MACRAMÉ

Deliverable Report D1.5

Summary Report about the 2nd Risk Assessors Summit

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[1] R= Document, report (excluding the periodic and final reports); DEM = Demonstrator, pilot, prototype, plan designs; DEC = Websites, patents filing, press & media actions, videos, etc.; DATA =Data sets, microdata, etc.; DMP = Data management plan; ETHICS = Deliverables related to ethics issues; SECURITY = Deliverables related to security issues; OTHER = Software, technical diagram, algorithms, models, etc.

[2] PU = Public, fully open, e.g. web (Deliverables flagged as public will be automatically published in CORDIS project's page); SEN = Sensitive, limited under the conditions of the Grant Agreement; Classified R-UE/EU-R = EU RESTRICTED under the Commission Decision No2015/444; Classified C-UE/EU-C = EU CONFIDENTIAL under the Commission Decision No2015/444; Classified S-UE/EU-S = EU SECRET under the Commission Decision No2015/444

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Acronyms Listed in this Document	
AdMas	Advanced Materials
AI	Artificial Intelligence
ALI	Air-Liquid Interface
AMA	Alveolar Macrophage Assay
ANT	Adult neurotoxicity
AOP	Adverse Outcome Pathway
BBB	Blood-brain barrier (BBB)
DNT	Developmental Neurotoxicity
ECHA	European Chemicals Agency
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable
FIB/SEM	Focused Ion Beam Scanning Electron Microscopy
GFM	Graphene Family Material
GR2M	Graphene-Related 2D Materials
HAXPES	Hard X-ray Photoelectron Spectroscopy
IATA	Integrated Approach to Testing and Assessment
ISO	International Organization for Standardization
MFA	Material Flow Analysis
NAMs	New Approach Methodologies
OECD	Organisation for Economic Co-operation and Development
PLGA	Poly(lactic-co-glycolic acid)
SEM	Scanning Electron Microscopy
SMEs	Small and Medium-sized Enterprises
SSbD	Safe and Sustainable by Design
STED	Stimulated Emission Depletion
TEM	Transmission Electron Microscopy
TG	Test Guideline
WEEE	waste electrical and electronic equipment
WPMN	Working Party on Manufactured Nanomaterials

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EXECUTIVE SUMMARY

The *Joint Regulatory Risk Assessors Summit: Advancing Safety & Sustainability Assessments of Advanced Materials*, hosted at the Organisation for Economic Cooperation and Development (OECD) in Paris and co-organised by four Horizon Europe projects *MACRAMÉ*, *nanoPASS*, *iCare*, and *ACCORDs*, gathered over 80 participants from regulatory authorities, academia, industry, and international organisations. The event aimed to explore how advanced materials can be assessed more effectively for safety and sustainability, and how innovation in materials and products can better align with regulatory expectations.

Over the course of two days (19-20 June 2025), the summit provided a platform to present both current challenges towards test methods applicable to advanced materials and concrete advances from the four EU projects. These included new tools and approaches for material characterisation, *in vitro* and *in silico* methods for hazard assessment, and strategies for life cycle analysis and exposure modelling. Discussions extended beyond regulatory uptake, covering practical implementation, data integration, and cross-disciplinary collaboration.

Breakout sessions invited participants to reflect on physical-chemical characterisation, human toxicology, and environmental fate, as well as overarching cross-cutting themes such as stakeholder engagement, validation processes, and communication challenges. In this context, the draft Informed Recommendations developed within the MACRAMÉ project were presented to stimulate discussions, contributing to broader conversations on test method development, standardisation, and regulatory uptake.

Across sessions, there was strong consensus on several points: the need for pragmatic and cost-efficient test methods, early and continuous dialogue between research and regulation, and improved coordination between stakeholder groups. Digital tools, FAIR data (i.e. Findable, Accessible, Interoperable, Reusable), and artificial intelligence (AI)-based approaches were widely seen as future enablers, though concerns remain regarding validation and acceptance. A frequently raised concern was the lack of sustained and strategically coordinated funding to bridge the gap between innovation and regulatory compliance.

The summit underscored that advancing safe and sustainable innovation of advanced materials depends not only on technical excellence but on openness, shared priorities, and long-term collaboration.

1 Introduction

1.1 Purpose and Context of the Joint Summit

The *Joint Regulatory Risk Assessors Summit: Advancing Safety & Sustainability Assessments of Advanced Materials* took place on 19–20 June 2025 at the OECD Headquarters & Conference Centre in Paris. Organised jointly by four Horizon Europe projects - MACRAMÉ, iCare, nanoPASS, and ACCORDs (see section 1.2) - the summit convened regulators, scientists, industry representatives, and standardisation bodies to address methodological and regulatory challenges in the safety assessment of advanced materials.

The Summit aimed to foster exchange between scientific research and regulatory practice by addressing open questions in the safety assessment of advanced materials. It focused on improving test methods, supporting harmonisation, and fostering uptake of New Approach Methodologies (NAMs) across different stages of material life cycles.

Scheduled directly after the OECD Working Party on Manufactured Nanomaterials (WPMN) meeting, the Summit built on ongoing OECD activities and enabled continuity in expert participation.

The four EU-funded projects provided the scientific basis for the Summit and served as a joint platform to identify shared needs, bring different stakeholders together and support the future development of OECD Test Guidelines (TGs) and standards for advanced materials.

1.2 Hosting Projects: MACRAMÉ, iCare, nanoPASS, and ACCORDs

The Joint Summit was co-organised by four Horizon Europe research projects funded under the call *HORIZON-CL4-2022-DIGITAL-EMERGING-01*. This call supports the development of advanced tools and methods to ensure the safe and sustainable use of nanomaterials and advanced materials, addressing key regulatory and industrial challenges throughout the full material life cycle.

Each of the hosting projects contributes to these goals by delivering practical, validated approaches that enable predictive, high-resolution, and life-cycle-based assessments. Together, they represent a cross-project effort to close the gap between rapid material innovation and reliable regulatory uptake of advanced methods to evaluate new materials.

MACRAMÉ develops advanced methodologies to detect, characterise, and assess the health and environmental risks of advanced materials across their life cycle. The project focuses on inhalable carbon-based advanced materials such as graphene-related materials, carbon nanotubes, and poly(lactic-co-glycolic acid) (PLGA) particles, addressing challenges in complex matrices and exposure scenarios. The project consortium demonstrates the applicability of its methods through five industrially relevant use cases, including applications of advanced materials in water filtration, drug delivery, battery management systems, thermal foils, and lubricants sprays. The goal is to support regulatory uptake through scientific-based approaches that inform the development, standardisation, and harmonisation of test methods, including proposals for OECD TGs and Guidance Documents.

iCare aims to establish an integrated model system to characterise and predict how nanomaterials affect brain health, ultimately supporting toxicity prevention. The project delivers industrially relevant tools and high-resolution imaging procedures to assess changes in nanomaterial morphology, composition, and reactivity in complex biological and environmental matrices. By generating reliable data and advancing standardised test

procedures, iCare contributes to bridging the gap between *in vitro* and *in vivo* testing and supports future regulatory frameworks.

nanoPASS develops and validates an animal-free, resource-efficient technology to predict long-term adverse outcomes of nanomaterials and advanced materials using *in vitro* and *in silico* approaches. It combines high-throughput *in vitro* models, time-resolved microscopy, and quantitative AOP-based modelling, calibrated with *in vivo* data from over 40 benchmark and industrial materials. The project aims to support regulatory uptake through OECD TG proposals and to provide industry with fast, reliable tools for hazard assessment.

ACCORDs aims to establish a practical and reliable characterisation framework that links the physical-chemical properties of 2D nanomaterials, particularly Graphene Family Materials (GFMs), with their toxicological profiles. By combining high-resolution imaging and correlative analysis, the project supports safe and sustainable use of GFMs across their life cycle and in complex environments. Its outcomes will inform standardisation, regulatory guidance, and commercial product development, strengthening Europe's leadership in digital and emerging technologies aligned with the European Green Deal[3].

In alignment with the objectives of the Horizon Europe call, all four projects aim to contribute to standardisation, regulatory innovation, and reliable test method development. Their collaboration at this summit reflects a shared commitment to advancing robust, harmonised tools that support safer, faster, and more sustainable innovation in the field of advanced materials.

1.3 Format and Audience

The Joint Regulatory Risk Assessors Summit was held as a two-day in-person event hosted at the OECD Headquarters & Conference Centre in Paris. The programme combined expert presentations, moderated panel discussions, a poster session, and interactive breakout groups. This structure was designed to promote both structured knowledge exchange and open, cross-sector dialogue.

A total of **97 participants** registered for the summit, representing a broad spectrum of stakeholders. These included representatives from **academia (38), industry (18), regulatory authorities (11), service providers (11), policy makers (6), NGOs (3)**, and others (10). The diversity of participants reflected the summit's goal of fostering dialogue across sectors and expertise. The breakout format in particular enabled focused discussion on priority topics while gathering stakeholder feedback on key MACRAMÉ draft recommendations related to method development, regulatory applicability, standardisation needs, and proposals for future OECD TG and Guidance Document developments.

1.4 Summit Framework and Agenda

The two-day summit was designed to facilitate both scientific exchange and collaborative discussion, fostering targeted interaction between the four Horizon Europe projects and stakeholders from research, regulation, and industry.

Day 1 focused on recent developments in test methods and regulatory challenges related to advanced materials, while Day 2 was dedicated to interactive sessions to gather feedback and define and refine recommendations. Key themes included characterisation, human health and environmental testing, and the applicability of methods across the material life cycle. The

[3] https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/european-green-deal_en; accessed 2025-09-24

agenda was designed to highlight scientific progress across the four projects, support regulatory dialogue, and inform future standardisation efforts. The full programme is provided in ANNEX A1, and a list of the presented posters, including the authors, can be found in ANNEX A2.

2 Summary of Plenary Sessions

2.1 Opening Remarks and Keynote

Welcome by the Host - Mar Gonzalez (OECD)

Mar Gonzalez welcomed participants on behalf of the OECD and expressed her appreciation for the joint efforts of the four Horizon Europe projects. She underlined how the work carried out by these projects directly supports the OECD's mission to develop standards for regulatory purposes. Reflecting on the history of the OECD WPMN, she noted that one of its earliest goals was to identify research needs related to environmental and human health aspects, which lead to the first EU-funded projects set in this area. It took several years to fine-tune developments that could effectively feed into policy and governance processes. Gonzalez emphasised how meaningful it was that the co-hosting projects were designed from the start with regulatory relevance in mind. She concluded by thanking the organisers and expressed hope for further collaboration in the future.

Introduction to the Projects - Steffi Friedrichs (AcumenIST)

Steffi Friedrichs opened her remarks by thanking the OECD Secretariat and emphasised that she was speaking on behalf of all four co-hosting Horizon Europe projects. She introduced the audience to the background and goals of the projects funded under the call *HORIZON-CL4-2022-DIGITAL-EMERGING-01*, noting that they are complementary in scope and united by a common objective: to contribute to the development of regulatory test methods and standards for advanced materials.

Her presentation outlined the key features of each project (see section 1.2 Hosting Projects: MACRAMÉ, iCare, nanoPASS, and ACCORDsfor detailed content):

ACCORDs focuses on cost-effective, correlative imaging-based characterisation for 2D materials; **iCare** integrates advanced imaging and modelling to assess the neurotoxicity of nanomaterials; **nanoPASS** bridges gaps in nanosafety through *in vitro* and *in silico* methods for animal-free prediction of long-term adverse outcomes; and **MACRAMÉ** develops advanced characterisation and hazard assessment methods across five real-world use cases involving three material families with a strong focus on translation into regulatory-relevant outputs, including guidance documents and OECD TG proposals.

While some projects are still ongoing, MACRAMÉ is approaching its conclusion and used the summit as a key opportunity to present draft recommendations and gather feedback to further refine these. Friedrichs concluded by encouraging participants to explore the posters and engage with project partners throughout the summit.

