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About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 38 countries in North and South America, Europe and the Asia and Pacific region, as well as the European Union, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several Partner countries and from interested international organisations attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank, Basel, Rotterdam and Stockholm Conventions and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

Foreword

The Organisation for Economic Co-operation and Development (OECD), through its Working Party on Manufactured Nanomaterials (WPMN), has played a pivotal role in advancing international cooperation on the safety of manufactured nanomaterials and advanced materials. Since its establishment, WPMN has provided a global platform for harmonizing approaches to the testing, assessment, and regulatory preparedness of nanomaterials. Building on this foundation, the WPMN has expanded its scope to address advanced materials (OECD, 2023a).

The OECD's work on advanced materials reflects a proactive response to evolving scientific and regulatory challenges. To support this, WPMN has initiated case studies as practical tools for exploring regulatory implications and identifying knowledge gaps. Recent examples include the MXenes case study (OECD, 2025) and the NanoCarrier case study (OECD, 2024). These efforts underscore the importance of method harmonization, robust characterization, and the development of guidance documents tailored to advanced materials.

Through collaborative workshops, stakeholder engagement, and the publication of technical reports, WPMN fosters a Safer and Sustainable Innovation Approach (SSIA) (OECD, 2020a), aiming to integrate safety and sustainability to foster safety and innovation. This foreword acknowledges the contributions of member countries, experts, and partners who have supported these initiatives, ensuring that regulatory frameworks remain fit-for-purpose in the face of rapid technological progress.

As advanced materials continue to shape the future of science and industry, the OECD WPMN remains committed to promoting international convergence, reducing duplication of efforts, and enabling responsible innovation that protects human health and the environment.

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

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Executive summary

To ensure safety and sustainable advanced materials and to enable that legislation keep path with innovation, it is of paramount importance to identify and address any emerging issue at the earliest possible stage.

Although there are various terms and definitions in the literature or used by different communities to describe these materials (e.g. graphene-based, graphene related 2D materials, or graphene-family materials), reaching consensus on terminology or the development of definitions was not within the scope of the workshop. In the following we will use graphene-related materials (GRM) to refer to materials that are composed of, derived from, or structurally related to graphene.

Within the OECD Working Party on Manufactured Nanomaterials (WPMN), the Steering Group on Advanced Materials held an expert workshop on GRM that took place 26-27 November 2024 at the OECD Conference Centre.

GRM are highly promising due to their extraordinary properties, enabling a wide range of functions across numerous applications. The expert workshop aimed to provide a comprehensive overview of these materials, including their general characteristics, as well as provide insights into specific types and application areas. Discussions centred on recent research findings, focusing on aspects such as safety, sustainability, and regulatory considerations, guided by the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa), which offers a pre-regulatory and anticipatory risk governance tool to advanced materials. Early4AdMa aims to enhance regulatory preparedness for advanced materials but also foster safe(r) and sustainable by design.

The report consolidates expert contributions and discussions from the OECD WPMN's GRM Workshop, focusing on advancing governance and best practices on robust risk assessment methodologies to address emerging challenges. Participants contributed insights on scientific advancements, data gaps, and the importance of developing reliable safety assessment tools, along with considering sustainability (OECD, 2022) related issues associated with the development of these materials. The workshop outlines considerable knowledge gaps on human health and environmental safety for GRM, along with suggested follow-up actions, including closing knowledge gaps, promoting standardized testing protocols, and fostering innovation while safeguarding health and the environment. The findings serve as an initial foundation for further exploration and dialogue, particularly within the OECD WPMN. Although there is no intention to assign responsibility for implementing specific actions, as that falls beyond the scope of this work, it does provide insights to inform the decision-making processes, which should encourage stakeholders such as industry, academia, and regulators to leverage the insights provided.

1 Background

Regulatory preparedness for advanced materials

Advanced materials with increasing complexities, structures, and functionalities are being developed (Giese et al. 2020). These advanced materials (OECD, 2023a) hold the potential for significant economic benefits and addressing critical societal challenges, such as the energy transition and the replacement of substances of concern (EC, 2019; EC, 2022; AMI2030, 2022). However, their advantages are accompanied by concerns surrounding safety, sustainability, and regulatory issues (OECD,2025; Ouhajji et al., 2025).

