSbD (Safe and sustainable by design) dimensions suggested by JRC SSbD Framework[7], but always including the functionality dimension as a key dimension of sustainability.

The *in vitro* results suggested excellent antibacterial and antiviral activities of some AgHEC (i.e. nanosilver nucleated in hydroxylethylcellulose matrix) design alternatives and AgCur (i.e. nanosilver nucleated in

curcumin matrix) design alternatives against Gram -, Gram + bacteria and the actually circulating SARS-CoV-2. AgCUR showed the best risk/benefit balance, as demonstrated by the high Selectivity Index for antiviral *in vitro* models, making this compound an optimal candidate to be further investigated for antiviral purposes. A deeper investigation of the mechanisms driving the different results in terms of toxicity and antimicrobial activity is ongoing to enrich the design space of new, potentially better SSbD validated alternatives.

Finally, open issues linked to regulation were shown such as what is released in Ag based aquasome and in which cosmetic ingredient category fall the specific applications.

Polymer NanoCarrier system loaded with a pesticide

Dr. Melanie Kah (The University of Auckland, New Zealand) presented Polymer NanoCarrier for pesticides. The key objectives of developing nanopesticides are to address the weaknesses of current pesticides and achieve 1) more efficient application (e.g. more stable suspensions, homogeneous crop coverage), 2) reduced undesired losses (e.g. via photolysis or transport to non-target area), 3) improved bio-interactions (e.g. via improved uptake by the target, controlled release or target delivery).

Exposure to pesticides during mixing-loading, application and after application must be considered in risk assessment. The durability of nanopesticides is a key parameter to assess exposure. The risk profiles of nanopesticides with short durability (e.g., fast release of the active ingredient from the NanoCarrier) is likely to resemble that of conventional products. Whereas risk profiles of long durability (e.g., very slow release) are likely driven by the NanoCarrier properties for a significant period.

A key challenge of risk assessment on NanoCarriers for pesticides relative to other applications is the diversity of exposure scenarios, including multiple non-target organisms and routes of exposure. Characterizing exposure while accounting for aging processes under environmental conditions is challenging but also necessary to define realistic worst-case scenarios, which are needed for risk assessment. Critical comparisons of nanopesticides with pure active ingredients and with existing products are helpful to guide hypothesis-driven assessments.

Nanomaterials in Medical Products

Dr. Anil Patri (U.S. Food and Drug Administration (FDA), United States) presented nanomaterials in Medical Products. Medical applications of nanotechnology are drug delivery for mostly cancer and radiation therapy, gene delivery, regenerative medicine, imaging devices, complex engineering of particles, and surfaces, etc. FDA regulatory frameworks and review processes adequately identify and manage potential risks associated with the use of nanomaterials in products. FDA has developed guidance documents[8] for that.

Submissions of human drug products containing nanomaterials to the FDA exist since the 1970s. However, there are various challenges, and the products have evolved from simpler drug delivery systems to highly complex, multicomponent, multifunctional structures and devices[9]. FDA is flexible to support innovation by promoting beneficial nanotechnology product development[10].

Liposomes were explained as the case study using Early4AdMa. Many liposomes are approved and used for generic drug products. There is also product-specific guidance for generic drug products available[11] and some standards[12] developed by the US FDA Nanotechnology Core Facility in collaboration with stakeholders. Liposomes have a very large number of applications and standardisation will facilitate more rapid commercialisation and transfer to the clinical domain.

Emerging products are very complex products. They also include the convergence of technologies with nanotechnology, and gene delivery systems for therapeutic applications. Nanomaterials are used more than before.

Regulatory challenges & questions - Perspective of the German competent authorities BfR and UBA

Dr. Doris Völker (German Environment Agency (UBA), Germany) presented the regulatory challenges and questions related to safety (and sustainability) of NanoCarriers from the perspective of the German competent authorities BfR and UBA. NanoCarriers have many application areas, thus many different regulations are affected in Europe (product-specific regulations, overarching chemicals regulation). NanoCarriers are generally covered by the different regulations addressing the safety of substances. However, there is no regulatory definition for (Nano)Carrier available. In some but not all of the various EU regulations (pharmaceuticals, biocides, plant protection products (PPP), cosmetics, food/feed, REACH/CLP) (different) definitions for nanomaterials are implemented. In order to acknowledge the specific function of NanoCarriers in the different applications, including their influence on fate and effects of the cargo on human and the environment, a separate safety assessment is required for every compound (carrier, cargo, and other building blocks[13]) as well as for the whole entirety.

There are several knowledge gaps regarding chemical safety:

- Carrier:
    - Behaviour and fate in relevant matrices (e.g., persistence, degradation, mobility)
    - (Eco-)Toxic potential of the carrier
- Cargo:
    - Change of toxicokinetics, environmental fate and behaviour of the active ingredient (in dependence of the carrier type)
    - Influence of carrier on bioavailability of active ingredients
    - Shift in (eco-)toxicity of the active ingredient due to the carrier
    - There are also regulatory needs and methodological gaps
- Regulatory needs:
    - Tailored information requirements to allow specific risk assessment of entirety beside individual building blocks
- Risk assessment needs:
    - Tailored guidance documents for safety assessment of carrier, and the entirety (beside the assessment of the cargo)
    - Testing strategies considering the influence of the carrier on the cargo
- Methodological gaps:
    - Analytic methods
    - Harmonised test methods to address possible influence of the carrier on the cargo
        - Influence on bioavailability, toxicokinetic and shift of (eco-)toxicity of the cargo
        - Influence on fate and behaviour of the cargo

- Fate, behaviour, and (eco-)toxic potential of the carrier and the entirety

Two research projects were highlighted. One is the EFSA NAMS4NANO Project[14]. This is a new project funded by EFSA with the aim to develop new approach methodologies for nanomaterials. The other project is a "Study on NanoCarriers and their environmental behaviour"[15]. The objectives of this project are to obtain an overview of (environmentally) relevant NanoCarriers and to identify the need for adaptation for the environmental risk assessment. The project will develop testing strategies to investigate the environmental behaviour and fate (mobility, non-intended release of the cargo, degradability of the carrier) for selected types of carriers in order to analyse challenges within environmental risk assessment of NanoCarriers as well as to propose experimental testing strategies to be implemented as part of a future specific environmental assessment of NanoCarriers.

Notes

[1] OECD (2020), Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products, Series on the Safety of Manufactured Nanomaterials No. 96, [ENV/JM/MONO(2020)36/REV1]

[2] Chariou, P. L., Ortega-Rivera, O. A., & Steinmetz, N. F. (2020), "Nanocarriers for the Delivery of Medical, Veterinary, and Agricultural Active Ingredients", *ACS nano*, 14(3), 2678–2701. https://doi.org/10.1021/acsnano.0c00173

[3] Singh, H. et al. (2015), "Nano-formulation of rifampicin with enhanced bioavailability: Development, characterization and in-vivo safety", *International Journal of Pharmaceutics*, 485(1-2), 138-151, https://doi.org/10.1016/j.ijpharm.2015.02.050.