Keynote - Eric Bleeker (RIVM): Needs of Regulatory and Policy Frameworks to Support Safe and Sustainable Advanced Materials

Eric Bleeker (RIVM) opened his keynote by outlining his dual role at the Dutch National Institute for Public Health and the Environment where he is advising policy makers and regulators on chemical safety, and as a participant in EU research projects to ensure that scientific outcomes remain relevant for policy. His presentation focused on insights from the MACRAMÉ project, particularly in relation to how current regulatory and policy frameworks can

address the challenges posed by advanced materials (D1.2 Need Assessment Report of regulatory & policy Frameworks).

He introduced the OECD's working description of advanced materials as rationally designed substances with enhanced properties and functions. However, this is a concept that lacks a clear regulatory definition and is likely to evolve over time, i.e. what we see as advanced today will no longer be regarded as advanced in the future. This fluidity makes it particularly difficult to assess such materials within legislative boundaries that need unambiguous definitions. He highlighted that advanced materials are considered key enabling technologies for Europe's strategic goals, including the Green Deal[4] and the digital transition[5]. However, these innovations often outpace the readiness of regulatory frameworks.

Drawing from lessons learned in the governance of nanomaterials, he pointed to common uncertainties: unclear legal obligations, insufficiently adapted hazard and risk assessment tools, and a lack of harmonised governance structures. Challenges also arise when advanced materials combine multiple functional components, complicating classification, exposure pathways, and life cycle considerations. He reviewed relevant European legislation (e.g., from general product safety and sustainable product design to chemical and waste regulations) noting that while some have been adapted for nanomaterials, advanced materials are not yet explicitly addressed.

He presented key recommendations from MACRAMÉ (D1.2 Need Assessment Report of regulatory & policy Frameworks) across four areas: regulatory integration, life cycle sustainability, FAIR data, and method development. These include the definition of specific groups of advanced materials, identification of regulatory gaps in waste streams, and tools for the practical implementation of Safe and Sustainable by Design (SSbD). He emphasised the need for incentives to promote prospective life cycle assessment, the importance of data provenance and sample traceability to support FAIR principles, and the role of New Approach Methodologies (NAMs) in test development. Combined imaging and analytical approaches were highlighted as essential for quantifying transformed advanced materials in chemical and biological matrices.

He concluded that only with early regulatory alignment, harmonisation, and cross-sector collaboration can the safe and sustainable use of advanced materials be ensured.

2.2 Stakeholder Panel: Challenges in Safety Testing of Advanced Materials

The panel session, moderated by **Thomas Kuhlbusch (BAuA)**, brought together representatives from stakeholder groups including regulatory authorities, international organisations, scientific institutions, industry, and policy makers. The panellists were: **Eric Bleeker (RIVM)**, **Blanca Suarez-Merino (BIAC, Temasol)**, **Virginia Rodriguez (ECHA)**, **Mar Gonzalez (OECD)**, **Tommaso Serchi (LIST)**, and **Anke Jesse (BMUKN)**.

Each panellist began with a brief opening statement, outlining their perspective on the challenges in safety testing of advanced materials. These statements highlighted the need for improved regulatory frameworks, the adaptation of TGs, the translation of new scientific approaches into practice, and the importance of legal and political coherence.

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4 https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/european-green-deal_en; accessed 2025-09-24

5 https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/europe-fit-digital-age/shaping-europes-digital-future_en; accessed 2025-09-24

Key themes and positions included:

- **Regulatory uncertainty and legal fragmentation**: Advanced materials are often not explicitly addressed in current legislation. This creates challenges in managing their increasing complexity and multifunctionality (Rodriguez, Bleeker, Jesse).
- **Need for precise and practical guideline updates**: Instead of revising entire OECD TGs, targeted adaptations, such as improvements to dispersion protocols, dose metrics, or endpoint definitions, can accelerate regulatory uptake and reduce development time (Suarez-Merino).
- **Misalignment between research and regulatory timelines**: The life cycles of research projects are typically much shorter than those required for regulatory standardisation and implementation. Without sustained and well-aligned funding, promising methodological developments risk fading after project completion without reaching their full potential (Serchi, Jesse).
- **Limited readiness for laboratories implementation**: Even validated methods may fail to achieve impact if laboratories are not incentivised or equipped to adopt them. Clear business cases and infrastructure support are needed (Suarez-Merino, Serchi).
- **Importance of life cycle perspective**: To ensure sustainability risk assessments must consider the entire life cycle of advanced materials. This includes transformations that occur during manufacturing, use, environmental exposure, and end-of-life stages (Bleeker, Serchi).
- **Demand for pragmatic, scalable methods**: Regulatory and industrial stakeholders require test strategies that are scientifically robust but also applicable in routine settings. This is particularly important for small and medium-sized enterprises (SMEs) and emerging sectors (Suarez-Merino, Gonzalez).
- **Early engagement and coordination**: Dialogue between researchers and regulators should start during method development. This helps to align expectations and ensures that scientific outputs meet regulatory needs (Friedrichs, Rodriguez, Bleeker).
- **Strategic communication and framing**: To gain public and political support, the value of safety testing must be linked to innovation, competitiveness, and societal benefit. As noted, *"Safety alone does not sell"* (Gonzalez).
- **Call for prioritisation and realism**: A structured, stepwise approach is needed to avoid overcomplexity. Rather than aiming for perfection, stakeholders should define priorities that enable timely and effective regulatory uptake (Serchi, Rodriguez).

The panel concluded with support for fostering collaboration, transparency, and harmonisation. As Eric Bleeker summarised: *"We are still struggling with nanomaterials - let's not make the same mistakes with advanced materials."* Thomas Kuhlbusch closed by emphasising the need to turn scientific foundations into regulatory practice: *"We have the knowledge - now we need to implement it."*

2.3 Characterisation of Advanced Materials in Test Systems and Complex Matrices

INTRODUCTION - DAN HODOROABA (BAM)

This session focused on current approaches and challenges in the physical-chemical characterisation of advanced materials, particularly in complex matrices and test systems. The presentations addressed correlative imaging, *in silico* tools, and method integration for regulatory use.

Hodoroaba opened the session by outlining five key challenges in the characterisation of advanced materials, especially carbon-based nanomaterials in complex matrices. These include the difficulty of identifying carbon and hydrocarbon-based micro- and nanomaterials in carbon-rich environments such as composites and biological systems, and the need to distinguish between various forms like soot, carbon oxides, graphene layers, and carbon nanotubes. He emphasised the high variability and complexity of commercial graphene-based materials, which complicates comparative analysis.

Further challenges involve the correlation of analytical methods, the development of faster and more accurate techniques, and the establishment of standard descriptors and reference materials. Hodoroaba also highlighted the need for a comprehensive characterisation framework that integrates adequate instrumentation with informatics tools to address the physical and chemical diversity of advanced materials. Lastly, he mentioned the importance of large volumes of high-quality data to support material optimisation and enable predictive approaches such as AI and SSbD.

CORRELATIVE MICROSCOPY: IDENTIFYING OBJECTS BY COMBINING TECHNOLOGIES - MAIKE STANGE (BAUA)

Maike Stange presented an advanced correlative microscopy approach for identifying respirable particles and fibres in complex matrices, with a focus on carbon-based materials such as graphene and nanotubes. She outlined the need to combine multiple techniques, including scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDS), Raman spectroscopy, and atomic force microscopy (AFM) to reliably determine key properties such as particle size, morphology, elemental composition, and molecular structure.

A major challenge arises from the fact that many advanced materials, like graphene or synthetic polymers, are carbon-based and difficult to distinguish from their environment using standard techniques. For instance, EDS cannot differentiate soot or defective carbon, making Raman spectroscopy essential for structural characterisation. To improve efficiency and reproducibility, the BAuA team developed two key software tools. FibreDetect[6], an AI-based system, enables automated segmentation, classification, and analysis of particles across SEM images. TiNA, a stage navigation system, allows seamless correlation of results across different instruments by tracking and aligning measurement coordinates.

Together, these tools support faster, reliable and reproducible, and more accurate analysis workflows, facilitating the identification of potentially hazardous particles in real-world samples.

NANOINFORMATICS METHODS AND *IN SILICO* CHARACTERISATION OF ADVANCED MATERIALS FOR PREDICTIVE TOXICOLOGY - VLADIMIR LOBASKIN (UCD)

Vladimir Lobaskin presented how computer-based (*in silico*) methods and informatics can be used to predict how advanced materials behave including whether they are toxic, safe, or

[6] Stobernack, Tobias, et al. "Predicting the morphology-driven pathogenicity of nanofibers through proteomic profiling." *Nano Today* 65 (2025): 102812. https://doi.org/10.1016/j.nantod.2025.102812

useful for certain applications. He raised a number of key questions: which properties make materials biocompatible or harmful, how do materials affect systems in biotechnology, medicine or food, and can we design them to be safe and sustainable from the start?

He explained that *in silico* methods can help, but there are challenges. Advanced materials are highly diverse, their systems are complex and large, and we often lack the data and models needed to simulate their behaviour at interfaces. In particular, good "force fields" - mathematical models for simulating particle interactions - are still missing for many materials.

Lobaskin introduced the concept of "InChI for Nano"[7], a tool that helps describe materials by their size, shape, composition, and structure. These descriptions (known as "descriptors") allow researchers to compare materials and classify them. He showed how simulations can be used to predict biological effects, such as toxicity, based on these descriptors and how these tools are already being used in projects like SmartNanoTox, NanoSolveIT, and nanoPASS.

He stressed that computer models are only as good as the data used to train them. If poor or incomplete data is used, the predictions will be unreliable. Therefore, it is essential to carefully assess and improve data quality before using it in AI models.

In summary, he showed that informatics and AI can strongly support the design of safer and more sustainable materials. However, this requires reliable data, harmonised descriptors for complex materials, and tools to assess and manage data quality.

Advanced physical-chemical characterisation & correlation of results with different Methods for GFMs - Dan Hodoroaba (BAM)

Dan Hodoroaba presented strategies for the advanced physical-chemical characterisation of graphene-related 2D materials (GR2M), with a focus on defining descriptors, comparing methods, and supporting standardisation. He outlined three key categories of descriptors: morphology, including lateral size, thickness and shape; chemistry, such as elemental composition, oxygen-to-carbon ratio and impurities; and structure, for example number of layers or flake arrangement.

A major challenge lies in the reproducible measurement of these descriptors across different laboratories. In an inter-laboratory comparison under the "Versailles Project on Advanced Materials and Standards" (VAMAS) initiative, assessments of graphene oxide flake size using SEM varied significantly depending on factors like sample preparation and image analysis approach. This highlighted the need for certified reference materials and harmonised measurement protocols to ensure consistent and comparable results.

Within the ACCORDs project, a structured documentation system called the "Analysis Passport" has been developed. It captures all relevant steps in material characterisation, e.g. from synthesis and handling to measurement and data evaluation, and helps correlate descriptors across various analytical methods.

Hodoroaba concluded that building a standardised and traceable characterisation framework is essential for regulatory applications of GR2M. Such frameworks also contribute directly to the development of safe and sustainable by design strategies.

Discussion Highlights

The discussion following the talks highlighted the need for a pragmatic and prioritised approach to method development. Instead of aiming for perfection, participants emphasised focusing on relevant endpoints, grouping materials, and accepting a degree of uncertainty to

[7] Lynch, Iseult, et al. "Can an InChI for nano address the need for a simplified representation of complex nanomaterials across experimental and nanoinformatics studies?" *Nanomaterials* 10.12 (2020): 2493. https://doi.org/10.3390/nano10122493

enable faster regulatory use. The concept of "absolute safety" was rejected in favour of realistic, context-specific assessments of safety and sustainability.

High-throughput methods were seen as important, but their application to real-world samples remains challenging. Many laboratories lack the resources for complex analyses, underlining the need for accessible, standardised methodologies. AI was recognised as a valuable tool for material design and analysis, provided data quality is ensured, and models can be validated or benchmarked. The discussion concluded with a call for clear communication, regulatory alignment, and methods that reflect both scientific and societal needs.

2.4 Human Health Models to Predict the Safety of Advanced Materials

INTRODUCTION - BLANCA SUAREZ-MERINO (TEMASOL)

Session III (ANNEX A1) focused on human health models to assess the safety of advanced materials, particularly in light of the growing push to reduce and replace animal testing in both the EU and the US. Chair Blanca Suarez-Merino opened the session by outlining key scientific and regulatory challenges in adapting existing test systems to the complexity of advanced materials.