For instance, some advanced materials may exhibit properties that are poorly understood in terms of hazards or may have high ecological footprints. Additionally, current test methods (e.g., OECD test guidelines and international standards) may be inadequate for thoroughly characterizing the potential hazards and exposure posed by these materials due to their unique properties. These challenges could lead to unacceptable health risks or environmental consequences when such materials are introduced to the market. Furthermore, societal acceptance and uncertainties regarding whether existing regulatory frameworks adequately address these materials may impede innovation in new advanced materials (Cummings et al. 2021).

To mitigate the potential negative impacts of these materials, while simultaneously enabling innovation, the OECD Working Party on Manufactured Nanomaterials (WPMN) recognised the need for identifying and address potential environmental, health and safety impacts as early as possible. The OECD has developed Early4AdMa (OECD, 2023b), a pre-regulatory anticipatory risk governance tool designed to identify potential issues and recommend follow-up actions for advanced materials. This tool has already been applied in several case studies, including nanocarriers (OECD, 2024) and MXenes (OECD, 2025). Early4AdMa aims to enhance regulatory preparedness for advanced materials but also foster safe(r) and sustainable by design.

OECD WPMN case study and workshop on graphene related materials

In the context of regulatory preparedness for advanced materials and within the OECD WPMN Steering Group for Advanced Materials, several delegations joined efforts to organise a workshop addressing the graphene-based materials. An ad-hoc group comprising representatives from Germany (UBA, BAM), the Netherlands (RIVM), United Kingdom (HSE), Spain (INIA); Sweden (Karolinska Institutet); South Africa (NWU); and BIAC (NIA) put forward an agenda and identified the discussions needs.

The case study aimed to identify potential issues with safety, sustainability, and regulatory gaps, and to propose potential follow-up actions for GRM. It was recognised that terminology varies, however reaching consensus on terminology or the development of definitions was beyond the scope of the workshop.

The case study was selected because it was considered that GRM are promising materials with extraordinary properties which can enable a variety of functions in a plethora of applications. The objective was to get an overview of graphene materials in general, as well insight in application areas, as well as

insight in potential safety, sustainability and regulatory issues, including the adequacy of test methods for these materials. As such, findings from recent research were discussed in relation to safety, sustainability as well as to regulatory issues, and supported by the OECD's Early Awareness and Action System for Advanced Materials (Early4AdMa) approach (OECD, 2023b).

The workshop was attended by 82 participants (either on-site or online) representing seventeen countries, the European Commission, Business at the OECD (BIAC) and invited experts from the research community and industry (Annex 1) with a particular focus on graphene related materials (GRM).

The agenda to the workshop (Annex 2) included several sessions aiming to: i) set the scene; ii) learn from the current state of knowledge on human health, environmental toxicity and predicting environmental releases from different graphene base materials; iii) learn about applications, products and commercialisation phase; iv) identify methodology testing issues and potential regulatory challenges associated with these materials; and finally v) discuss indicators and knowledge gaps related to safety, sustainability, and regulatory concerns to inform recommendations that can foster Regulatory Preparedness (RP) and a Safer and Sustainable Innovation Approach (SSIA)[1].

This report summarises the discussions that took place during the OECD Workshop. As such, it includes short summaries of the presentations provided, as well as the main points raised during the discussions. It is expected that the findings from this workshop can continue stimulating the dialogue between different stakeholders coming from the policy, sustainability, safety, innovation fields, and identify specific actions that can assist regulators, policy makers, industry, researchers and innovators to address and develop GRM in a safe and sustainable way.

[1] Visit: https://www.oecd.org/en/topics/sub-issues/nanomaterials-and-advanced-materials/safer-and-sustainable-innovation-approach-ssia-nano-enabled-and-other-emerging-materials.html

2 Presentations made during the Workshop on Graphene-Related Materials

The OECD WPMN workshop on GRM took place 26-27 November 2024 at the OECD Conference Centre and there was also an opportunity for remote participation. The views expressed in this document do not necessarily reflect those of all the participants, and the listed participants do not explicitly endorse the statements made herein.