[4] Jain, A.K. and S. Thareja, (2019), "In vitro and in vivo characterization of pharmaceutical nanocarriers used for drug delivery", *ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY*, 47(1), 524–539, https://doi.org/10.1080/21691401.2018.1561457.

[5] https://www.hielscher.com/pharmaceuticals-encapsulated-in-lipid-nanoparticles-with-ultrasonics.htm

[6] Zielińska A. et al. (2020), "Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology", *Molecules*, 25(16), 3731, https://doi.org/10.3390/molecules25163731.

[7] European Commission, Joint Research Centre (2022), "*Safe and sustainable by design chemicals and materials - Framework for the definition of criteria and evaluation procedure for chemicals and materials*", https://data.europa.eu/doi/10.2760/487955

[8] http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

[9] D'Mello, S. R. et. Al (2017), "The evolving landscape of drug products containing nanomaterials in the United States", *Nature Nanotechnology*, 12, 523–529, https://doi.org/10.1038/nnano.2017.67

[10] Nanotechnology Task Force: https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force

[11] Product-Specific Guidances for Generic Drug Development (fda.gov)

[12] https://www.astm.org/get-involved/technical-committees/committee-e56/subcommittee-e56/jurisdiction-e5608

[13] Carrier = the „carrying“ entity; Cargo = the „carried“ entity (usually an active ingredient); Entirety = all building blocks (carrier, cargo, any other needed building block)

[14] NAMS4NANO: Integration of New Approach Methodologies results in chemical risk assessments: Case studies addressing nanoscale considerations. - LOT 1: Review of tools and developing a ‘Qualification System for NAMs’ (NAMS4NANO LOT1) - BfR (bund.de)

[15] Examination and further development of strategic approaches for dealing with advanced materials in chemical safety“ – Study on nanocarriers and their environmental behaviour – FKZ 3722664010, financed by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and consumer protection: Research and development projects on nanomaterials | Umweltbundesamt; executed by the University of Natural Resources and Life Sciences in Vienna: University of Natural Resources and Life Sciences, Vienna (BOKU) - Research portal

3 Assessment of NanoCarriers using Early4AdMa Step 5

Discussion on the assessment of NanoCarriers based on their application

On the second day, break-out group discussions were held in two sessions. There were three groups based on NanoCarrier application in cosmetics, pesticides, and medicinal products. Participants were allocated to specific groups based on their area of expertise and combining governmental, industry and academic perspectives. Selected exemplary types of NanoCarriers within these applications were discussed by implementing step 5 of the assessment of the Early4AdMa. This chapter summarises the discussion. The basis for discussions within the three break out groups was provided by the application related presentations at day 1.

As time was limited during the BOG discussion and not all questions could be answered, the possibility was given to the participants to provide written input. As follow up to the workshop, the secretariats called for further comments to questions of step 5 of Early4AdMa related to the discussed cases. Several comments were submitted by Japan (National Institute of Health Sciences) and Germany (UBA) and are summarised in the chapter additionally.

In the following subchapters the figures of the context description of each specific example discussed were included. The figure descriptions include beside others information on benefits, market-entry stage, expected scale of application as well as relevant release compartments and transformation forms during life cycle. The context descriptions were provided at the beginning of the breakout discussions.

NanoCarrier type for cosmetic application

Chaired by: Doris Völker (UBA), Rapporteur: Jutta Tentschert (BfR)

The group discussed an example for a cosmetic application of a NanoCarrier. In addition to the presentations on the first day, an overview of this application was prepared in advance and presented to the experts (Figure 3.1).

Figure 3.1. Context description of the specific example of a cosmetics application of NanoCarrier discussed

Context: Case 1 – cellulose encapsulated Silver Nanoparticles for cosmetic use

- Application area: Area 5 – Personal Care
- Focus of assessment: material in (one or more) specific product (creams, lotions, gels)
- Benefit, benefit for whom, and anticipated magnitude of benefit (as compared to a conventional material/product): silver is an oligo element reactive at very low dose application, cellulose surrounding matrix improves hydrophilicity and the control of product viscosity, improving applicability, effectiveness and compatibility in different cosmetic formulation, overall cellulose encapsulated silver promotes the stability and controlled release of active ingredients (silver ions and NPs interacting with biological target), silver nanoparticles represent an alternative strategy to the use of antibiotic resistance chemicals.
- Socio-economic considerations (criticality raw materials, child labor etc): concerns about bio-persistency; silver mining partly in low- and middle-income countries, implication on antibiotic resistance
- Market-entry stage[3]: TRL 4-6
- (Anticipated) scale of application (of material, and if specific product(s) are considered, fraction related to product(s))[4]: medium to large scale
- Relevant **anticipated** release compartment and (transformation) forms during life cycle (see table):

	During production[1]	During use	End-of-life	Other[2]
Compartment(s) of release (e.g. air, water, soil)	Closed system, processed at liquid state and room temperature, however wastewater may be possible	wastewater	Wastewater	Silver mining: water
Form(s) of release (e.g. pristine, embedded in matrix, transformed, corona formation)	Pristine, in dispersion	embedded in cosmetic matrix/formulation	embedded in cosmetic matrix/formulation; transformed (overlaid)	
Mechanism(s) of release (e.g. due to use, weathering, sanding)	Rinsing, spilling	Washing off skin	rinsing	

[1] During production of the material and/or during production of an AdMa-enabled product.
[2] Other life stages like mining of raw materials or transport.
[3] In TRLs with TRL 1-3 representing a formulated concept of the nanocarrier type, TRL 4-6 representing the development in laboratory and testing of the prototype and TRL 7-9 representing usage, availability and close to market penetration.
[4] large, medium, limited scale or unknown

Within this breakout group, emphasis of discussion was on human health and environment safety assessment of the exemplary cosmetic application of cellulose encapsulated nanosilver. Due to time reasons the questions on the applicability of regulatory frameworks were only discussed in low detail and the questions related to "Sustainability" could not be discussed at all.

Safety Assessment - Human health

The discussion on potential signals regarding human health were mainly attributed to the cargo of the carrier system which are silver nanoparticles while there was no concern identified arousing from the cellulose capsules. The SCCS[1] concluded that silver may pose health risk for consumers[2]. Based on this view, some of the questions on human health were answered with “yes” indicating towards a signal.

In that sense, it was highlighted several times that the outcome of the safety assessment could be very different in case of another cargo.

Insecurity on potential signals was identified in cases of questions which related to a shift in properties of the cargo (e.g., toxicity or skin penetration) mediated by the encapsulation. Some participants raised concerns that such properties might be enhanced by encapsulation. There was also the opinion that such shifts might be positive in terms of lowering hazards or exposure.

However, as dedicated studies to answer questions on e.g., specific toxicological endpoints, kinetic profiles or barrier crossing capabilities are not available, knowledge gaps remain.

Safety Assessment - Environment

A high number of signals was identified based on the questions on environment safety assessment. These were mainly attributed to environmental concerns of the cargo silver nanoparticles, its potential release, and the potential release of silver ions to the environment. Silver is known to be toxic to aquatic organisms. Thus, signals were identified for more than 70% of the questions.