She highlighted challenges across various biological levels, including the interaction of nanomaterials with cellular receptors, effects at the organ level such as channel clogging or uneven distribution in organ-on-chip systems, and issues at the whole-organism level related to biological barriers and exposure routes. Suarez-Merino emphasised that current models were mostly developed for soluble chemicals and need to be critically re-evaluated for advanced materials, especially in the context of material transformation and dosimetry.

DEVELOPMENT AND APPLICATION OF *IN VITRO* MODELS TO ASSESS NEUROTOXICITY OF ADVANCED MATERIALS, THE ICARE APPROACH - ERNESTO ALFARO-MORENO (INL)

Ernesto Alfaro-Moreno introduced the iCare project's approach to assessing neurotoxicity of advanced materials, motivated by increasing evidence that nanoparticles, including pollution-derived magnetite (Fe_3O_4), can reach the human brain and may contribute to neurodegenerative diseases such as Parkinson's disease.

The iCare strategy combines high-resolution imaging, *in vitro* models, and *in silico* tools to characterise material interactions in biologically relevant systems. Key technologies include fluorescence microscopy (Stimulated Emission Depletion (STED), MINFLUX), high-content imaging assays, and multiplexed biochemical readouts. These enable the detection of aggregation, inflammation, genotoxicity, oxidative stress, and epigenetic changes induced by materials such as graphene, graphene oxide, silver, and silicon dioxide.

Advanced *in vitro* systems, including blood-brain barrier (BBB) models and mini-brain organoids, are central to the project. They offer physiologically relevant platforms to study permeability, cellular uptake, and potential damage caused by nanomaterials. Integration of real-time sensors with the BBB model is underway to allow continuous, label-free monitoring of neurotoxicity biomarkers across these models.

Alfaro-Moreno concluded that while the test systems are still under development, the approach demonstrates how realistic, high-throughput, and multiparametric assays can contribute to safer material design and early hazard identification in the context of brain health.

IN VITRO TESTING OF ADVANCED MATERIALS FOR EFFECTS ON THE LUNG - MARTIN WIEMANN (IBE)

Martin Wiemann presented advanced *in vitro* models being developed and refined in MACRAMÉ to assess the effects of inhalable advanced materials on the lung. The choice of a suitable model depends largely on the size and deposition behaviour of the particles, with different

models targeting either bronchial or alveolar regions. He introduced the Alveolar Macrophage Assay (AMA), which uses serum-free rat-derived cells and allows for imaging-based, dose-related assessment of cytotoxicity. Measured endpoints include lactate dehydrogenase (LDH) release, lysosomal damage, TNF-alpha, and reactive oxygen species, and results show correlation with short-term *in vivo* inhalation studies.

Wiemann emphasised that the preparation of test materials is critical. Depending on their life cycle stage, materials such as incinerated or abraded graphene composites must be processed and filtered to obtain respirable fractions. He described various exposure systems for air-liquid interface (ALI) cultures, including semi-ALI pipetting, the Vitrocell Cloud system for aerosolised suspensions, and PowderX for dry powder delivery. A newly developed fluidizer enables the exposure of cells to aerosolised fibrous materials.

Comparative testing showed that models such as AMA, AlveolAir, and MucilAir responded differently, underlining the importance of model selection and complementarity. A multi-laboratory validation study within MACRAMÉ is currently underway to support OECD recognition of the AMA.

Wiemann concluded that *in vitro* lung testing of advanced materials requires tailored preparation steps, appropriate exposure methods, and model systems matched to particle characteristics and deposition behaviour.

VALIDATING ANIMAL-FREE IN-VITRO-LEARNED DIGITAL TWIN FOR QUANTITATIVE INFLAMMATION PREDICTION FROM ACUTE TO CHRONIC CONDITION ADDRESSING 4 OECD TGS - JANEZ ŠTRANCAR (INFINITE)

Janez Štrancar presented a digital twin approach developed by Infinite Biotech to predict inflammation caused by advanced materials over time. Based on *in vitro* data and backscattering microscopy, the system models time-dependent biological responses and addresses four OECD TG (403, 412, 413, 452) without animal testing.

The method uses early key event markers, such as neutrophil fractions, to simulate mode-of-action and progression from acute to chronic effects. It enables prediction from a single exposure and detects differences between materials with identical composition but varying structure.

Validated with benchmark materials, the system shows high reproducibility and prediction accuracy. Štrancar positioned it as a promising NAM, offering ethical, cost-efficient, and mechanistically informed safety assessment.

ADVANCED INSIGHTS INTO CELLULAR INTERNALISATION OF 2D MATERIALS - DAMJANA DROBNE (UNIVERSITY OF LJUBLJANA)

Damjana Drobne presented recent advances from the ACCORDs project on how 2D materials such as graphene oxide interact with biological systems at the cellular level. She explained that different imaging techniques are required depending on the scale and nature of the question. While standard light microscopy and electron microscopy provide complementary views, focused ion beam scanning electron microscopy (FIB/SEM) offers a unique capability: it allows researchers to cut into individual cells and observe the internal localisation of nanomaterials with high spatial resolution.

This approach is particularly valuable for verifying whether particles like graphene are truly internalised, and for differentiating between actual cellular uptake and sample preparation artefacts. Although molecular-level artefacts are a known issue in biological imaging, Drobna noted that at the level of material localisation within cells, artefacts are less prominent. Still, careful validation using different preparation methods and complementary techniques is essential.

A major point raised was the need to make imaging data FAIR. Drobne advocated for the creation of shared image databases, with links to preparation protocols, metadata, and annotation tools. This would not only improve reproducibility and transparency but also enable future use of AI to analyse large image-based datasets.

The presentation also connected imaging observations to biological mechanisms relevant to risk assessment, such as lysosomal accumulation, persistent inflammation, and particle-induced acute-phase responses. These processes are part of established adverse outcome pathways (AOPs) like AOP237 (substance interaction with lung cell components leading to atherosclerosis) and AOP302 (lung surfactant function inhibition leading to decreased lung function), and are relevant for developing predictive *in vitro* systems and digital models. Overall, the use of correlative imaging supports the development of mechanistic, material-specific safety profiles that inform regulatory decision-making.

Discussion Highlights

The brief discussion following the presentations focused on the challenges of distinguishing real material uptake from imaging artefacts. Participants agreed that advanced microscopy techniques such as FIB/SEM offer valuable insights, but complementary methods like cryo-TEM may be necessary to confirm whether observed structures truly represent internalised nanomaterials. The importance of making imaging data FAIR was underlined, with suggestions that annotated image datasets could be used to train AI models and support deeper pattern recognition. Questions were also raised about material identity and form, for example whether observed structures were truly graphene or graphite fragments. Finally, the biological relevance of these findings was reinforced by linking intracellular particle accumulation to inflammatory responses and potential downstream health effects.

2.5 Ecotoxicity, Release, Fate and Environmental Testing of Advanced Materials

Introduction - Iseult Lynch (University of Birmingham)

Iseult Lynch introduced the session by outlining key challenges in environmental testing of advanced materials. She noted that dispersing these materials realistically is difficult, as stabilisers may affect environmental relevance and homogeneity is hard to maintain without any biological macromolecules, especially in soil or aquatic systems. Exposure conditions are also challenging, with uncertainty about whether direct contact or leachate testing is more appropriate for advanced materials.

Effect assessment is complicated by particle-specific interference such as scattering, shading, or binding of signalling molecules or nutrients, which can distort standard endpoints. Many ecotoxicological assays were not designed for particulate materials, and organisms may actively avoid exposure under the laboratory test conditions. Lynch illustrated these points using Daphnia-based test systems developed by her team and from the literature.

Expanding the use of standardised *in vitro* ecotoxicity assays - Alberto Katsumiti (GAIKER)

Alberto Katsumiti presented recent work on adapting and extending *in vitro* ecotoxicity assays using fish cell lines as alternative methods for the safety assessment of advanced materials. While over 4,000 human cell lines exist, only a small number of standardised fish cell lines are currently available. OECD TG 249, based on the rainbow trout RTgill-W1 line, represents an important milestone but remains underused.

Katsumiti demonstrated how dispersion protocols and exposure systems must be tailored for complex materials like graphene or nanoplastics. Using artificial freshwater enriched with

natural organic matter, his team developed low-energy methods to stabilise suspensions and reduce artefacts such as radical formation. They applied these protocols across multiple projects, including MACRAMÉ and iCare, to assess endpoints related to inflammation, neurotoxicity, and membrane integrity.

Advanced screening approaches included the use of different fish cell types (gill, liver, gonadal, brain), co-culture models, and extended exposures up to 28 days. Results indicate that neurotoxic effects may be more pronounced than hepatotoxicity or general cytotoxicity, highlighting the need to select appropriate markers and systems based on tissue-specific sensitivity. Katsumiti concluded by emphasising the potential of fish-based NAMs for regulatory use, provided that dispersion, dosimetry, and interference issues are properly addressed.

C. elegans in Neuro-Nanosafety: A Translational Bridging Model and NAM Tool - Nivedita Chatterjee (INL)

Nivedita Chatterjee introduced *Caenorhabditis elegans* (*C. elegans*) as a versatile alternative model for both human and environmental toxicology. As a nematode with a fully mapped genome and high homology to human genes, *C. elegans* offers unique advantages for predictive toxicology. Its relevance is further supported by its role in three Nobel Prize–winning discoveries and its recent inclusion in emerging standardisation efforts, such as ASTM E271-01 and initiatives under ISO. Chatterjee presented *C. elegans* as a bridging model, since it is relevant both for human toxicity and for ecotoxicity assessments, with applicability to adverse outcome pathways including developmental neurotoxicity (DNT) and adult neurotoxicity (ANT). The model allows the evaluation of phenotypic endpoints such as lifespan, locomotion and neuron integrity, as well as molecular endpoints including gene expression. Experimental workflows include developmental exposure from the egg stage through adulthood, with specific attention to glutamatergic and dopaminergic neurodegeneration.

Chatterjee also introduced high-throughput and high-content analysis platforms that integrate microfluidics, robotics and AI to track behavioural and neuronal changes in *C. elegans* in real time. A case study using silver nanoparticles demonstrated differential neurotoxicity in Alzheimer-like mutant strains compared to wild type.

Chatterjee called for greater awareness and standardisation of *C. elegans*–based assays, particularly in the regulatory space. While some participants were unfamiliar with the model's capabilities, she emphasised its potential to complement or reduce reliance on mammalian models, especially when combined with "humanised genetic strains" and mechanistic endpoints.

Material Flow Analysis: A basic pillar for regulatory risk assessment and beyond - Luis Mauricio Ortiz Galvez (EMPA)

Luis Mauricio Ortiz Galvez presented Material Flow Analysis (MFA) as a foundational tool for understanding how advanced materials move through and are released from technical systems across their life cycle. By applying transfer coefficients and mass balance modelling, MFA can identify release points during production, use, and disposal, and support the development of realistic exposure scenarios.

Ortiz Galvez illustrated this with the MACRAMÉ use cases, such as graphene oxide in water filters and PLGA-based inhalable antibiotics, highlighting how materials are transformed or released in different environmental compartments. MFA outcomes are essential for estimating predicted environmental concentrations, which feed into environmental fate modelling and risk assessment.

Ortiz Galvez stressed that MFA also contributes to sustainability assessments by supporting life cycle inventories and linking risk assessment with life cycle assessment. Despite uncertainties

in input data and challenges in modelling transformations, MFA is increasingly recognised as a key method for supporting SSbD strategies.

DISCUSSION HIGHLIGHTS

The discussion following these presentations explored practical challenges in testing advanced materials across diverse media and exposure systems. One recurring issue was interference caused by the matrix itself. For instance, materials embedded in silicones may not contact cells effectively due to flotation or phase separation. This raises questions about what observed effects truly indicate toxicity or physical artefacts. Participants emphasised the difficulty of interpreting results, especially when comparing the same material in different environments such as air, water, or biological media.