Overview on Graphene Family Materials and their properties - Mary Gulumian (NW University, South Africa)

Mary Gulumian opened the workshop with an overview on GRM and their properties, providing a detailed explanation of the physicochemical characteristics and their implications for human health, environmental safety, and regulatory frameworks. The presentation emphasized the need to develop structure–activity relationships to assess toxicity and support Safe-by-Design (SbD) strategies. She also mentioned that properties such as defect types, surface chemistry, lateral dimensions, and functionalization are linked to biological interactions and environmental behaviour. The presentation highlighted the importance of accurate characterization methodologies, the impact of processing techniques like sonication, and the challenges posed by assay interference. She also reviewed international standards and OECD Test Guidelines (TGs) that could be relevant to GRM, identified data gaps, and called for further research to address information gaps to support regulatory preparedness, that may compromise the innovation of these materials when not addressed. The speaker acknowledged a broad set of terms used to refer to graphene materials (such as graphene family materials (GFM), graphene-related materials (GRM) and graphene-based materials (GBM),) and emphasized that there was no intention in her presentation nor at the workshop to agree on specific terminology (Gulumian and Fadeel, 2025).

Mary Gulumian emphasized the relevance of OECD Test Guidelines (TGs)[2] and Guidance Documents (GDs) in the regulatory assessment of graphene family materials (GFMs). She highlighted that while many OECD TGs were originally developed for chemicals and several of them are specific to nanomaterials, their applicability to GFMs requires careful consideration of the unique physicochemical properties of these materials—such as defect density, layer number, lateral dimensions, and surface chemistry. Specific TGs like TG 124 (Volume Specific Surface Area), TG 125 (Particle Size Distribution), and TG 318 (Dispersion Stability) were discussed as particularly relevant, though she noted limitations such as the unsuitability of Brunauer, Emmett and Teller (BET) analysis due to small interlayer spacing. Gulumian also pointed out that some TGs not yet adopted for nanomaterials—such as TGs 201, 202, 203, 236, and 249—could be adapted for GFMs, provided issues like media interactions and fluorescence interference are addressed.

[2] See https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/test-guidelines.html

She advocated for the inclusion of GFM-specific considerations in OECD documents and stressed the need for validated interference-free toxicity testing methods to support regulatory decisions and safe-by-design strategies.

The main message from the opening presentation was an invitation to work towards the aim to ensure the safe and sustainable development of GFMs, that it is essential to integrate comprehensive physicochemical characterization with validated, interference-free toxicity testing, and to align these efforts with evolving international standards and regulatory requirements.

Graphene characterisation and terminology - Charles Clifford (NPL, UK)

Charles Clifford presented the current state of terminology and characterization for graphene-related two-dimensional 2D materials, focusing on international standardization efforts led by ISO, CEN, and IEC. He emphasized the complexity and diversity of materials marketed as “graphene,” which range from single-layer sheets to powders made of thick, multi-layered platelets with varying lateral sizes. This variability has led to confusion in the marketplace on graphene-related 2D materials and underscores the need for validated methods for characterization and clear definitions.

To address this, ISO has developed a classification framework (ISO/TS 9651:2025) and conducted international interlaboratory studies under the VAMAS initiative. These efforts have resulted in standardized terminology and measurement protocols, including the definition of Graphene-Related 2D Materials (GR2M), which encompasses materials with one to ten layers—such as graphene, graphene oxide (GO), reduced graphene oxide (RGO), and functionalized variants—while excluding graphite and thicker flakes.

Clifford highlighted key characterization techniques such as BET surface area analysis, Raman spectroscopy, Transmission electron microscopy (TEM), and X-ray photoelectron spectroscopy (XPS), which are essential for understanding material composition and structure. He concluded by urging stakeholders to adopt existing ISO standards to ensure consistency and scientific rigor in the physicochemical description and characterization graphene-related materials.