Also here, it was highlighted that the responses for the carrier entirety might be biased by the cargo with well-known ecotoxic effects and that the outcome of the safety assessment could be very different in case of another cargo. Concern was expressed among the participants that the benefits of designing and applying the carrier for cosmetic application which could be applied to carry different cargos, will be diminished by the negative outcome based on the assessment of the selected cargo.

With regard to fate and exposure, participants expressed concerns regarding changes in persistency, mobility and the potency for exposure of environmental compartments.

Knowledge gaps were identified regarding influence of the encapsulation on the ecotoxicity as well as on uptake and bioaccumulation of the cargo.

Applicability of Regulatory Frameworks

Even though characterisation as well as sample preparation to determine e.g. hazard and fate are possible for the assessed NanoCarrier, participants identified challenges with regard to a proper analysis within complex media.

If and to what extent the investigated NanoCarrier will be covered by the respective regulations on cosmetics will depend on the definition of nanomaterials used in that regulations and to what extent it will fit for the investigated NanoCarrier.

The group was of the opinion even though the investigated NanoCarrier is covered by the cosmetic regulations, there is a lack for provisions within those regulations that explicitly address the NanoCarrier character.

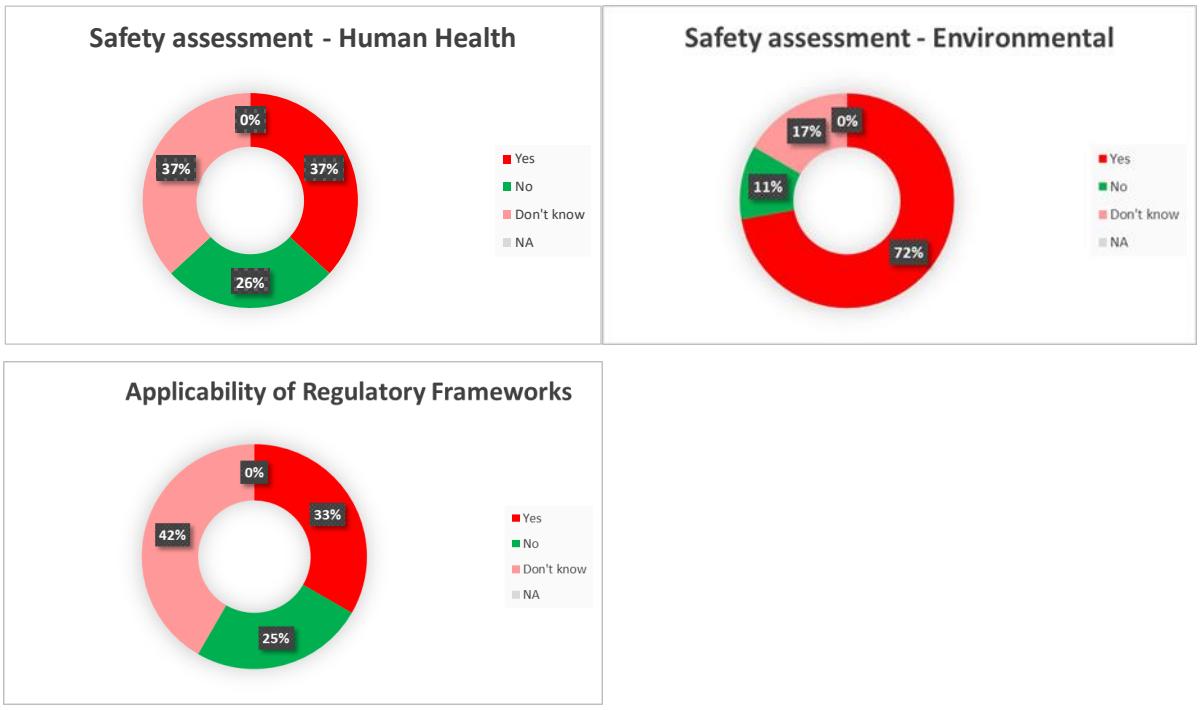
However, depending on the flexibility within the specific cosmetic regulation, it might be possible that the existing provisions will allow to address the specific NanoCarrier properties to some extent. It is also not clear whether or to what extent provisions covering human health and environment safety issues of NanoCarriers are addressed by the information requirements of cosmetic regulations.

The group identified the need for specific test methods and guidance to target specific human health and environmental safety issues of NanoCarriers.

Due to missing expertise, no remark was made about the coverage of NanoCarriers by legislation or guidance addressing sustainability aspects.

An overview on the distribution of answers “Yes”, “No”, “Don’t know” and “not applicable” to the questions of step 5 of the assessment is given in **Figure 3.2.**

Figure 3.2. Results of step 5 of the Early4AdMa for the specific example of a cosmetic application of NanoCarrier discussed



Note: “Yes” represent a signal of concern, “No” represents absence of a signal of concern, “Don’t know” means that a question could not be answered based on available information, and “NA” means that a question was not applicable or not relevant.

Written feedback from the follow up to the workshop

One respondent delivered answers to the Early4AdMa step 5 questions on the applicability of regulatory frameworks as well as on sustainability.

About needed test methods and assessment strategies to target potential environmental safety issues and by this improve the applicability of regulatory frameworks, one respondent highlighted the need for methods that assess the fate of the encapsulation and the effect of the encapsulation on the active substance, respectively. This includes mobility, degradation and un-intended release of the active substance.

With regard to the questions on implications for sustainability, one response was achieved mainly highlighting the amount of missing knowledge, e.g., regarding the possibility for recycling of raw material or waste arising during production but also regarding the demand for energy, water and land consumption during manufacturing, production and use. However, as at least the active ingredient was identified as problematic substance, challenges for sustainability at various life cycle stages were expressed. For the

cosmetic application of NanoCarriers, end of life questions, i.e., on recyclability and reusability after use seem not applicable.

NanoCarrier type for pesticide application

Chaired by Hubert Rauscher (EC-JRC), Rapporteur: Michael Hess (UBA)

The group discussed an example for a pesticide application of a NanoCarrier. In addition to the presentations on the first day, an overview of this application was prepared in advance and presented to the experts (Figure 3.3).

Figure 3.3. Context description of the specific example of a pesticide application of NanoCarrier discussed

Context: Case 2 - Polymer nanocarrier system loaded with a pesticide

- Application area: Area 7 – Agriculture
- Focus of assessment: material in (one or more) specific product
- Benefit, benefit for whom, and anticipated magnitude of benefit (as compared to a conventional material/product): tailored pesticide application (reduced amounts, reduced side effects, new application fields); for professional (and possible consumer) use; high benefit for professional, consumer and environment due to less exposure but consistent/improved service
- Socio-economic considerations (criticality raw materials, child labor etc):
- Market-entry stage[3]: TRL 7-9
- (Anticipated) scale of application (of material, and if specific product(s) are considered, fraction related to product(s))[4]: large scale
- Relevant **anticipated** release compartment and (transformation) forms during life cycle (see table):

	During production[1]	During use	End-of-life	Other[2]
Compartment(s) of release (e.g. air, water, soil)	Closed system, however wastewater may be possible	Air, water, soil	Water	
Form(s) of release (e.g. pristine, embedded in matrix, transformed, corona formation)	Pristine, in dispersion	In dispersion or aerosol, pristine; transformation in the environment	In dispersion, pristine, transformed (overlaid)	
Mechanism(s) of release (e.g. due to use, weathering, sanding)	Rinsing, spilling	Spraying, spilling	Rinsing, spilling	

[1] During production of the material and/or during production of an AdMa-enabled product.
[2] Other life stages like mining of raw materials or transport.
[3] In TRLs with TRL 1-3 representing a formulated concept of the nanocarrier type, TRL 4-6 representing the development in laboratory and testing of the prototype and TRL 7-9 representing usage, availability and close to market penetration.
[4] large, medium, limited scale or unknown

To facilitate the discussion the group chose polymeric NanoCarrier loaded with Azoxystrobin as specific example for discussion which illustrates a possible use for fungicidal application. Due to time reasons the discussions focused on “Safety Assessment – Human health” and “Safety Assessment – Environmental”. Questions on “Applicability of Regulatory Frameworks” and “Sustainability” were not discussed.