Several participants noted that existing TG often fail to reflect real-world exposure conditions, especially for materials undergoing transformation or used in complex formulations. This led to calls for broader endpoints beyond conventional measures like Daphnia immobilisation, suggesting alternatives such as assessment of heart rate or lipid accumulation.

The discussion also addressed the need for more robust quality control and minimum standards in test development. With commercialisation of advanced materials outpacing regulatory tools, participants debated whether definitions based on size or structure (e.g. nanomaterials vs. advanced materials) are still useful. Instead, participants suggested that more emphasis should be placed on function, exposure context, and realistic use conditions. Regarding test systems, it was noted that some existing protocols may lack sensitivity or specificity for advanced materials, particularly in fish or invertebrate models. Creative assay development and validation, including the use of "humanised" model organisms, was seen as essential to fill these gaps and support regulatory readiness.

Finally, the role of MFA was discussed as a way to support environmental risk assessment and circular economy goals. Probabilistic modelling approaches and expert judgement were presented as tools to deal with data uncertainties, especially in the context of second-use materials and recycling streams. Participants agreed that closer collaboration with industry, recyclers, and regulators will be crucial to developing relevant and scalable testing strategies.

2.6 Challenges and Solutions in Testing Industrial Relevant Samples Along the Material Life Cycle

INTRODUCTION TO THE CHALLENGES BY THE CHAIR - IZTOK URBANČIČ (IJS)

Iztok Urbančič introduced the session by highlighting key challenges in testing advanced materials across their life cycle. He pointed out that sampling, handling, characterisation, and data analysis each bring uncertainties, especially as materials change during use or recycling. Addressing these steps in an integrated way is essential for reliable and relevant risk assessment.

REPRESENTING MATERIAL LIFE CYCLES IN REGULATORY-RELEVANT DATA - THOMAS EXNER (7P9)

Thomas Exner discussed the importance of unambiguous identification and characterisation of the material state as part of the data structure and traceability of its origin and transformation steps when assessing advanced materials across their entire life cycle. He emphasised that understanding a material's properties and of differences of seemingly identical materials might not be possible from the final product alone (based on an acceptable level of physicochemical characterisation) but information on the production process, transformation steps, and intended use must also be considered. Data gaps at any stage can hinder exposure assessment and regulatory decision.

To address this, Exner introduced the concept of study design maps[8] (formerly introduced as instance maps). These allow structured tracking of data provenance, mapping where and how a material has been studied, and linking it to relevant life cycle stages. He stressed that harmonisation and integration of such data are essential for developing safe-and-sustainable-by-design strategies, which can be made less time consuming and distributed across all data producers based on the structure provided by the maps.

A discussion followed on the alignment of these maps with emerging tools such as Digital Material / Product Passports. While their terminology may differ, both approaches aim to create transparent, consistent documentation of material properties and use contexts. Exner concluded that this level of clarity is critical to bridge information between innovation, regulation, and market requirements.

Relevance and applicability of alternative (eco)toxicity methods in industrial settings - Elise Morel (TEMASOL)

Elise Morel presented efforts under the iCare project to develop an Integrated Approach to Testing and Assessment (IATA) for predicting the neurotoxicity of advanced (nano)materials. The motivation stems from the lack of harmonised classification for neurotoxicants under current EU regulations, which still rely heavily on animal testing. The proposed IATA combines *in vitro* assays, *in silico* tools, and read-across strategies to offer a mechanistic, vertebrate-free alternative that is more adaptable to early innovation stages. Morel illustrated the relevance of the iCare framework for industry through use cases involving battery casings and graphene materials. She also highlighted the importance of testing materials across their life cycle, including intermediate and end-of-life stages by using abrasion, swabbing, or sonication methods. Since real-time sampling often yields too little material, simulated processes are preferred to ensure sufficient and reproducible quantities for testing.

The iCare IATA supports hazard classification, labelling, and read-across, and is designed to inform digital product passports, life cycle assessments, and future SSbD regulations. Morel concluded that validated, scalable testing strategies like this can help to close regulatory gaps and better reflect the realities of advanced materials in industrial applications.

In depth analysis of commercial functionalised graphene nanoplatelets towards structure-activity relationships - Jörg Radnik (BAM)

Jörg Radnik presented results from the ACCORDs project focusing on structure–activity relationships for functionalised graphene nanoplatelets. His talk highlighted the importance of detailed chemical and morphological characterisation throughout the production process, from powders to suspensions and inks, to better understand the materials' behaviour, function, and safety in application.

Using surface-sensitive techniques such as X-ray photoelectron spectroscopy (XPS) and hard X-ray photoelectron spectroscopy (HAXPES), the team identified changes in the oxygen-to-carbon ratio and the loss of fluorine during material processing. These transformations influence how graphene interacts with its matrix and ultimately affect product performance. Even though these materials often make up only a small fraction of the final product, they can strongly determine properties such as conductivity and surface reactivity.

Radnik emphasised the challenges in analysing mixtures, especially in matrices such as water, and the need for standardised methods and reliable reference materials. He called for a coordinated effort across research and industry to improve data quality and reproducibility. Building robust structure-activity relationships will require sustained funding, increased

[8] Punz, Benjamin, et al. "Instance maps as an organising concept for complex experimental workflows as demonstrated for (nano) material safety research." *Beilstein Archives* 2024.1 (2024): 26. https://doi.org/10.3762/bjnano.16.7

awareness, and the integration of operando analysis that links material structure to function in real time.

SAMPLING AND TESTING INDUSTRIALLY RELEVANT MATERIALS: POSSIBILITIES AND PITFALLS - CHRISTINA ISAXON (LUND UNIVERSITY)

Christina Isaxon presented practical insights from nanoPASS on collecting and characterising airborne and industrially relevant particles across different stages of the material life cycle. These included engineered nanoparticles such as cobalt nickel (CoNi) and nickel molybdenum (NiMo) alloys, cement particles, dental materials, micro- and nanoplastics, and emissions from waste electrical and electronic equipment (WEEE) recycling. The diversity of materials and industrial settings posed challenges for sample retrieval, reproducibility, and downstream analysis.

High-volume samplers were, in most cases, used to collect airborne particles under real-world conditions, followed by careful post-processing (e.g., sonication in methanol, drying under nitrogen) to prepare them for testing. However, these preparation steps can alter particle properties such as surface area or magnetic behaviour, introducing uncertainty. This highlights a common trade-off between precision and real-world relevance.

To assess health effects, the collected samples were tested using a validated *in vitro* and *in silico* models predicting lung inflammation from acute to chronic exposure. Interestingly, this model does not require detailed material characterisation, as biological response data alone serve as inputs.

Isaxon also reflected on the broader challenge of collaborating with industry. While access to real samples is essential for regulatory relevance, companies often hesitate to engage due to concerns over liability, intellectual property, or unintended findings. Participants stressed the need for early-stage collaboration, transparency, and trust to build meaningful industry-science partnerships.

PROGRESS TOWARDS STANDARDISATION OF TOXICITY TESTING FOR SSBD OF GFMS - MARY GULUMIAN (NWU)

Mary Gulumian presented progress made in the ACCORDs project toward standardising toxicity testing for SSbD of Graphene Family Materials (GFMs). She began by revisiting the OECD's definitions of Safe-by-Design and SSbD, emphasizing that safety considerations must be integrated early in the innovation process and across the full product life cycle including synthesis to disposal.

A key focus of her presentation was on the unique surface properties of GFMs, such as defect density, C/O ratio, and the ability to generate carbon-based free radicals. These surface characteristics are critical for determining how GFMs interact with biological systems and the environment, yet they are often insufficiently accounted for in standard *in vitro* toxicity tests. Gulumian underlined that even common sample preparation steps like sonication can significantly alter surface properties, which in turn may lead to erroneous toxicity results.

She pointed out that most existing toxicity assays were not developed with materials like GFMs in mind and often suffer from interference effects. Given the biodurability of GFMs, short-term assays may also fail to predict long-term or organ-level effects. Therefore, toxicity testing must consider not only chemical composition but also structural and morphological features such as edge defects and synthesis-induced alterations.

As part of ACCORDs, efforts have been made to identify the surface properties most relevant to toxicity and to establish correlations between those features and observed biological effects. This includes exploring label-free assay systems, which are less prone to interference and more suited for establishing structure-activity relationships. Ultimately, these advances aim to

support the development of validated, reproducible, and standardised methods tailored for GFMs and to provide innovators with guidance on integrating safety and sustainability from the earliest stages of material design.

DISCUSSION HIGHLIGHTS

The discussion following this group of presentations focused on the practical challenges of testing advanced materials, particularly the importance of surface properties and how they change in real-life conditions. Testing in water alone was seen as insufficient, as materials behave differently in biological or environmental media. Endotoxin testing and consideration of corona formation were highlighted as essential steps in early assessments.

Several participants emphasised that methods used in early innovation do not need to be fully validated, but they must be fit for purpose and provide reliable, relevant results. There was a call to clearly distinguish between standardised and formally validated methods, and to ensure that test approaches remain flexible enough to support SSbD.

A recurring concern was how to account for changes in materials across their life cycle. Projects like ACCORDs are working to develop guidance that addresses this. Finally, the discussion underscored the importance of early and open collaboration with industry. While concerns about intellectual property can limit cooperation, trust-building and clear mutual benefits were seen as key to successful partnerships.

2.7 Recommendations on Needs for TG & Standard Developments

EUROPEAN TEST METHOD AND VALIDATION STRATEGY - MONIQUE GROENEWOLD (NL)

Monique Groenewold presented the European Test Method and Validation Strategy on behalf of the Dutch Ministry of Infrastructure and Water Management. The strategy responds to the need for reliable, regulation-ready testing methods that are capable of capturing realistic biological effects of chemical substances and materials. It aims to support regulatory risk assessment while reducing reliance on animal testing.

Key initiatives included a technical workshop held in Amsterdam in December 2024 and a high-level policy conference in January 2025, bringing together 70 stakeholders from 15 countries, including regulators, industry, NGOs, and international organisations such as the OECD. These events identified the limited availability of validated methods from research and stressed the importance of coordinated prioritisation and funding across Europe.

As a follow-up, a pre-task force was launched to draft a governance model for EU-wide coordination. The initiative promotes shared responsibility, cross-sector integration, and better use of existing infrastructure. A broader stakeholder consultation is planned for autumn 2025, with a final proposal expected by early 2026.

INTRODUCTION TO THE INFORMED RECOMMENDATIONS ON NEEDS FOR TG AND STANDARD DEVELOPMENT - ELISABETH HEUNISCH (BAUA)

Elisabeth Heunisch introduced the MACRAMÉ project's Informed Recommendations on the Needs for TG Development and Method Standardisation. These recommendations aim to support the creation of OECD TG, Guidance Documents, and technical standards that are tailored to the regulatory assessment of advanced materials and products containing them.

The recommendations pursue three overarching objectives: to highlight specific standardisation needs, to enable regulatory testing that is relevant and feasible for stakeholders (including regulators, industry, and academia), and to provide a clear, forward-looking framework for method development. Developed through an iterative process, by combining expert insights and stakeholder consultation, they are intended as an output to promote long-term regulatory preparedness.

Twelve individual recommendations were presented, grouped across key areas of safety assessment. These include:

- Physical-chemical characterisation of advanced materials
- Detection and quantification of advanced materials in biological matrices
- Testing of multi-component advanced materials
- Predicting toxic potential of fibres based on physical-chemical properties
- Sample preparation for safety testing of advanced materials
- Controlling and describing the dosimetry of advanced materials
- Testing and assessment strategies for risk evaluation based on exposure points
- Identification of releases of (transformed) advanced materials along the life cycle
- Influence of physical transformations in the environment on risk profiles
- Standardised release testing of advanced materials over their life cycle
- Use of life cycle information as part of material characterisation
- Sharing of safety-relevant information across the life cycle

The draft recommendations were subject to initial public consultation and formed the basis for structured feedback sessions during the breakout discussions at the Joint Regulatory Risk Assessors Summit (see Chapter 3). Finalisation and publication are foreseen by the end of the MACRAMÉ project.