Synthesis [synthesis methods and scalability; precursors, energy expenditures] - Stephen Hodge (Versarien, UK)

Stephen Hodge, representing Versarien plc, a United Kingdom-based advanced materials manufacturer, presented on the synthesis methods of graphene materials. He emphasized the variability in graphene products across different companies, noting that no two materials are exactly alike.

Versarien operates several companies, including: a central manufacturing oversight entity; two United Kingdom subsidiaries spun out from the University of Manchester and University of Cambridge, focusing on graphene nanoplatelets and graphene dispersions; Gnanomat in Spain, which functionalizes carbon materials with metal and metal oxide nanoparticles to create hybrid materials for energy storage.

The company conducts R&D in Manchester and Cambridge, leveraging state-of-the-art equipment often unavailable to other graphene producers. Versarien manufactures a wide range of graphene-related materials, including graphene oxides, and integrates them into polymer compounds, such as rubbers, thermoset and thermoplastics to create intermediates. Versarien’ s application focus is on industries such as leisure and construction (e.g., reducing cement usage).

Versarien also participates in the Horizon Europe iCare project, which explores graphene applications in concretes and rubber and assesses nanotoxicology in collaboration with industry and academic partners.

Graphene's versatility spans in different applications such as coatings, composites, energy storage, electronics, and semiconductors. For example: Graphene oxide is used in smartphones; Graphene nanoplatelets are applied in ship hull coatings; Reduced graphene oxide (RGO) is undergoing clinical trials for use in brain electrodes. Given this diversity, standardization across industries and materials is critical.

Graphene synthesis methods fall into four main categories, based on: Carbon source; Chemical substances; Water and electricity usage; and environmental change potential.

These methods are broadly classified into top-down and bottom-up approaches:

a. Top-Down Methods

- Liquid-phase exfoliation (e.g., sonication, ball milling, high-shear mixing): Low cost, lower quality, high energy consumption.
- Electrochemical exfoliation: Uses voltage to cause ion intercalation between graphite layers, producing large graphene sheets with partial oxidation.
- Chemical oxidation (e.g., Hummer's method): Produces graphene oxide using strong acids and oxidizers. High yield but generates hazardous waste.
- Reduction of graphene oxide: Converts GO back to RGO using chemicals (e.g., hydrazine, vitamin C), thermal, or photochemical methods.

It was noted that electricity usages dominate the current carbon footprint.

a. Bottom-Up Methods

- Chemical Vapor Deposition (CVD): High-quality graphene grown on copper using methane at ~1000°C. Requires transfer to target substrates.
- Epitaxial growth on silicon carbide: High cost and carbon footprint.
- Emerging methods: Use of waste materials (e.g., plastics, food waste) or biogas to produce crumpled or defective graphene, with potentially carbon negative outcomes.

Graphene nanoplatelet powder production has scaled to multiple tonnes in recent years. The industry has responded to the need to adhere to chemical regulation by forming a Graphene REACH Registration consortium and achieving REACH registration for: i) Graphene: 10–100 tonnes (EU); and ii) Graphene oxide: 1–10 tonnes (EU). A joint chemical safety report was submitted to ECHA for graphene, covering applications and potential exposure scenarios. However, challenges remain:

- Reduced graphene oxide (RGO) is not yet registered due to lack of manufacturers.
- Functionalized graphene and hybrid nanomaterials (e.g., graphene with metal nanoparticles) require further toxicological evaluation.
- Testing labs often lack experience with nanomaterials, and OECD guidelines may not be fully suitable.

The conclusion for this presentation was that Graphene is transitioning from hype to real-world applications, but manufacturing methods are diverse. Safety and environmental data remain limited. Regulatory progress is slow and costly, especially for SMEs who are currently dominating the production of graphene. Further investment and collaboration could unlock graphene's full commercial potential.

Relevant types and their promising (future) applications - Beatriz Alonso (Graphenea)

Beatriz Alonso from Graphenea, a Spanish company with over 15 years of experience in graphene production, presented on the different types of graphene materials and their future applications.

Graphenea specializes in two main types: i) Graphene Oxide (GO) – used in bulk applications (grams to kilos); and CVD Graphene (Chemical Vapour Deposition) – used in the semiconductor industry. Each type has distinct production methods, physical-chemical properties, and application areas.