Safety Assessment - Human health

Many signals for hazard to human health were identified. Signals are mainly attributed to the active ingredient.

For exposure it is likely that consumers and workers can be exposed to the NanoCarrier as a whole or to the released active ingredient.

For several questions the group identified data gaps like for behaviour and kinetics of the NanoCarrier.

While some questions were completely clear as to whether the NanoCarrier as a whole, including the active ingredient, had to be analysed, some questions seemed more related to the active ingredient or the carrier itself, which led to a sense of indeterminacy.

When comparing advanced materials with conventional materials or conventional ingredients, it was sometimes unclear what conventional materials were. There should be more clarity in the guidance and in the Early4AdMa system itself.

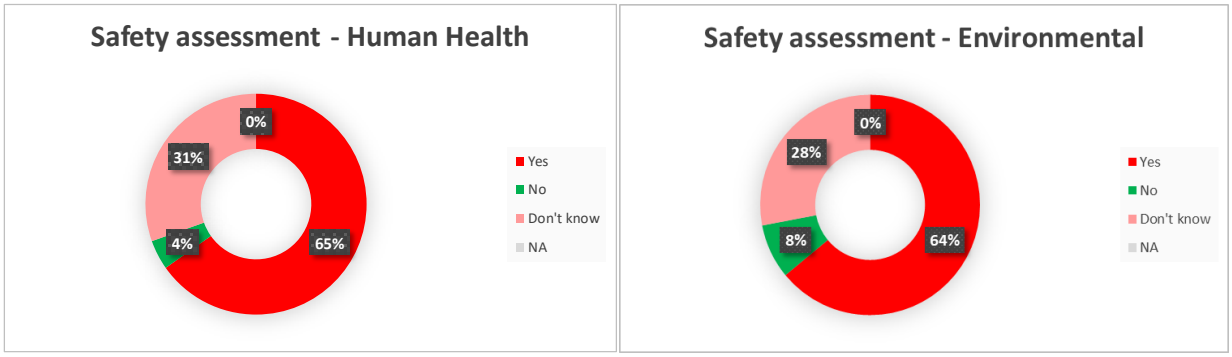
Safety Assessment - Environment

Also, for environment many signals for hazard were identified which are attributed to the active ingredient. Furthermore, it is unknown if e.g., the carrier changes or increases the hazard of the active ingredient.

Due to the application in the open environment (e.g., spraying of crop fields) and conceivable application, high and direct exposure to environment compartments can be expected by the NanoCarrier as a whole or by the released active ingredient.

An overview on the distribution of answers “Yes”, “No”, “Don’t know” and “not applicable” to the questions of step 5 of the assessment is shown below (**Figure 3.4**).

Figure 3.4. Results of step 5 of the Early4AdMa for the specific example of a pesticide application of NanoCarrier discussed



Note: “Yes” represent a signal of concern, “No” represents absence of a signal of concern. “Don’t know” means that a question could not be answered based on available information, and “NA” means that a question was not applicable or not relevant.

Written feedback from the follow up to the workshop

One respondent delivered answers to the Early4AdMa step 5 questions on the applicability of regulatory frameworks as well as on sustainability.

That respondent considered the example NanoCarrier type generally covered by the regulations on pesticides however it is believed that provisions that explicitly address or allow to address the NanoCarriers characteristics, but also environmental safety issues are lacking. In addition, there is a need for test

methods and assessment strategies that allow to target potential environmental safety issues of NanoCarriers applied as pesticides. It is furthermore expected that analysis of the NanoCarriers in complex matrices is challenging due to the complexity and organic compounds of e.g., environmental matrices as well of the NanoCarrier, but also to be able to differentiate if the NanoCarrier is still intact (carrier shell and cargo) or if/when carrier and cargo went apart.

With regard to the questions on implications for sustainability, the respondents mainly highlight the amount of missing knowledge, e.g., regarding the energy, water and land demand for raw material extraction but also during manufacturing, production, transport, use or consumption or regarding the possibility for recycling of raw material or waste arising during production. However, as at least the active ingredient was identified as problematic substance, challenges for sustainability at various life cycle stages were expressed. For the pesticide application of NanoCarriers, end of life questions, i.e., on recyclability and reusability after use do not seem to be applicable. On the other hand, it is assumed that the use of NanoCarriers lead to less need of substance application and consequently less energy demand during application compared to a reference (i.e., pure active substance).

NanoCarrier type for medicinal application

Chair: Kathrin Schwirn (UBA), Rapporteur: Anna Pavlicek (BOKU)

The group discussed an example for a medical application of a NanoCarrier. In addition to the presentations on the first day, an overview of this application was prepared in advanced and presented to experts (**Figure 3.5**).

Figure 3.5. Context description of the specific example of a Cosmetics application of NanoCarrier discussed

Context: Case 3 – Generic Liposome NanoCarrier type for medicinal product application

- Application area: Area 1 – Health care and medicine
- Focus of assessment: material in (one or more) specific product
- Benefit, benefit for whom, and anticipated magnitude of benefit (as compared to a conventional material/product): tailored active ingredient application (reduced amounts, improved effectiveness, reduced side effects, new therapy possibilities); patients; high societal benefit; ability to treat disease that are otherwise untreatable currently or have limited options
- Socio-economic considerations (criticality raw materials, child labor etc): influence on health care costs
- Market-entry stage[3]: TRL 4-6, TRL 7-9
- (Anticipated) scale of application (of material, and if specific product(s) are considered, fraction related to product(s))[4]: large
- Relevant **anticipated** release compartment and (transformation) forms during life cycle (see table):

	During production[1]	During use	End-of-life	Other[2]
Compartment(s) of release (e.g. air, water, soil)	Closed system, however wastewater may be possible	Waterwater	Wastewater (assuming incorrect disposal)	
Form(s) of release (e.g. pristine, embedded in matrix, transformed, corona formation)	Pristine, in dispersion	embedded in matrix/dispersion, possible transformation in patient's body	embedded in matrix/dispersion, pristine, transformed (overlaid)	
Mechanism(s) of release (e.g. due to use, weathering, sanding)	rinsing	Elimination upon patient passage	spilling	

[1] During production of the material and/or during production of an AdMa-enabled product.
[2] Other life stages like mining of raw materials or transport.
[3] In TRLs with TRL 1-3 representing a formulated concept of the nanocarrier type, TRL 4-6 representing the development in laboratory and testing of the prototype and TRL 7-9 representing usage, availability and close to market penetration.
[4] large, medium, limited scale or unknown

To facilitate the discussion the group chose a generic liposome encapsulated Doxorubicin as specific example for discussion which illustrates a use as chemotherapeutic drug agent. Due to time reasons the discussion focused on "Safety Assessment – Human health" and "Applicability of Regulatory Frameworks". Questions on "Safety Assessment - Environment" and "Sustainability" were not discussed.