3 Breakout Sessions

3.1 Topics and Group Setup

The summit featured six parallel breakout sessions, each composed of 10 to 14 participants. The sessions were thematically structured to reflect the key domains of the MACRAMÉ Informed Recommendations, covering:

- Physical-Chemical Characterisation I
- Physical-Chemical Characterisation II
- Human Toxicology I
- Human Toxicology II
- Environmental Toxicology and Fate I
- Environmental Toxicology and Fate II

While the MACRAMÉ recommendations served as the foundation for discussion, the sessions also addressed broader, cross-cutting issues relevant to the safety assessment and regulatory integration of advanced materials. Participants explored both specific recommendations and overarching themes such as stakeholder engagement, standardisation processes, and regulatory alignment.

Each session was guided by a shared set of questions designed to elicit practical and strategic insights:

- What is your experience with the different stakeholder groups (as presented in the introduction to the breakout sessions)? Are they playing the roles you think they should play? Are there other important groups?
- What are the incentives for stakeholders to participate in the standardisation process? How can different groups be motivated? What could you contribute (as an expert, institution, or team)? What would you need to take up these recommendations?
- How can we encourage the development of tools and methods required for regulatory compliance of advanced materials? How can we ensure these are integrated into the standardisation process (e.g., characterisation techniques, NAMs, or life cycle analysis)?
- Are the recommendations the right ones? Are there gaps? Is anything missing that is essential for advanced materials or life cycle considerations?

The feedback from all sessions was presented in a final plenary discussion and will be used to refine the MACRAMÉ Informed Recommendations. Reports from the individual breakout sessions are provided in ANNEX A3.

3.2 Reflections and Panel Discussion from Breakout Sessions

Each breakout sessions held during the Joint Regulatory Risk Assessors Summit concluded with a brief report by a rapporteur who presented the key findings in a dedicated breakout session. The written summaries provided by the groups are included in the ANNEX A3 of this report. While the sessions were initially intended to provide feedback on the MACRAMÉ Informed Recommendations, in line with the set of questions above the actual discussions often took a broader and more strategic perspective. Instead of focusing on specific recommendations, participants addressed overarching themes such as stakeholder roles, incentives for standardisation, and pathways to regulatory uptake.

The following section summarises the main discussion points, grouped by the thematic focus of the breakout sessions:

PHYSICAL-CHEMICAL CHARACTERISATION

Discussions in the physical- and chemical characterisation groups revealed ongoing uncertainty about the definition and scope of advanced materials. This was particularly relevant in relation to borderline categories such as microplastics. Participants emphasised the need for improved terminology and better approaches to grouping materials in order to ensure regulatory clarity. The discussion on stakeholder roles focused on improving communication and explaining uncertainty more effectively. This was seen as a way to enable long-term trust and broader engagement. Industry participation was considered important but remained limited. Practical engagement models, such as collaborative measurement initiatives, were suggested to involve industry actors in method development. Incentives for engagement included access to validated protocols, the potential to reduce long-term uncertainty, and opportunities for cost savings. Participants also stressed the need to involve smaller actors such as contract research organisations and small and medium-sized enterprises.

HUMAN TOXICOLOGY

In both human toxicology groups, participants identified a gap between the timelines and expectations of scientific research and those of regulatory processes. A consistent message

was the need for a clearer and more structured regulatory framework to support the implementation of new approach methodologies. This includes transparent acceptance criteria and guidance for method validation. Participants discussed the risks faced by researchers, such as limited recognition of scientific work in regulatory standards, and by industry, including the possibility that a non-animal test method may not be accepted. There was general agreement that mutual understanding of the two stages of method development and validation is essential. Suggestions included compiling dossiers to support regulatory acceptance and combining multiple types of assays to demonstrate reliability. The importance of clear and consistent terminology was emphasised, particularly for complex endpoints such as neurotoxicity. The idea of a coordinated network for method development and application was proposed as a useful step forward.

Environmental Toxicology and Fate

The environmental groups pointed to a need for better alignment of stakeholder roles in the standardisation process. Regulators tend to focus on hazard assessment and the practical usability of TG, while researchers are often unaware of regulatory constraints and priorities. End-users such as industry or laboratories are not consistently involved in developing test methods. Participants saw incentives for participation across all groups. These included early access to regulatory expectations for industry, scientific recognition and funding opportunities for researchers, and improved tools and guidelines for regulators. To support compliance, the group suggested promoting methods that address key technical challenges such as dispersion and transformation. Participants also emphasised the need for integrative, cross-disciplinary collaboration to build shared language and align activities across different scientific and regulatory communities. A better understanding of what each stakeholder group needs and values was seen as critical for establishment of the relevance and acceptance of future TG.

Overall, the breakout discussions reflected a shared ambition to improve coordination, uptake, and practical relevance of test methods for advanced materials. Although the MACRAMÉ Informed Recommendations were used as a starting point, participants mainly the explored broader questions about structure, process, and collaboration that must be addressed to ensure effective implementation.

4 Way Forward and Closing Statements of the Summit

Thomas Kuhlbusch (BAuA) opened the closing session by reaffirming that the Joint Summit represented a collaborative effort from the outset and that such joint engagement will be essential to move forward. One key building block for the future is the continued development and refinement of test methods that are fit for risk assessment purposes, particularly in relation to advanced materials and their life-cycle-specific challenges. He also emphasised that this technical work must be complemented by broader efforts such as the Malta Initiative. This voluntary initiative brings together stakeholders to define shared priorities for OECD TG development and to promote a science-based regulatory landscape that supports a safe and sustainable Europe.

Kuhlbusch summarised the summit's key messages, including the need for clearly articulated, science-based regulatory tools, effective communication to highlight the urgency of these efforts, and targeted networking to identify and respond to the concrete needs of regulators and researchers. The MACRAMÉ-informed recommendations and the stakeholder breakout group discussions were presented as important steps toward this goal.

Looking ahead, Steffi Friedrichs (AcumenIST) announced further joint activities including the third online Joint Workshop on Harmonisation and Standardisation of Test Methods, scheduled for 3-4 November 2025. In addition, follow-up projects under Horizon Europe's Cluster 4 were already underway with projects launched in January 2024.

Mar Gonzalez (OECD) closed the meeting by thanking all participants and emphasising the collective spirit that defined the summit. She acknowledged the "avalanche of knowledge" shared over the two days and noted that, while many challenges remain, all contributions were clearly aligned toward a common goal. Her final message was one of encouragement: to maintain the momentum, continue the collaboration, and build on the progress made together.

5 Summit Outcomes

The Joint Regulatory Risk Assessors Summit highlighted a collective commitment to improving the safety and sustainability assessment of advanced materials through collaborative, science-based approaches. Across presentations, discussions, and breakout sessions, several key outcomes and shared priorities emerged:

- The need for pragmatic test method development that is cost-efficient, reproducible, and applicable across the advanced materials life cycle.
- The importance of aligning research with regulatory needs early to ensure that methods can feed into OECD and EU frameworks efficiently.
- A call for improved communication and shared understanding between scientists, regulators, and industry including definitions and data formats towards regulatory/stakeholder expectations.
- Prioritisation and standardisation were mentioned as critical to support implementation and adoption of methods.
- Digital tools, FAIR data, and AI-based analysis were frequently mentioned as future enablers, but concerns remain about validation and regulatory acceptance.
- A recurring concern was the lack of sustained, strategically coordinated funding to bridge the gap between research, validation, and regulatory uptake, risking the delay or stagnation of promising methods.

The Joint Summit, organised by the four EU-funded projects, reinforced that meaningful progress in the field depends not only on technical excellence, but on shared purpose, openness, and continued collaboration across disciplines and sectors.

ANNEX

ANNEX A1 – AGENDA OF THE JOINT REGULATORY RISK ASSESSORS SUMMIT

Table 1: Agenda of the Joint Regulatory Risk Assessors Summit – Advancing Safety & Sustainability Assessments of Advanced Materials Day 1.

19th June 2025		
Time	**Topic**	**Chair/Presenter**
Session I	**Introduction and Setting the Scene**	Thomas Kuhlbusch (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin; BAuA)
09:00 – 09:30	Welcome to the OECD	Mar Gonzalez (Organisation for Economic Co-operation and Development; OECD)
	Welcome by organisers Short introduction to MACRAMÉ, iCare, nanoPASS and ACCORDs	Steffi Friedrichs (AcumenIST)
09:30 – 09:40	*Keynote* Needs of regulatory and policy frameworks to support safe and sustainable advanced materials	Eric Bleeker (National Institute for Public Health and the Environment; RIVM)
09:40 – 10:30	*Panel discussion* What are the issues in safety testing of advanced materials?	Chair: Thomas Kuhlbusch (BAuA) Panellists: Eric Bleeker (RIVM) Blanca Suarez-Merino (Business and Industry Advisory Commission at OECD; BIAC) Virginia Rodriguez (European Chemicals Agency; ECHA) Mar Gonzalez (OECD) Tommaso Serchi (Luxembourg Institute of Science and Technology; LIST) Anke Jesse (Bundesministerium für Umwelt, Klimaschutz, Naturschutz und nukleare Sicherheit; BMUKN)
10:30 – 11:00	Tea, Coffee & Posters	
Session II	**Characterisation of Advanced Materials in Test Systems and Complex Matrices**	Dan Hodoroaba (Bundesanstalt für Materialforschung und -prüfung ; BAM)
11:00 – 11:05	Introduction to the challenges by the chair	Dan Hodoroaba (BAM)
11:05 – 11:20	Correlative Microscopy: identifying objects by combining technologies	Maike Stange (BAuA)
11:20 – 11:35	Nanoinformatics methods and *in silico* characterisation of advanced materials for predictive toxicology	Vladimir Lobaskin (University College Dublin; UCD)

19th June 2025		
Time	**Topic**	**Chair/Presenter**
11:35 – 11:50	Advanced physico-chemical Characterisation & Correlation of Results with different Methods for GFMs	Dan Hodoroaba (BAM)
11:50 – 12:20	Discussion	
12:20 – 12:30	Poster pitches	
12:30 – 13:30	Lunch & Posters	
Session III	**Human Health Models to Predict the Safety of Advanced Materials**	Blanca Suarez-Merino (TEMASOL)
13:30 – 13:35	Introduction to the challenges by the chair	Blanca Suarez-Merino (TEMASOL)
13:35 – 13:50	Development and Application of *In Vitro* Models to Assess Neurotoxicity of Advanced Materials, the iCare approach	Ernesto Alfaro-Moreno (International Iberian Nanotechnology Laboratory; INL)
13:50 – 14:05	*In vitro* testing of advanced materials for effects on the lung	Martin Wiemann (IBE)
14:05 – 14:20	Validating animal-free in-vitro-learned digital twin for quantitative inflammation prediction from acute to chronic condition addressing 4 OECD TGs	Janez Strancar (Infinite)
14:20 – 14:35	Advanced insights into cellular internalisation of 2D materials	Damjana Drobne (University of Ljubljana; UL)
14:35 – 14:50	Discussion	
14:50 – 15:00	Poster pitches	
15:00 – 15:30	Tea, Coffee & Posters	
Session IV	**Ecotoxicity, Release, Fate and Environmental Testing of Advanced Materials**	Iseult Lynch (University of Birmingham; UoB)
15:30 – 15:35	Introduction to the challenges by the chair	Iseult Lynch (UoB)
15:35 – 15:50	Expanding the use of standardised *in vitro* ecotoxicity assays	Alberto Katsumiti (GAIKER)
15:50 – 16:05	*C. elegans* in Neuro-Nanosafety: A Translational Bridging Model and New Approach Methodology (NAM) Tool	Nivedita Chatterjee (INL)
16:05 – 16:20	Material Flow Analysis: A basic pillar for regulatory risk assessment and beyond	Luis Mauricio Ortiz Galvez (Eidgenössische Materialprüfungs- und Forschungsanstalt; EMPA)
16:20 – 16:50	Discussion	
16:50 – 17:00	Poster pitches	
Session V	**Poster Session**	
18:00 – 20:00	Cocktails	

Table 2: Agenda of the Joint Regulatory Risk Assessors Summit – Advancing Safety & Sustainability Assessments of Advanced Materials Day 2.