Several CVD Graphene examples of very distinct applications were provided including: i) Electronics & Photonics (CVD graphene acts as a semiconductor); ii) Sensors: due to its ultra-thin structure (~0.3 nm), it is highly sensitive and can be functionalized for specific targets; iii) COVID-19 Detection (graphene was functionalized to detect the spike protein at attomolar (i.e. 10^{-18}) concentrations using a Graphenea card connected to electrical equipment) iv) ; Antibiotic Selection: Suspended bilayer CVD graphene can detect bacterial nano-motion within an hour, reducing the need for traditional culture methods.

Regarding applications of Graphene Oxide, examples included: i) Composite Materials & Lubricants: Used in aerospace, automotive, and hydrogen storage tanks to enhance mechanical and barrier properties benefits include reduced use of expensive materials (e.g., platinum), improved absorbance, and better thermal management; ii) Water Purification: via the development of nanofiltration and anti-fouling membranes; iii) Industrial additives: Applied in asphalt to improve hot mixing and reduce energy consumption; or iv) High-Temperature Membranes: Used in paper mills to concentrate waste and reduce water evaporation costs.

It was shown that there are promising applications that can reduce costs and improve efficiencies in different sectors. However, there are several challenges to be overcome such as scaling up, the process for moving from lab-scale to market-ready applications, while maintaining cost-effectiveness and environmental safety. From the regulatory perspective, there is a lack of harmonized standards for nanomaterials. The regulatory differences between jurisdictions pose challenges for SMEs due to limited resources and unclear guidance, slowing industrial adoption.

State of the knowledge on human health - Bengt Fadeel (Karolinska Institutet, Sweden)

The presentation offered a detailed overview of current knowledge regarding the potential health effects of graphene-related materials, especially graphene oxide. Despite being discovered over two decades ago, graphene is still considered a relatively new material and there are remaining knowledge gaps. Early studies, published more than a decade ago, showed that so-called graphene nanoplatelets could cause pulmonary inflammation and frustrated phagocytosis, highlighting the importance of particle size and aerodynamic properties.

Under the EU-funded Graphene Flagship initiative, researchers developed a classification system for graphene-related materials based on the number of layers, carbon-to-oxygen ratio, and lateral dimensions (Wick et al. 2014; ISO/TS 9651:2025). Furthermore, a key focus was ensuring that the materials were free from bacterial endotoxin, which might skew toxicity test results, and this led to the development of a macrophage-based assay for detection of endotoxin. Studies using graphene oxide revealed that both small and large flakes (Rodrigues et al 2018) were readily engulfed by human macrophages without causing cell death. Moreover, neutrophils were shown to degrade graphene oxide within hours, with smaller flakes degrading more rapidly than the large flakes.

Further investigations confirmed that degradation products of graphene oxide were non-cytotoxic as well as non-genotoxic. Studies in mice showed that intravenously injected graphene oxide degraded in the spleen over a period of nine months, as shown by Raman mapping. Finally, a human study involving 14 volunteers exposed to small or ultra-small graphene oxide (Rodrigues et al 2018) showed no harmful effects, although the study had limitations such as short follow-up and the use of a highly purified material which may not resemble industrial samples (Andrews et al. 2024).

Life cycle studies examined polymer composites reinforced with reduced graphene oxide (RGO). While pure RGO showed modest cytotoxicity, the abraded composites containing a small amount (2.5 wt%) of RGO did not. Other investigators analysed commercial graphene samples from 36 producers and found significant variability and impurities, which were linked to cytotoxicity rather than the graphene itself. The same investigators studied graphene oxide samples procured from 34 commercial vendors with similar results.

The presentation concluded that not all graphene materials are alike, and graphene-related materials are not “asbestos-like” materials insofar as degradation of graphene-related materials occurs albeit at different rates depending on the material properties. There is a growing knowledge base, but standardized test methods and careful material characterization are needed. Moreover, real-world (industrial) samples and life cycle perspectives are essential for accurately assessing the health impacts of graphene-related materials.