Safety Assessment - Human health

For the discussed case a lot of signals for concern on human hazard were identified. This observation was mainly attributed to the properties of the active ingredient which is quite toxic to serve the purpose as chemotherapeutic drug agent. Regarding possible hazards based on the liposome carrier, questions arouse on the influence of impurities remaining from the synthesis process or due to an improper working carrier.

For exposure, it is not expected that consumers and the wider population are likely to be exposed except patients. Considering the potential for exposure during life cycle, potential occupational exposure during production was deemed possible.

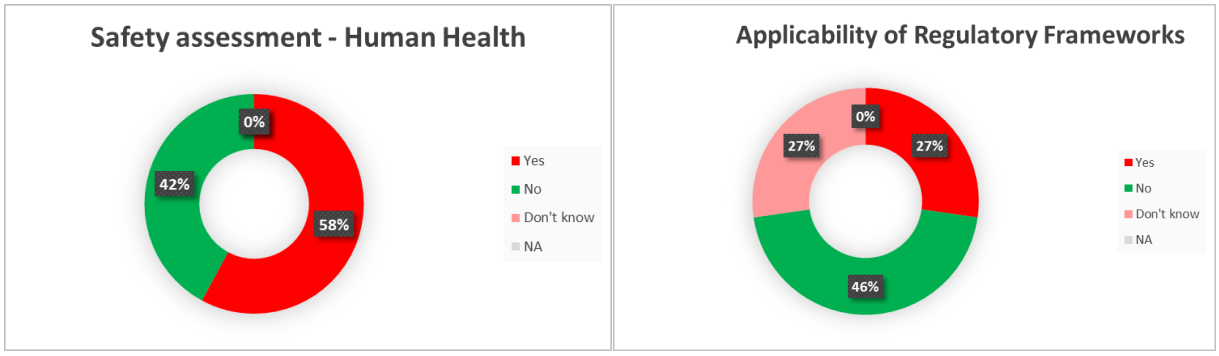
Applicability of Regulatory Frameworks

There are a lot of methods or techniques available for analytics and sample preparation, especially for characterization. However, the standards for those are not established.

In general, these materials are covered by regulations. However, the group was unaware if corresponding regulations in the various regions explicitly address or eventually allow to address the multicomponent character of the material. It was discussed that it may be necessary to determine whether the existing information requirements are currently sufficient or whether some amendments are required, especially to address environmental safety issues.

An overview on the distribution of answers “Yes”, “No”, “Don’t know” and “not applicable” to the questions of step 5 of the assessment is as shown below (**Figure 3.6**).

Figure 3.6. Results of step 5 of the Early4AdMa for the specific example of a medicinal application of NanoCarrier discussed



Note: “Yes” represent a signal of concern, “No” represents absence of a signal of concern, “Don’t know” means that a question could not be answered based on available information, and “NA” means that a question was not applicable or not relevant.

Written feedback from the follow up to the workshop

Two respondent delivered answers to the Early4AdMa step 5 questions on human health safety, the applicability of regulatory frameworks as well as on sustainability.

One respondent highlighted that toxic potential of some of the nanomedicines origins from the toxic property of the drug.

The other respondent indicated a lot for signals of concern on environmental hazard. This observation was partly attributed to the properties of the active ingredients but also due to the combination/multicomponent nature of the NanoCarrier which might have influences on the fate and effects of the active ingredient. However, there are several open questions which relate already to existing data gaps on the environmental hazard and fate of the active ingredient while this substance can be found during environmental monitoring.

With regard to the questions on implications for sustainability, the second respondent mainly highlighted the amount of missing knowledge, e.g., regarding the energy, water and land demand for raw material extraction but also during manufacturing, production, transport, use or consumption or regarding the possibility for recycling of raw material or waste arising during production. However, as at least the active ingredient was identified as problematic substance, challenges for sustainability at various life cycle stages

were expressed. On the other hand, it is assumed that the use of NanoCarriers lead to less need of substance application. For the medicinal application of NanoCarriers, end of life questions, i.e., on recyclability and reusability after use seem not applicable.

Notes

[1] EU Scientific Committee on Consumer Safety

[2] SCCS Scientific Advice on the safety of nanomaterials in cosmetics: https://health.ec.europa.eu/system/files/2022-08/sccs_o_239.pdf

4 Evaluation and formulation of potential follow up actions

The aim of break out session 2 discussion was to formulate potential follow up actions to address the signals identified in break out session 1 and to give feedback on the use of the Early4AdMa. Input from participants were gained via pre-defined questions provided via Mentimeter. In the following subchapters the feedback from the participants is summarised.

NanoCarrier type for cosmetic application

For the NanoCarrier case discussed for cosmetic application, biggest concerns were observed for the topic “Safety assessment - Human Health”, followed by issues related to “Sustainability” and “Applicability of Regulatory Frameworks”. The less concern was seen for “Safety assessment - Environment”. Based on the feedback received biggest data gaps exist regarding the topic “Sustainability” but also issues related to “Applicability of Regulatory Frameworks”. Less remaining data gaps were identified for “Safety assessment - Human Health” and “Safety assessment - Environment”.

About identified follow up actions for human health and environmental safety assessment, it was mentioned that innovators and designer should draw more attention to safety drawbacks while highlighting advantages. However, also funding agencies should be engaged more, e.g., by funding research on fate and behaviour of NanoCarriers in the environment and implications how encapsulation may provide a shift in environmental fate of the cargo. Research is also needed to investigate persistence and accumulation in the environment. More conclusive data on toxicity of different NanoCarrier applications within cosmetics need to be collected by industry. It was also mentioned that analysis methods will probably need adaptation.

A specific risk assessment strategy is needed for NanoCarriers, considering releases of the active ingredient from the carrier (in time and space). To improve regulatory risk assessment, it needs to be determined which parts of the carrier system are considered as regulatory relevant which will afford discussion between e.g., science and regulatory agencies. In addition, specific characterisation requirements needed for a proper assessment should be proposed by regulatory agencies. To address the identified regulatory gaps and to improve the regulatory framework for NanoCarriers (in cosmetic application), discussions on needed adaptations should take place, e.g., in the EU by the European Commission and Member States. Such discussion should also include the adaptation of the nanomaterial definition in the cosmetic regulation. It was also mentioned that the SCCS should take up work on assessing the influence of encapsulation on effects of cosmetic active ingredients. For this, it was proposed to share observations like identified uncertainties and insufficient provisions with regulatory relevant bodies like SCCS.