20th June 2025		
Sessions	**Topic**	**Presenter**
Session VI	**Challenges and Solutions in Testing Industrial Relevant Samples Along the Material Life Cycle**	**Iztok Urbančič (Jozef Stefan Institute University of Ljubljana; IJS)**
09:00 – 09:05	Introduction to the challenges by the chair	Iztok Urbančič (IJS)
09:05 – 09:20	Representing material life cycles in regulatory-relevant data	Thomas Exner (Seven Past Nine ;7P9)
09:20 – 09:35	Relevance and applicability of alternative (eco)toxicity methods in industrial settings	Elise Morel (TEMASOL)
09:35 – 09:50	In depth analysis of commercial functionalised graphene nanoplatelets towards structure-activity relationships	Jörg Radnik (BAM)
09:50 – 10:05	Sampling and testing industrially relevant materials: Possibilities and Pitfalls	Christina Isaxon (Lund University)
10:05 –10:20	Progress towards standardisation of toxicity testing for SSBD of GFMs	Mary Gulumian (Northwest University ;NWU)
10:20 – 10:50	Discussion	
Session VII	**Recommendations on Needs for TG & Standard Developments**	Sean Kelly (Nanotechnology Industries Association; NIA)
10:50 – 11:00	European Test Method and Validation Strategy	Monique Groenewold (NL)
11:00 – 11:15	Introduction to the informed recommendations on needs for TG and standard development	Elisabeth Heunisch (BAuA)
11:15 – 11:30	Tea, Coffee & Posters	
11:30 – 13:00	*Breakout group discussion* Physical-Chemical Characterisation I Physical-Chemical Characterisation II Human Toxicology I Human Toxicology II Environmental Toxicology and Fate I Environmental Toxicology and Fate II	 Elisabeth Heunisch (BAuA), Maike Stange (BAuA) Vasile-Dan Hodoroaba (BAM) Anna Pohl (BAuA) Martin Wiemann (IBE), Blanca Suarez-Merino (TEMASOL) Tommaso Serchi (LIST), Iseult Lynch (UoB) Thomas Exner (7past9), Alberto Katsumiti (GAIKER) Eric Bleeker (RIVM), Christian Seitz (AIST)

20th June 2025		
Sessions	**Topic**	**Presenter**
13:00 – 14:00	Lunch & Posters	
14:00 – 14:45	*Panel discussion* With one representative from each breakout group Including a discussion with the audience	Chaired by Sean Kelly (NIA)
Session VIII	**Way Forward and Closing of the Meeting**	**Thomas Kuhlbusch (BAuA)**
14:45 – 14:55	Setting the scene, Malta Initiative and key messages of summit	Thomas Kuhlbusch (BAuA)
15:05 – 15:15	New projects and next steps	Thomas Kuhlbusch (BAuA)
15:15 – 15:30	Closing of the meeting by OECD	Mar Gonzalez (OECD)

ANNEX A2 – POSTERS PRESENTED AT THE JOINT REGULATORY RISK ASSESSORS SUMMIT

Table 3: Posters Presented and Contributing Authors

Poster Title	Authors	Affiliations
Analytical Tools in Material Science: Unveiling Order in Graphene Oxide Synthesis Through A Design of Experiment and Chemometric Strategy Based on Tour's Method	Francesco Pellegrino, Andrea Rossi, Elena Corrao, Eugenio Alladio, Damjana Drobne, Vasile-Dan Hodoroaba, Kerstin Jurkschat, Veno Kononenko, Loay Akmal Madbouly, Paul Mrkwitschka, Sara Novak, Jörg Radnik, Špela Saje, Rosangela Santalucia, Fabrizio Sordello	University of Torino; University of Ljubljana; BAM; Oxford University
AOP237: Particle-Induced Acute Phase Response Leading to Atherosclerosis	Ulla Vogel, Claudia T. Gutierrez, Jorid B. Sørli, Pernille H. Danielsen, Niels Hadrup, Anne T. Saber	National Research Centre for the Working Environment, Denmark
AOP302: Lung surfactant inhibition as a predictor for lung toxicity	Jorid B. Sørli, Sreyoshee	National Research Centre for the Working Environment, Denmark
Correlative chemical imaging to reveal the nature of different commercial graphene materials	Robert Schusterbauer, Mario Sahre, Paul Mrkwitschka, Thorid Lange, Amaia Zurutuza, Elliot Jones, Ievgen Donskyi, Jörg Radnik, Vasile-Dan Hodoroaba	BAM (Germany); Freie Universität Berlin; Graphenea; Haydale Ltd (UK)
Detection of Advanced Materials in Cells by High Resolution Imaging Methods	Antje Vennemann, Daniel Breitenstein, Oliver Gräb, Alexander Köhrer, Svenja Seiffert, Lucie Chupin, Nazende Günday-Türeli, Martin Wiemann	IBE R&D Institute for Lung Health (Germany); Tascon GmbH (Germany); BASF SE (Germany); Carbon Waters (France); My Biotech GmbH (Germany)
Establishing realistic dry aerosol exposure conditions at the Air-Liquid Interface (ALI) with an *in vitro* lung model	Aline Chary, Charlotte Stoffels, Marina Azuaga Moreso, Carla Ribalta Carrasco, Dirk Brossell, Rob Vandebriel, Tommaso Serchi	LIST (Luxembourg); BAuA (Germany); RIVM (Netherlands)
Establishment of human-based *in vitro* models to evaluate neurotoxicity	Itziar Polanco Garriz, Endika de la Iglesia, Ander Miner, Felipe Goñi de Cerio, Alberto Katsumiti	GAIKER Technology Centre, BRTA, Spain
Extending the use of standardised *in vitro* ecotoxicity models to support neurotoxicity testing	Mikel Isasi-Vicente, Vanesa Benito, Felipe Goñi de Cerio, Alberto Katsumiti	GAIKER Technology Centre, Basque Research and Technology Alliance (BRTA), Spain
Freshwater planarians as bioindicators for nanoparticles toxicity assessment	M. Bernardeschi, M.C. Lefevre, N. Chatterjee, G. Ciofani	Istituto Italiano di Tecnologia (Italy); International Iberian Nanotechnology Laboratory (Portugal)
From short-term to long-term exposures: expanding the capabilities of *in vitro* ecotoxicity models	Mikel Isasi-Vicente, Rita Ewela Ojo, Isabel Rodríguez-Llopis, Vanesa Benito, Felipe Goñi de Cerio, Alberto Katsumiti	GAIKER Technology Centre, BRTA, Spain

Poster Title	Authors	Affiliations
Holistic, reliable and practical Characterisation Framework for GFMs, a correlated approach including Imaging-based techniques	Daniel Fernandez, Damjana Drobne, Sara Novak, Francesco Pellegrino, Dan Hodoroaba, Mary Gulumian, Alexander Doolin, Barry Hardy, Eugenia Valsami-Jones, Kertin Jurkschat, Meike Van Der Zande	Fundación Idonial; University of Ljubljana; BAM; North West University; Haydale; Edelweiss Connect; University of Birmingham; Oxford University; Wageningen Food Safety Research
HTS tests for toxicity assessment and their adaptation to nanomaterials	Dorota Kwiatek, Natalia Karczewska, Joanna Kosman, Francesca Canyelles Font, Adrian Rufli, Jacek L. Kolanowski	Institute of Bioorganic Chemistry, Polish Academy of Sciences; Adam Mickiewicz University (Poland); Victor Chang Cardiac Research Institute (Australia)
Inhalation Exposure and Cytotoxicity of Graphene-Enabled Advanced Materials: Focus on End-of-Life	Govind Gupta, Jimmy Vernaz, Antje Vennemann, Maike Stange, Ziting Wang, Sarah Zehnder, Bernadett Boda, Lucie Chupin, Vera M. Kissling, Daniel Breitenstein, Martin Wiemann, Samuel Constant, Peter Wick, Tina Buerki-Thurnherr	Empa (Switzerland); IBE R&D Institute for Lung Health (Germany); BAuA (Germany); Carbon Waters (France); Toscon GmbH (Germany); Epithelix (Switzerland)
Knowledge Infrastructure supporting image-based characterisation of 2D graphene materials	A. A. Abdelwahab, P. P. Ankli, R. Bugiel, A. Logachov, D. Drobne, S. Novak, E. Kranjc, S. Saje, F. Pellegrino, E. Alladio, F. Sordello, E. Corrao, D. Hodoroaba, J. Radnik, P. Mrkwitschka, L. Madbouly, Y. Akdemir, M. Gulumian, V. Wepener, C. Andraos, K. Boodhia, E. Jones, A. Doolin, K. Leuchtenberg, E. ValsamiJones, C. Rocca, B. Ibrahim, D. Singh, S. Chakraborty, K. Jurkschat, C. Johnston, M. VanDerZande, D. Fernandez, P. Queipo, C. Clifford, B. Hardy	Edelweiss Connect (Switzerland); University of Ljubljana (Slovenia); Università di Torino (Italy); BAM (Germany); North West University (South Africa); Haydale (UK); University of Birmingham (UK); University of Oxford (UK); Wageningen Food Safety Research (Netherlands); Fundación Idonial (Spain)
Raman Spectroscopy and X-ray Photoelectron Spectroscopy of Commercial Functionalised Graphene	Loay Akmal Madbouly, Paul Mrkwitschka, Jörg M. Stockmann, Heinz Sturm, Alexander Doolin, Vasile-Dan Hodoroaba, Jörg Radnik	BAM (Germany); Haydale Ltd (UK)
Reconstituted Primary Human Bronchial Epithelial Cell Model to Study the Effects of Advanced Materials on Mucociliary Clearance-Mediated Innate Immunity in Lungs	Ziting Wang, Jimmy Vernaz, Nikolaos Tagaras, Bernadett Boda, Tina Buerki-Thurnherr, Giacomo Reina, Vera M. Kissling, Samuel Constant, Govind Gupta, Peter Wick	Empa (Switzerland); Epithelix Sàrl (Switzerland)
Sampling Challenges in Real Industrial Settings: Lifecycle Insights from EV battery casings and ATEX Tanks	M. Martínez-Junquera, E. Villaro, J. Gómez	Avanzare Innovacion Tecnologica S.L, Spain

Poster Title	Authors	Affiliations
The Alveolar Macrophage Assay (AMA): Validation by Interlaboratory Comparison and Testing of Advanced Materials	Antje Vennemann, Oliver Gräb, Emanoela Tha, Lan Ma-Hock, Robert Landsiedel, Aline Chary, Pamina Weber, Tommaso Serchi, Martin Wiemann	IBE R&D Institute for Lung Health (Germany); BASF SE (Germany); Luxembourg Institute of Science and Technology (LIST)
The fluidizer as a means of air exposure to advanced materials	Rob Vandebriel, Carla Ribalta Carrasco, Evert Duistermaat, Renée de Boeck, Jolanda Vermeulen, Véronique de Bruijn, Elisabeth Heunisch, Anna Pohl, Dirk Broßel	RIVM (Netherlands); BAuA (Germany)
The power of FIB-SEM: Visualising Material internalisation	Špela Saje, Sara Novak, Francesco Tatti, Damjana Drobne	University of Ljubljana (Slovenia); FEI Italia (Italy)
Towards realistic lung exposure *in vitro*: an alveolar model approach with MACRAME Control Materials	Aline Chary, Marina Azuaga Moreso, Charlotte Stoffels, Servane Contal, Tommaso Serchi	LIST (Luxembourg)
Validating animal-free in-vitro-learned digital twin for quantitative inflammation prediction from acute to chronic condition addressing 4 OECD TGs	Iztok Urbančič, Hana Kokot, Tobias Stöger, Pernille Høgh Danielsen, Ulla Vogel, Tilen Koklič, Janez Štrancar	Jožef Stefan Institute (Slovenia); Helmholtz Zentrum Munich (Germany); NFA Copenhagen (Denmark); Infinite Biotech (Slovenia)

ANNEX A3 – REPORTS OF THE BREAKOUT SESSIONS AT THE JOINT REGULATORY RISK ASSESSORS SUMMIT

BREAKOUT GROUP ON PHYSICAL-CHEMICAL CHARACTERISATION I

What is your experience with the different stakeholder groups (presented in the introduction to the breakout group discussion)? Are they playing the role you think they should play? Are there other important groups?