State of the knowledge on environmental toxicity - Mona Connolly (INIA, CSIC, Spain)

The presentation by Mona Connolly provided a comprehensive overview of current research and understanding regarding the environmental toxicity of advanced materials, particularly graphene-based materials. It emphasized how this knowledge can support safety assessments within frameworks like the OECD Early4AdMa system. Research in this area has grown steadily, with around 25 publications annually, mostly focusing on freshwater organisms such as fish, algae, and crustaceans, while terrestrial and marine species remain underrepresented.

The presentation highlighted the importance of physicochemical characterization in determining environmental risk. Characteristics such as hydrophobicity, dark coloration, reactivity, degradation potential, and high absorption capacity influence how these materials interact with and affect biological systems. Graphene’s morphology, including monolayer and multilayer structures, affects its surface area and reactivity, which in turn impacts biological interactions. Sharp-edged structures can damage cell membranes, while larger sheets may trap organisms, leading to immobilization and metabolic disruption. Recent findings suggest that graphene oxide can degrade in aquatic environments through self-generated radicals, forming porous sheets and fragments.

Despite these insights, predicting environmental behaviour remains challenging. There is evidence that graphene materials transform in the environment, but the extent and implications of these transformations are not fully understood. Regulatory assessments are complicated by limited data and the lack of standardized testing methods. Most current regulations focus on aquatic environments, with standardized tests primarily conducted on fish and crustaceans. A bibliographic review revealed that while many studies have examined graphene toxicity in fish, few followed standardized protocols, making comparisons difficult. Embryo studies showed sublethal effects and mortality at relatively low concentrations, indicating potential hazards.

The Graphene Flagship conducted acute toxicity studies using commercial graphene oxide and few-layer graphene, measuring actual exposure concentrations and using turbines to maintain stability. These studies found no mortality in fish, even at high concentrations, but did report sublethal effects. *In vitro*

studies showed that graphene materials could enter fish cells, causing membrane damage and oxidative stress, although uptake varied depending on the material.

Studies on Daphnia used standardized guidelines and produced consistent half maximal effective concentration (EC50) values, though variations were noted based on material size and species sensitivity. Algae studies showed inhibitory effects on growth, but results varied widely due to media differences and testing conditions. The use of stabilizing agents like humic acid improved material dispersion stability but also reduced observed toxicity, suggesting that such agents may mask true effects.

Bioaccumulation was also addressed, with only one fish study using carbon-14-labeled graphene to quantify uptake. Larger graphene sheets showed significantly higher bioaccumulation and distinct distribution patterns compared to smaller ones.

In conclusion, graphene-based materials exhibit unique properties and morphologies that influence their environmental behaviour and toxicity. There is evidence of transformation and degradation in aquatic environments, but data on the hazards posed by these processes are limited. Reported EC50 values suggest that graphene oxide may fall into the acute ecotoxicity category 3 (EC50 >), supported by embryo mortality data. Further research is needed to address critical testing aspects, including stability monitoring, assay interference, and the applicability of existing guidelines. Bioaccumulation data are particularly limited due to analytical challenges, underscoring the need for improved measurement techniques and use of standardized approaches.

Predicting environmental releases of different forms of graphene-based materials - Bernd Nowack (EMPA, Switzerland)

Bernd Nowack from EMPA, Switzerland, presented his team's research on predicting environmental releases of various forms of graphene-based materials. The study used material flow models to estimate how graphene is released from products throughout their lifecycle, followed by environmental fate models to understand how these materials behave once in the environment. In some cases, simplified fate modeling was used to provide worst-case scenario estimates of environmental concentrations.

The research focused on three types of graphene-based materials: graphene, graphene oxide, and reduced graphene oxide (RGO). The model spans the full lifecycle of these materials—from production to end-of-life—mapping their movement through technical systems and into environmental compartments. It incorporates data on production volumes, product distribution, and application areas from 2000 to 2030, using probabilistic modeling to forecast future trends. The study anticipated a significant increase in graphene production, which could lead to higher environmental releases over time.