SSbD was mentioned as important instrument to improve safety and sustainability of NanoCarriers that should by applied by innovators.

With respect to actions needs for sustainability, next to applying SSbD, it was emphasized to set up a frame for sustainability assessment in order to identify further research but also information needs which could then, e.g., be considered in upcoming legislation. Finally, the need for specific LCAs to also identify environmental impacts along the whole life cycle of NanoCarriers and all its components was highlighted.

OECD may continue to host stakeholder meetings to follow up on action needs.

Due to time reasons no specific remarks or recommendations regarding the applicability of the Earl4AdMa framework based on the discussion of the cosmetic application of the NanoCarrier example were received.

NanoCarrier type for pesticide application

For the NanoCarrier case discussed for pesticide application, the biggest concerns were conceived for the topic “Safety assessment - Environment” followed with distance by “Safety assessment - Human Health”, “Applicability of Regulatory Frameworks”, and “Sustainability”. “Safety assessment - Environment” was also indicated as topic with the biggest data gaps followed with distance by “Applicability of Regulatory Frameworks”, “Sustainability”, and “Safety assessment - Human Health”.

With respect to safety assessment on human health and the environment but also in context of regulatory frameworks, the evaluation and development of standardised methods was one of the main actions needs that was put forth. As an example, the need for a test guideline to assess the durability / persistence[1] of NanoCarriers was mentioned. A potential outcome pointing towards long durability/persistence might also influence the adaptation need for methods on ecotoxicity towards longer test duration. Activities should be taken up by standard development organisations (such as OECD), but also industry, academia and regulatory agencies like EFSA and ECHA.

Furthermore, regulatory frameworks should be reviewed by regulatory bodies whether NanoCarrier for pesticides application are adequately covered, where gaps exist and if additional information requirements are needed to adequately address NanoCarriers in existing regulatory frameworks; as example durability/persistency was mentioned. It was suggested that such frameworks should be adapted where necessary. Revisions were also suggested for REACH. The definition for nanomaterials was seen as too narrow for NanoCarriers, and adaptation was suggested. In addition, a harmonized definition of NanoCarriers across different regulations is needed. Information for assessment should be provided by industry, including information on the known active ingredient or known standard formulation.

For NanoCarriers for pesticide application several research needs were identified for academia, industry and regulators. Analytical methods and accompanying guidance are needed to characterise NanoCarriers and their specific surface functionalities and/or investigate organic NanoCarriers in environmental matrices. Studies on clearance and accumulation for polymeric coatings, effects of PEG-coatings, environmental fate and behaviour in the various compartments including durability/persistence in aqueous media, transport, release of degradation and reaction products were proposed as well as the development of NAMs and AOPs, and investigating ecotoxicity including toxico-dynamic shift in different species. Investigation into better proxies for environmental partitioning coefficients, bioconcentration factors, mobility and bioaccumulation criteria is needed. Environmental monitoring should be considered by authorities.

OECD should facilitate collaboration between innovators, industry, regulators, and policy in the framework of e.g., a Trusted Environment and Safer and Safer and Sustainable Innovation approach[2]. Collaboration includes beside others the application of Safe-and-Sustainable-by-Design principles and training on NanoCarriers and their relation to different aspects of sustainability and legislation. Collaboration can also help to find and establish good practice.

With regards to sustainability, it was suggested that academia could further investigate into social impacts by comparative studies including other existing solutions. Also, indicators are needed for sustainability that can help to find a balance between product functionality and environmental friendliness. Industry should be involved to improve the balance between risk and benefits. Academia and consultants should perform comparative life cycle assessments. Furthermore, research is suggested on polymers that are biodegradable and that improve soil properties (including fertilisation) as well as on the reuse of the polymers.

Public campaigns by local authorities addressing workers and consumers were suggested to increase acceptance through raising awareness of the chances nano-enabling can provide.

It was highlighted that NanoCarriers should be further discussed at dedicated conferences, specific workshop sessions e.g., at SETAC or NanoSafe, and stakeholder workshops of OECD. This can help also for the communication and dissemination of stakeholder opinions.

With respect to the application of the Early4AdMa general remarks were that it is a useful approach, but it should be applied case-by-case. A description and other information relevant for the Early4AdMa approach of the reference material for comparison is needed and to specify more precisely what substance/material (e.g., carrier, constituent, pre-formulation) is subject of the assessment. It was noticed that questions are lacking in Early4AdMa for the possible need of additional regulations for advanced materials, and on existing/marketed formulations. It was unclear to some participants if different exposure scenarios should be considered for the exposure assessment, who will decide to start an assessment and how, and how to start discussion in an early stage.

NanoCarrier type for medicinal application

For the NanoCarrier case discussed for medicinal application, the biggest concerns were regarded for the topic “Safety assessment- Human health” followed by “Safety assessment- Environmental”. Less concern was indicated regarding “Applicability of Regulatory Frameworks” and “Sustainability”. In contrast, biggest data gaps were indicated for “Safety assessment- Environmental” and “Sustainability” followed by “Safety assessment- Human health” and “Applicability of Regulatory Frameworks”.

With respect to safety assessment on human health and the environment but also in context of regulatory frameworks, the development of standardised methods and methodology was one of the main actions needs that was put forth. This includes reproducible characterisation, analytic methods, and methods to assess environmental fate and behaviour. Such methods are needed for safety assessment but also efficiency assessment. Activities should be taken up by standard development organisations like OECD, industry, academia, and regulatory bodies.

A further common point raised was the need to develop assessment frameworks by regulators to adequately assess the specificities of NanoCarriers in medicinal application including subjects of durability, distribution, and possible side effects. In this context, already existing methods and frameworks should be disseminated and cooperation between different frameworks should proceed. Furthermore, existing information requirements should be reviewed regarding their appropriateness to assess the human and environmental safety of NanoCarriers in medicinal application.

For academia, research on AOP and predictive NAMs, for reproducible analytics assays, on environmental behaviour (e.g., persistence, fate, transformation), on substitution of problematic co-formulants, on methods to measure properties of complex and heterogeneous surfaces and coatings, on consequences for the food chain, and by controlled (large-scale) field experiments were formulated as tasks. Besides that, high-quality reproducible science is needed for medicinal products using innovative concepts to meet medicinal needs.

In relation of the research needs as well as for method development, funding agencies and politics were highlighted as those responsible to enable such activities.

For the topic on sustainability, it was noted that more data is needed on energy and resource demand as well as waste generation and possible rebound effects over the life cycle of NanoCarriers for medicinal application. Furthermore, industry should take into consideration the energy demand during production, waste management and possible pollution. Principles of SSIA (Safe and sustainable innovation approach) and SSbD should be considered. To facilitate such approaches, regulators were referred to develop decision tools that help to evaluate parameters (e.g., energy demand, waste generation, use of water, cost efficiency) that are key when producing NanoCarriers.

With respect to the application of the Early4AdMa general remarks were that more specific case studies are needed to evaluate the applicability. The question aroused if questions within the Early4AdMa should also address physical-chemical risks. Questions should be supplemented to enquire non-specific effects and non-specific reactions. Focusing on the discussed case, it was highlighted that it is challenging to apply the Early4AdMa. Conflicts might arise due to the perspective of the assessment: assessing the carrier alone could lead to different outcome than the carrier together with the active ingredient. For medicinal application the questions also might need a rethinking as the system originally focuses on general chemicals. Anyhow, NanoCarriers should be evaluated case by case.