The discussion revealed that there is a large gap in the understanding of regulatory bodies and stakeholders with regard to the handling and importance of test guidelines and standardisation procedures. Institutes and companies are often underrepresented in the summits, as this is often seen as an unnecessary expense, as is participation in round robin tests and conferences. In addition, a new product can usually not be held back for economic reasons until all regulations have been checked and evaluated, as the previous procedure was mainly based on approval procedures and compliance with previous regulations and the unique selling point on the market must be utilised for innovations. As long as no clear benefit is seen for the stakeholders here, they will probably not become intensively involved in the future either. To date, regulatory bodies have tended to be viewed as obstacles to industrial production and growth, as a great deal of time is spent discussing details, but few clear statements are made in the broader context. Teaching institutions such as universities and other educational establishments also need to rethink the importance of regulation and standardisation. So far, this has been a completely insignificant subject area and is therefore not included in the curriculum. This means that there is no training of specialised regulatory personnel, even if the stakeholders were willing to invest money and provide this as a position in their companies.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (e.g. as an expert, your institution, your group)? What would you need to pick these recommendations up?

The advantages of intensive communication and cooperation with regulatory structures need to be better communicated to stakeholders by experts. Communication has to become easier and faster both between regulators and companies and within companies. Furthermore, cooperation with industry should be sought before involving regulatory authorities.

Discussions on adapting to the state of the art should take place early on and quickly so that the industry does not suffer any disadvantages from working with regulators due to rapid advances in the state of the art. Clear, indisputable definitions must be provided so that the industry can comply with them.

The principle of FAIR data use and data storage must be implemented in both directions by regulators and industry to ensure good cooperation and rapid exchange of information.

Accordingly, educational institutions should place greater emphasis on teaching regulatory knowledge and quality management. The validation of data and results should also be a priority, and time and money should be allocated for this purpose. In addition, universities and research institutions, as well as the publication platforms they aim to use, should focus on characterising the materials used. Good scientific practice must once again be brought to the fore and not be overshadowed by scaremongering and media hype. At present, regulatory publications are often less frequently cited and appear in less glamorous journals. The focus

must once again be placed on health issues and occupational medicine. In this context, it is important to standardise terminology in order to avoid misunderstandings. Building understanding and mutual trust is key between regulators and industry so that industry is not reinforced in its fear that its products will be banned and that cooperation with regulators will put it at a disadvantage.

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

It should be clarified and understood that the classification of a material as, for example, an AdMa or nanomaterial must not have a direct negative impact on the product and its marketing, even though this has been the perception to date, with quality criteria and measurement methods appearing very arbitrary and often being determined by a small number of individuals and their agenda. Also, discussions should not focus on one or two materials but include a larger variety of materials. In addition, there are sometimes differing statements in qualitative and quantitative exposure models. But still animal testing is said to be the most efficient way for exposure testing. Fundamental harmonisation and standardisation of measurement methods would have to be applied here, and new methods and developments should be communicated more quickly and simply, as after several years of regulatory evaluation, the materials mentioned can no longer be described as 'advanced', as well as the use of animal testing is more and more detested. Improvement only can be achieved by FAIR data use as well. The harmonisation of terminology has to become a mayor goal. Additionally, the climate change puts time pressure on the inventions of AdMas and therefore long regulatory decision making can no longer be waited for.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

The informed recommendations accurately reflect the problems associated with Test Guideline developments and the standardisation of test methods and provided a good basis for discussion. The problems are well addressed, challenges have been identified and the necessary further steps have been formulated. Including all stages of the life cycle of a particular material are important for further risk assessment and environmental toxicity.

However, all of these recommendations once again only offer vague possibilities, even though stakeholders have repeatedly called for clearer and simpler implementation. Overall, the stakeholder management should be overthought and adapted.

BREAKOUT GROUP PHYSICAL-CHEMICAL CHARACTERISATION II

The discussion started with a more general concern about the need for a definition of "advanced materials" and whether the recommendations on test method development are advanced material specific.

The diversity of advanced materials and the importance of simple and pragmatic methods were discussed as well as the difference between pristine advanced materials and advanced-materials-containing products along their lifecycle. Furthermore, the inclusion of micro- and

nanoplastics in the group of advanced materials and therewith the recommendations was discussed. It was mentioned that nanoplastics was proposed to the WPMN and that it was not taken up with the reasoning that it is not manufactured as such. The CBC is not addressing the topic and a corresponding workshop will be held. The international differences were mentioned (e.g. US).

It was discussed whether the term "advanced (nano)materials" would be better suited to address the nano-specific properties. However, the term is objective whereas the term "advanced" can be very subjective. And also other materials can be "advanced" but do not fall under the nanomaterial definition (e.g. advanced alloys, ceramics). It was concluded that the field will stay dynamic.

What is your experience with the different stakeholder groups (presented in the introduction to the breakout group discussion)? Are they playing the role you think they should play? Are there other important groups?

The experience was shared that many industrial companies do not want to be listed in nanomaterial-related lists in order to avoid being associated with nanomaterials and their potential risks. Maybe this will change with advanced materials. The reluctance to nanomaterial-associated products by many consumers also depends on the practical advantage seen or not seen by the consumers.

Communication is key in order to explain and inform about benefits, uncertainties, and risks of use of nanomaterials and advanced materials, but also mitigation of these risks. Good communication needs to be achieved not only within the respective communities but also into the general public. The responsibility and possibility to achieve good communication is not only in the field of regulatory risk assessment but goes beyond this field. Especially communicating uncertainty is very tricky. Especially, uncertainty decrease can be difficult to explain (e.g. in case of COVID the general public did not understand the decrease of uncertainty with time). In addition, real good communication needs appropriate funding and resources.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (e.g. as an expert, your institution, your group)? What would you need to pick these recommendations up?

First, the incentives for using nanomaterials were discussed. Nano carriers were mentioned as example for having benefits for the delivery of pharmaceuticals, cosmetics and pesticides.

Then, the discussion was shifted towards the incentives to participate in the standardisation process. Standardisation decreases uncertainty and saves money on a long-term perspective. The test should be accepted by other stakeholders as well. This is one of the incentives to use OECD Test Guidelines as they fall under the mutual acceptance of data agreement once the tests are performed together with following the rules for Good Laboratory Practice. Accredited laboratories can play a crucial role here.

Research as well as funding for regulatory research along the life cycle should motivate the stakeholders to change their business-as-usual. Industry needs to be trained and informed about what is being developed in research. Governmental bodies should not only implement existing methods but also need training and structures that facilitate the further development.

It was discussed that having a label would be beneficial for companies. In addition, subsidizing testing of nanomaterials and advanced materials for especially small and medium size enterprises was suggested as potential tool to support the testing of these materials.

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

EDX was mentioned as a method that is already validated and works quite well and efficient for the quantification of the elemental composition of graphene-based materials. IAM-I was discussed as partnership that could contribute to the test method development and standardisation. In addition, a survey among the industry could help identifying their needs. This is exemplary done in South Korea in form of a so-called "Measurement club" between industry and governmental institutes (meeting twice/year) having the same long-term goal. A communication channel is highly needed, however, it is time consuming.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

Due to the recent approval of the OECD WPMN Guidance on Sample Preparation and Dosimetry the recommendation 6 Controlling and Describing the Dosimetry of Advanced Materials was mentioned to be maybe not so relevant any more. A last point discussed was AI and the need to evaluate possibilities to regulate it.

BREAK OUT GROUP HUMAN HEALTH I

What is your experience with the different stakeholder groups (presented in the introduction to the break out group discussion)? Are they playing the role you think they should play? Are there other important groups?

There was a general feeling that exchange between academia and regulators was not dynamic enough. Academia innovates because they are driven by scientific publications with high impact factors, but this is not generally aligned with needs from a regulatory perspective. Most academics in the group had not been in contact with regulators and in this summit, regulators seem to be under-represented. Industry associations were seen to cover the gap between regulators and academia, since the have academia also as members and they are part of regulatory discussion groups.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (as expert, your institution, your group? What would you need to pick these recommendations up?

Within the group we had partners which were familiar with standardisation activities such as South Africa, Japan, Thailand and Switzerland. Most of these activities had been performed in the context of EU projects, and in one case, the activity was stop once the project ended. The standardisation activities were split as follows: South Africa (Mary Gulumian, academia), Thailand (Uracha Ruktanonchai, National Laboratory), Japan (Masahi Gamo, academia), Switzerland (Cordula Hirsh from Empa and Blanca Suarez-Merino from TEMASOL).

Currently the main incentive from industry to pursue standardisation activities is either to own technology to be able to license it to a Contract Research Organisation (CRO) or to develop

cheaper alternatives to in vivo experimentation (as it was the case of the Alveolar Macrophage Assay). In both cases investors had to be found and were represented by industry. In the case of Japan there was a motivation to adapt a short-term in vivo inhalation study to nanomaterials, so it could be further used for NAM validation. Switzerland highlighted that they had the capability to sponsor validation projects though currently none was on-going.

One incentive mentioned was recognition, academic laboratories live on international recognition, which allowed them to get grants, standardisation activities have no recognised authors, even their contribution to this workshop did not lead to their name being linked to any publication, and this, from an academic perspective, does not help them getting grants. If authorship could be included in a standard, things would be viewed different from an academic perspective. Hence, once a novel approach is developed, and published, from an academic perspective there is no incentive to continue to validation.

If there is a clear business niche, some companies could pick the tests up and sponsor standardisation activities as long as they could see revenue later (some examples were provided).

To pick the recommendations up they need to be aligned with academic research interests. Academic groups are generally specialised in particular topics where they build reputation through publications. During the summit we have seen some examples on interesting models developed by academia and research centres, but regulators are generally not aware of this type of research and academia has no interest in validation. To pick those topics up regulatory research may need to be better recognised, for now it does not seem to be innovative enough to attract scientists. Scientists are also on short term contracts and move around, which makes it more complicated to follow particular tests. In any case it boils down to the lack of recognition of standards regarding authorship (example for this was this summit).

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

This was seen as a catch 22 situation, if we have no methods to guarantee safety of novel materials, companies may not invest due to regulatory uncertainty, however, to understand the gaps we need novel materials undergoing regulatory processes. The OECD AdMa group and their case studies was recognised as a good step forward to understand where we need to focus, in a collaborative way (so costs are spread among participants of the groups). It would be important to give publicity to case study findings through the right channels (good reputation journals, OECD reports). At the end of the day all goes down to funding, besides industry, perhaps Member States could provide some of their internal funding to regulatory research. One final comment included the current stakeholders being engaged, since some of the running activities (like the work on the work on the Test Method Validation Strategy) was not known to some attendants. And the topic came up again, if we are just talking to ourselves and failing to reach key stakeholders.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

Young scientists in the group are not familiar with what is needed for AdMa, they don't follow those discussions. Regarding regulators, the recommendations were well accepted, but none

were really familiar with life cycle needs. In general one point which was missed from the recommendations was to add an extra topic on when a particular test makes sense to be used in a particular situation, eg if a material makes a gel upon exposure with water, it does not make sense to apply ecotoxicity assays to that particular material, sine the results will be based on mechanical actions, rather that biological pathways. So, some examples on when one a particular test may be waived due to not being appropriate would be welcomed.

BREAKOUT GROUP HUMAN HEALTH II

What is your experience with the different stakeholder groups (presented in the introduction to the breakout group discussion)? Are they playing the role you think they should play? Are there other important groups?

It was discussed that there is misalignment among stakeholders—regulators, researchers, industry—on expectations, timelines, and priorities. REACH is vast, and academic approaches often miss regulatory relevance. The dialogue is complex and fragmented, even within agencies, and mutual understanding needs to be improved. OECD experts voiced a criticism that academics don't approach the OECD/regulators in the appropriate way: The regulatory question should be at the heart, and the method development needs to be targeted to a specific end-point. Validation should also be end-point-specific. However, there is increasing knowledge in the stakeholder groups also on how to approach one another.