Notes

[1] The terms “durability” and “persistence” were used interchangeably and without clear description during the discussion. While “durability” is often use in the context human health, the accurate term within environmental risk assessment is “persistence”. Persistence is the result of an assessment of the stability of a substance in the environment (based e.g. on ready bio-degradability).

[2] OECD (2020), Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products, Series on the Safety of Manufactured Nanomaterials No. 96, [ENV/JM/MONO(2020)36/REV1]

5 Summary and conclusions

NanoCarriers promise benefits for various fields of applications like medicine, pesticides, biocides, cosmetics, and food. Therefore, they feature an example of advanced materials with many different types and applications, thus differentiated discussions and dedicated early warning assessment are needed.

An OECD Workshop on NanoCarriers was organised by the German Environment Agency (UBA), the German Federal Institute for Risk Assessment (BfR), and with support of the EU H2020 project ASINA. It was held online on 14 and 15 June 2023. 83 participants representing 16 OECD Member Countries, as well as observers from South Africa and Thailand involving different stakeholder groups participated in the workshop.

The aims of this workshop were to discuss NanoCarriers used in different applications and to use the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa) to identify knowledge gaps and signals of possible concerns, regarding their safety and/or sustainability. To facilitate the discussion several presentations were given by experts. Based on the signals identified using the Early4AdMa system, action needs were formulated by the participants.

When assessing specific NanoCarriers by the Early4AdMa system, e.g., those carrying active ingredients with intended toxic potential used in pesticide and medicinal application but also in cosmetic application, reflections that need to be taken are more complex than for AdMa that can be understood as an industrial chemical. Due to the complexity of NanoCarriers, differentiated considerations are to be made with respect to the implications originating from the carrier versus those originating from the cargo but also versus those originating from the entirety of a NanoCarrier. It can be summarised that for the discussed cases the active substance mainly influences the outcome for signals of concern regarding safety while the contribution of the carrier to the outcome remains low or unknown. This also requires an adequate reflection in the reporting of gained signals and currently a case-by-case consideration of NanoCarriers is deemed as a way forward. The transferability of the identified signals to identical or similar carrier with deviating cargo and vice versa requires a critical expert judgement and might turn out to be limited.

Knowledge gaps were identified regarding potential risks of NanoCarriers to health and the environment, e.g., toxic potential and fate of the carrier, change in fate/effect of the active substance due to the carrier. Furthermore, there is missing knowledge regarding the energy, water, and land demand for raw material extraction but also during manufacturing, production, transport, use or consumption or regarding the possibility for recycling of raw material or waste arising during production. In contrast, end of life questions, i.e., on recyclability and reusability after use seem not applicable within the context of the discussed applications of NanoCarriers.

With respect to regulatory frameworks, it can be summarised that only a few regulatory frameworks consider the influence of NanoCarriers within their obligations or provide sufficient guidance on how to assess them. Anyhow, this can differ between countries and regulatory areas. Therefore, review of the affected obligations and guidance is needed to identify adaptation needs and to meet them.

Appropriate obligations and guidance for NanoCarriers require suitable test methods. For instance, there is a need to be able to investigate and evaluate the extent to which transport/protection via a carrier can influence the fate and effect of (already well studied) active substances. In turn, this also implies the

development of analytical methods that allow identification and characterization of NanoCarriers in complex matrices.

Based on the discussions and outcomes of the workshop, the following conclusions regarding needed actions can be derived:

With regard to the signals and open questions identified for NanoCarriers during the Workshop, it is recommended that the OECD's WPMN:

- obtains an overview about ongoing research activities and review how this support to fill data gaps and by that to substantiate the identified signals.
- prioritises which application area, questions and signals are of interest of WPMN to
    - further discuss safety and sustainability of NanoCarriers and their applications in order to identify common signals and give joint guidance for similar carrier structures and similar active substance modes of action. Although, information on very specific examples can facilitate that task, discussion should preferably be broadened to more general types or similar groups of NanoCarrier.
    - promote closing information gaps, method development and harmonisation, establishment of assessment guidance; initiate collaboration with committees depending on expertise and competence (e.g. WP on Pesticides).

With respect to a possible future update of the Early4 AdMa, it is recommended that the OECD's WPMN:

- takes up challenges, specific proposals for further questions, and ambiguities identified during the workshop on NanoCarriers.
- identifies and proposes solutions how to deal with questions which need to be answered in a differentiated way for the different building blocks of an AdMa to aid cases with similar challenges like for NanoCarriers (i.e. cases for which signals are driven mainly by one (non-advanced) component). Yet, for an overall assessment the entirety of the AdMa should be assessed in principle.

Regulation/Policy should review affected regulatory frameworks and guidance for possible adaptation needs to appropriately cover NanoCarriers and amend them if necessary. Funding should be provided to close information gaps and to facilitate method development and harmonisation by research projects.

Industry should contribute with their knowledge and expertise to

- close data gaps of various aspects: e.g., structure and functionality of NanoCarriers, behaviour and safety of the NanoCarriers entirety as well as the contribution of the carrier to it, further sustainability issues (e.g., resource demand and waste generation during production, saving of active substance during use).
- support method development and harmonisation

Academia should carry out research that provide answers to open questions, particular to facilitate appropriate risk assessment of NanoCarriers and to help to assess the sustainability of their whole life cycle. Furthermore, academia should participate into method development and harmonisation.

Annex A. Agenda

BETTER POLICIES FOR BETTER LIVES

German Federal Institute for Risk Assessment

OECD's Working Party on Manufactured Nanomaterials (WPMN)

Steering Group on Advanced Materials

WPMN Workshop on Advanced Materials: Nanocarriers

To be held online the 14-15th of June 2023

DRAFT AGENDA

1st DAY - 14 JUNE 2023			
Agenda point	**Title**	**Presenter**	**Time (CET)**
1.	Welcome and Introduction	Kathrin Schwirn, UBA, GER	11:00-11:10
2.	The Early4AdMa system: background and notes on use	Elmer Swart, RIVM, NL	11:10-11:30
3.	Results of a research on types and applications of nanocarriers	Bernd Giese, BOKU, AT	11:30-11:50
4.	Overview of NanoCarrier Synthesis	Duangporn Polpanich, NANOTEC, TH	11:50-12:10
Break: 12:10-13:10			
5.	Nanocarriers in cosmetic: SSbD strategies for stabilising and delivering active ingredients	Anna Costa, CNR-ISTEC, IT	13:10-13:30
6.	Polymer nanocarrier system loaded with a pesticide	Melanie Kah, University of Auckland, NZ	13:30-13:50
Break: 13:50-14:00			
7.	Nanomaterials in Medical Products	Anil Patri, FDA, USA	14:00-14:20
8.	Regulatory challenges & questions - Perspective of the German competent authorities BfR and UBA	Doris Völker, UBA, GER	14:20-14:40
9.	Summary of day 1	Mar Gonzalez, OECD	14:40-15:00

2nd DAY - 15 JUNE 2023			
Agenda point	**Title**	**Presenter**	**Time (CET)**
10.	Welcome back and introduction into day 2	Andrea Haase, BfR, GER	11:30-11:45
11.	**Break out Group Session 1: assessment of NanoCarriers by Early4AdMa step 5**		11:45-13:00
	a) NanoCarrier type for cosmetic application	Chair: Doris Völker (UBA) Rapporteur: Jutta Tentschert (BfR)	
	b) NanoCarrier type for pesticide application	Chair: Hubert Rauscher (JRC) Rapporteur: Michael Hess (UBA)	
	c) NanoCarrier type for medicinal application	Chair: Kathrin Schwirn (UBA) Rapporteur: Anna Pavlicek (BOKU)	
Break: 13:00-13:45			
12.	**Break out Group Session 2: evaluation and formulation of potential follow up actions**		13:45-14:30
13.	a) NanoCarrier type for cosmetic application	Chair: Doris Völker (UBA) Rapporteur: Jutta Tentschert (BfR)	
	b) NanoCarrier type for pesticide application	Chair: Hubert Rauscher (JRC) Rapporteur: Michael Hess (UBA)	
	c) NanoCarrier type for medicinal application	Chair: Kathrin Schwirn (UBA) Rapporteur: Anna Pavlicek (BOKU)	
Break: 14:30-14:45			
14.	Report back to the plenary	By the BOG chairs/rap	14:45-15:45
15.	Summary of the WS	UBA	15:45-16:00
END OF THE WORKSHOP			

Annex B. Participants List

Australia

Nobheetha Jayasekara – Australian Industrial Chemicals Introduction Scheme (AICIS)

Barbara Patsalis – National Industrial Chemicals Notification and Assessment Scheme

Austria

Bernd Moritz Giese – University of Natural Resources and Life Sciences Vienna (BOKU)

Sabine Greßler – University of Natural Resources and Life Sciences, Vienna (BOKU)

Maximilian Kinzl – Environment Agency Austria

Florian Part – University of Natural Resources and Life Sciences, Vienna (BOKU)

Alexander Pogany – Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology

Canada

Wendy Bruce – Health Canada

Kwasi Nyarko – Environment and Climate Change Canada

Costa Rica

Melissa Camacho – Laboratorio Nacional de Nanotecnología

Germany

Harald Bresch – Federal Institute for Materials Research and Testing (BAM)

Andrea Haase – Federal Institute for Risk Assessment (BfR)

Michael Hess – Federal Environmental Agency (UBA)

Kristin Hirte – Federal Environment Agency (UBA)

Andrea Holzwarth – Federal Institute for Risk Assessment (BfR)

Sondra Klitzke – German Environment Agency, (UBA)

Ute Resch-Genger – Bundesanstalt fur Materialforschung und -prüfung (BAM)

Kathrin Schwirn – German Environment Agency (UBA)

Jutta Tentschert – Federal Institute for Risk Assessment (BfR)

Doris Völker – Federal Environment Agency (UBA)

Italy

Maria Alessandrelli – National Institute of Health (ISS)

Isabella De Angelis – National Institute of Health (ISS)

Japan

Masashi Gamo – National Institute of Advanced Industrial Science and Technology (AIST)

Akiko Ohno – National Institute of Health Sciences (NIHS)

Yuhji Taquahashi – National Institute of Health Sciences (NIHS)

Kunihiko Yamazaki – Ministry of the Environment

Akihiko Hirose – Chemicals Evaluation and Research Institute (CERI)

Korea

Min Beom Heo – KRISS

Tae Geol Lee – Korea Research Institute of Standards and Science

Netherlands

Eric Bleeker – National Institute of Public Health and the Environment (RIVM)

Monique Groenewold – National Institute of Public Health and the Environment (RIVM)

Floris Groothuis – National Institute of Public Health and the Environment (RIVM)

Tom Nederstigt – Institute of Environmental Sciences (CML), Leiden University

Cornelle Noorlander – National Institute for Public Health and the Environment (RIVM)

Elmer Swart – National Institute of Public Health and the Environment (RIVM)

Martina Vijver – Institute of Environmental Sciences (CML), Leiden University

New Zealand

Melanie Kah – The University of Auckland

South Africa

Mary Gulumian – North West University

Spain

María Fernández-Cruz – National Institute for Agriculture and Food Research and Technology (INIA), CSIC

José María Navas Antón – National Institute of Agriculture and Food Research and Technology (INIA)

Sweden

Penny Nymark – Institute of Environmental Medicine, Karolinska Institutet

Switzerland

Sabine Frey – FOPH

Michel Wildi – Federeal Environment Office of Switzerland

Thailand

Pavadee Aungkavattana – National Nanotechnology Center (NANOTEC)

Duangporn Polpanich – Nanolife and Cosmeceuticals Research Team, NANOTEC

Waluree Thongkam – National Nanotechnology Center (NANOTEC)

United Kingdom

Fatima Nasser – Department for Environment Food and Rural Affairs (DEFRA)

Olivia Osborne – UK Food Standards Agency

United States

Souhail Al-Abed – US EPA

James Alwood – US EPA

Vladimir Murashov – US NIOSH

Anil Patri – Food and Drug Administration (FDA)

Abhilash Sasidharan – US Environmental Protection Agency (EPA)

European Union

Kirsten Rasmussen – Direcorate Health, Consumers and Reference Materials, EU JRC

Hubert Rauscher – Directorate Health and Food, EU JRC

Juan Riego Sintes – European Commission/DG Joint Research Centre

International Council on Animal Protection in OECD Programmes (ICAPO)

Monita Sharma – PETA Science Consortium International

Business at OECD (BIAC)

Gottlieb-Georg Lindner – Evonik Operations GmbH

Masaaki Okuda – Tayca Corporation

Francis Peters – Consultant (World Business Council for Sustainable Development, WBSCSD)

Martin Reuter – VCI

Jacques-Aurelien Sergent – Solvay

William "Jay" West – American Chemistry Council

Invited Experts

Danail Hristozov – University of Venice, EMERGE

Eva Ehmoser – University of Natural Resources and Life Sciences, Vienna (BOKU)

Jolinde Kettelarij – National Institute of Public Health and the Environment (RIVM)

Aarathi Naidu – Australian Industrial Chemicals Introduction Scheme (AICIS)

Rosita Pang – Australian Industrial Chemicals Introduction Scheme (AICIS)

Joyce R. Araujo – Instituto Nacional de Metrologia, Qualidade e Tecnologia

Fabio Silva – Agência Nacional de Vigilância Sanitária (Anvisa)

Nashira Vieira O'Reilly Cabral Posada – Agência Nacional de Vigilância Sanitária (Anvisa)

Wei Zhong – Australian Government Department of Health and Aged Care

Anna Costa – ISTEC-CNR

Hee-Kyung Na – KRISS

Anna Pavlicek – Institute of Technology Assessment, Austrian Academy of Sciences

Melissa Faria – Leitat Technology Center

Hemda Garelick – IUPAC

OECD Secretariat

Ester Carregal Romero

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