Basic science researchers pursue novelty, but there's a missing layer of applied expertise such as testing/metrology labs. An additional educational pathway, e.g., master studies programme in measurement science, could fill this gap, especially if tied to contract research organisations (CROs). However, jobs must exist for these graduates. Automation (e.g., liquid handling) can reduce operator error but requires system-level thinking. Two phases are needed: identifying sources of error, then applying knowledge to regulation. Institutions like LIST/EMPA might help translate science into legislative actions, but only if there's regulatory demand—industry typically acts only when required to by law.

When responsibility is unclear, the precautionary principle dominates, often halting innovation and discouraging industry engagement due to regulatory uncertainty.

Proving "absence of effect" is a philosophical problem and is inherently difficult. There is a need to define what counts as "safe enough" from a regulatory perspective. When can we draw the line that we have sufficient evidence that something is safe enough? *In silico* methods offer early insights and should guide testing strategies efficiently, even if experimental confirmation is eventually needed.

Some agencies (e.g., FDA, EMA) allow early engagement with regulators, improving alignment and uptake. Others (e.g., EFSA, ECHA) restrict pre-submission dialogue due to conflict-of-interest concerns. OECD's BIAC offers early involvement, but the obligation to share all data—including failed studies—discourages participation.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (e.g., as an expert, your institution, your group)? What would you need to pick these recommendations up?

There is little incentive (e.g., institutional key performance indicators (KPIs)) for participation in ring trials or inter-lab comparisons (ILCs) in many research-focussed organisations, although this varies between institutions—some see regulatory engagement as societal impact, others

deprioritise it. International standards, like ISO for Nanoparticle Tracking Analysis (NTA), paved the way for research to feed into standardisation.

In countries like Thailand, regulators rely on academic labs where the technical infrastructure resides. Industry co-funds testing to meet national or OECD requirements. However, globally, industry resists duplicate testing and needs confidence that NAMs will be accepted by regulators before transitioning away from so-called gold standard animal tests.

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

A strong call to adapt regulation to enable use of NAMs is needed to shift regulation away from validation of NAMs based on the comparability of the result to those from animal tests. Animal tests are, at best, 60% predictive of impacts in humans, yet regulators expect NAMs to be 95% predictive. NAMs must be judged on performance, not concordance with flawed *in vivo* methods. Using well-understood benchmark materials (e.g., quartz, diesel, asbestos) can demonstrate NAM relevance. Initiatives like One Substance One Assessment and artificial intelligence (AI) tools can increase efficiency and data throughput.

US EPA have already evaluated the agreement between *in vivo* and NAMs based on scatter of *in vivo* data – 0.55-0.7%. Anything above this means overfitting data so predictions for substances not in training set will be very off.

Currently only a sub-sampling of submitted dossiers can be evaluated. AI can help here as well (e.g., efforts in PARC to automate assessment of dossiers with only the final step being performed by experts reduces time for checking dossier compliance / completeness from 2 hours to 5 minutes pre dossier). In 20 years from now, assuming NAMs are accepted – e.g., immune tests are faster and cheaper – will there be a driver to lower the tonnage trigger for testing of chemicals? When we can test faster, we should be able to test far more substances and then have a much greater understanding of our exposure risks.

Genotoxicity and inflammation are endpoints with NAMs already available. These can be used to define acceptable effect thresholds. With faster, cheaper testing, we could lower tonnage triggers and expand chemical safety evaluations. Regulatory frameworks must evolve now to accommodate these innovations.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

These recommendations are progressing in the right direction – generally and specifically for advanced materials. A key consideration regarding transformations of advanced materials is whether grouping and read-across based on the pristine / as-synthesised forms makes sense or whether we need to revise the basic premise. This was not discussed at the breakout but will be presented in Deliverable 3.5 from MACRAMÈ.

BREAK OUT GROUP ENVIRONMENTAL TOXICOLOGY AND FATE I

What is your experience with the different stakeholder groups (presented in the introduction to the break out group discussion)? Are they playing the role you think they should play? Are there other important groups?

Stakeholder groups are gradually coming together, working as a team to address the challenges in Environmental toxicology of nanomaterials and advanced materials (AdMa). There's a growing understanding of what the industry can contribute, alongside a better grasp of the overall process. Industry representation is predominantly driven by material producers, who are facing increasing regulatory pressures (i.e. Network for Safety and sustainability of Chemicals and materials, NSC).

However, different stakeholders still have varying opinions on which types of nanomaterials are most relevant—whether lab-produced or those found in the environment. While much of the research focuses on mechanisms, which are largely studied in universities, there is an ongoing effort to integrate more regulatory relevance into academia. For instance, topics like AOPs (Adverse Outcome Pathways) in ecotoxicology are being increasingly incorporated into university curricula, partly due to funding opportunities and greater acceptance of regulatory science. This is further supported by the overlap with human toxicity research, particularly in areas such as endocrine disruption, although there is still room for further emphasis.

Additionally, there needs to be more focus on the entire lifecycle and environmental impact, which is an area of great interest to industry. This is being driven in part by societal pressure and consumer demand for more sustainable practices.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (as expert, your institution, your group? What would you need to pick these recommendations up?

Stakeholders may be motivated to engage in the standardisation process by the recognition—such as having their names listed—when their method is adopted as an official test method, thereby enhancing its visibility and practical application. However, a key challenge is addressing the significant time frame—typically 5 to 10 years—from method development to formal test guideline establishment. Stakeholders need clarity on who would be willing to contribute and how they can engage in this long process.

Funding for test guideline development is also a crucial incentive, as it supports the resources required for the standardisation effort. One question to consider is whether the burden of this process should be distributed across more stakeholders and, if so, who these additional contributors might be.

While nomination processes are working to some extent, round robin tests (such as those organised by VAMAS or NETVAL-ECVAM) have seen a decline in laboratory participation over time, despite initial interest. This raises questions about the long-term funding incentives for involvement, especially when participation seems to diminish as the process progresses. Additionally, there are less groups working on validation of ecotoxicology methods—why is this the case, and how can we encourage more involvement?

Finally, quick feedback from method developers is essential for maintaining momentum and ensuring continuous engagement in the standardisation process.

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

To encourage the development of tools and methods required for regulatory compliance of AdMa, we first need a clear regulatory framework tailored to these materials. Given the wide variety of AdMa, each with distinct properties and behaviours, test methods should be tailored to the specific type of AdMa being assessed. Additionally, it may be more effective to shift our focus from categorising by material types to identifying key exposure points and exposure type (including leachates, break-down/degradation products), as this approach could better address the range of materials and scenarios involved.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

Regarding the recommendations, a few questions and gaps need to be addressed:

- What exactly is meant by "profound risk assessment"? It's important to clarify the scope and criteria for such assessments to ensure consistency.
- Recommendation 4: Why limit the focus to fibres? It may be beneficial to broaden the scope to include other forms of AdMa, depending on the risk and relevance.
- Gaps: There is a need for a recommendation that outlines the applicability domain, helping to define which AdMa can be assessed with each specific method. This would ensure more comprehensive coverage across material types.
- The use of the term "advanced" in regulatory contexts might be problematic. It is too vague and temporal, and should be avoided to maintain clarity and precision in regulations.
- Semantic gap: Clear terminology is crucial. We need to define terms and concepts as part of the test guidelines and guidance documents. Correctly naming and categorizing materials ensures consistent understanding and application.

BREAKOUT GROUP ENVIRONMENT TOXICOLOGY AND FATE II

What is your experience with the different stakeholder groups (presented in the introduction to the breakout group discussion)? Are they playing the role you think they should play? Are there other important groups?

Different stakeholder groups introduced in the breakout discussion reflect a landscape where roles are defined but not always optimally aligned. Regulators are chiefly concerned with hazard assessment and ensuring that test guidelines are practical and enforceable, whereas risk assessors depend on established guidelines but could sometimes benefit from greater methodological flexibility. Researchers, however, often underappreciate regulatory requirements, which can hinder the translation of scientific innovation into regulatory practice. Meanwhile, industry actors and laboratory end-users (e.g. CROs) are directly affected by test guidelines. They, therefore, require stronger engagement in test guidelines development to ensure usability and regulatory compliance.

While these groups largely perform roles consistent with their mandates, there is substantial room for improvement in fostering integration and communication between the different

stakeholder groups. Notably, there is a pressing need to consider the specific contexts and constraints faced by startups and small to medium-sized enterprises. Their size limits possibilities for engagement, resulting in their perspectives often being underrepresented despite their growing role in technological innovation. Additionally, promoting a cross-cutting and integrative approach could help establish a shared language and mutual understanding among all stakeholders. This could ensure that test guideline development remains both scientifically robust and practically relevant.

What are the incentives for stakeholders to participate in the standardisation process? How can the different stakeholder groups be motivated? How and what could you contribute (e.g. as an expert, your institution, your group)? What would you need to pick these recommendations up?

Stakeholders are driven to participate in the standardisation process by incentives tailored to their distinct missions and operational needs. For industry and CROs, early access to emerging information and improved market preparedness, as well as foresight regarding future regulatory expectations constitute significant motivators. Researchers incentives lie in opportunities to access specialised expertise, publish findings, and secure funding streams tied to method validation and regulatory relevance. Regulators, in turn, are motivated by the imperative to ensure that test guidelines allow enforcement and regulatory clarity. For regulators this requires test guidelines that are scientifically robust, practicable, and aligned with regulatory frameworks.

To enhance stakeholder motivation, it is essential to cultivate channels for early and continuous dialogue, create tangible benefits such as co-authorship opportunities or recognition of contributions, and clarify how participation directly impacts regulatory outcomes and market access. However, to effectively implement recommendations, structured platforms for engagement, clearer guidance on stakeholder expectations, and support for dedicating resources and time to collaborative activities within the standardisation process would be beneficial.

How can we encourage development of the tools and methods required for regulatory compliance of advanced materials? How can we ensure that the appropriate tools and methods being developed move into the standardisation process? For example, characterisation techniques for new advanced materials, NAMs to replace animal testing or life-cycle analysis of materials?

Encouraging the development of tools and methods required for regulatory compliance of advanced materials necessitates a coordinated strategy that bridges scientific innovation with regulatory applicability. Central to this effort is fostering interdisciplinary collaboration between researchers, industry (including SMEs and service providers like CROs), and regulators to identify regulatory needs early and align research objectives with those requirements. Funding mechanisms specifically targeted at method development and validation for regulatory purposes are crucial and should include regulatory prioritisation. In addition these funding mechanisms will provide both resources and a clear mandate for researchers and developers.

New tools are continuously being developed, including advanced characterisation techniques, new approach methodologies intended to replace animal testing, or life cycle analyses. To ensure that such newly developed tools transition effectively into the standardisation process, it is essential to establish transparent pathways for method evaluation, validation, and regulatory acceptance. This includes creating clear criteria for assessing scientific robustness, practical feasibility, and relevance to regulatory frameworks. Additionally, promoting data

sharing, establishing common terminology, and developing guidance documents can accelerate harmonisation and uptake. The integration of innovative tools into standardisation depends on building mutual trust and ongoing dialogue among all stakeholders. This should ensure that regulatory science keeps pace with technological progress while maintaining rigorous standards for safety and environmental protection.

Are the recommendations the right ones? Are there gaps? If yes, what is missing? Is this the essence of what we need for advanced materials or life cycle considerations?

The recommendations outlined reflect essential priorities for advancing the regulatory landscape for advanced materials and integrating life cycle considerations. They rightly emphasise the need for stakeholder alignment, early involvement of industry and researchers, and the development of robust, practical tools and methods. However, certain gaps remain. Notably, there is insufficient emphasis on mechanisms to systematically integrate life cycle thinking into test guideline development, including the assessment of impacts across all stages of a material's existence, from production through disposal. Moreover, the recommendations could more explicitly address the importance of data infrastructure and digital tools to manage complex information on advanced materials, particularly given the challenges of characterising novel properties and behaviours. There is also a need for clearer strategies to ensure regulatory acceptance of new approach methodologies, including defined validation pathways and criteria for equivalence with established methods.

Specific measures to support startups and SMEs in navigating the regulatory environment and contributing meaningfully to standardisation processes deserve greater focus. Overall, while the current recommendations capture the essence of what is needed, further refinement is necessary to ensure comprehensive coverage of both technological and practical challenges inherent in regulating advanced materials and incorporating life cycle considerations.