To address changes in product distribution, the team analysed current and emerging applications. Major applications include batteries, wind turbines, and electronics, each with unique lifecycles that influence release estimates. Due to the long-term life expectation of these materials, it is foreseen that by 2030, most graphene produced today could still be in use, with only a small portion reaching disposal stages such as incineration or landfilling. Regarding incineration, a large portion of the graphene materials is expected to oxidize to CO_2, with residuals ending up in landfills or soil.

Environmental modeling showed very low predicted concentrations: approximately 1 nanogram per Liter in surface water and around 60 nanograms per kilogram in soil, increasing to 20 micrograms per kilogram in sludge-treated soils. These estimates are based on generic graphene, but the study emphasizes the importance of considering the diversity of graphene forms, coatings, and sizes, which affect transformation and toxicity.

The evaluation was extended to include the different forms of graphene used in different applications. Using dynamic probabilistic material flow analysis (DMFA), the study categorized graphene materials into

three types based on data on use of the different forms for specific applications. It was also noted that some forms are used in long-lifetime products, such as wind turbine blades, which means that they will not reach their end-of-life by 2030.

The research group also conducted a risk assessment using predicted environmental concentrations (PEC) and predicted no-effect concentrations (PNEC) from ecotoxicological data available in the literature. Despite limited data, the PEC/PNEC ratio indicated no current environmental risk from graphene-based materials in surface water.

The presentation concluded that quantifying environmental releases based on product-specific use is essential, and prospective modeling is necessary due to the expected rapid growth in graphene production. Access to accurate data on production volumes and usage types is critical, and it is crucial to distinguishing between different graphene forms for effective exposure and risk assessments. Finally, the speaker acknowledged the modeling work carried out by PhD student Hyun-joo Hong under the EU Sunshine Project.

Evaluation of Early4AdMa for graphene-epoxy composites with a focus on end of life - Veronique Adam (TEMAS Solutions, Switzerland)

The presentation focused on two aspects. First information was presented on a case study on few-layer graphene (FLG) used in battery management systems for its functionalisation enabled surface bonding properties and thermal conductivity. This case study was part of the EU project MACRAME. Secondly, it highlighted potential difficulties in answering questions from Early4AdMa (step 5) and draw some conclusions on the lessons learned in applying this approach.

Within MACRAME value chain analysis was performed in 5 cases studies, including Safe and Sustainable by Design (SSbD), Life Cycle Assessment (LCA) and Multifactor Authentication Risk Assessment (MFA RA). Based on these, methods on imaging, sample preparation, characterization, detection, also human and ecotoxicity were developed (see: https://macrame-project.eu/).

The presentation included a description of a case study as well as the responses retrieved when applying the Step 5 of the Early4AdMa with the aim of highlighting potential difficulties in answering the questions and draw conclusions on the case study. The pilot scale case study used was a FLG in battery management systems, where the functionalities are surface bonding and thermal conductivity. FLG brings several benefits such as making the composite used in battery management systems lighter than conventional materials, while it avoids the use of metals.

Keeping in mind that Early4AdMa is meant as a pre-regulatory and anticipatory risk governance tool for advanced materials, a multidisciplinary team used the case study to respond to the questions for the Step 5. Early4AdMa step 5 includes 65 questions with four types of possible answers (*Yes*, *No*, *Not Applicable* and *Don't know*) where a "Yes" gives a warning. The results obtained showed that for this case study, all the questions were relevant to the end-of-life particles. There were none 'Not Applicable" answers. There was a majority of "Yes" answers to aspects related to Safety Human Health, Safety Environment, Regulatory Frameworks and Sustainability. And there were missing areas that could be considered related to functionality and socio-economic sustainability. Based on this screening, the Early4AdMa results indicate that the material used in the case study is neither safe nor sustainable. For this reason, it was recommended that a comprehensive Safe and Sustainable by Design (SSbD) assessment—although not the primary objective of Early4AdMa—could be conducted to evaluate additional aspects relevant to advanced materials (AdMa), such as functionality. For this reason, it was suggested that a full SSbD assessment, which is not the primary aim of Early4AdMa, could be performed to consider other aspects relevant to AdMa, such as functionality.

The speaker used MACRAME's case study on FLG to respond to the questions of the Step 5 of Early4AdMa. Based on this, her feedback included the following:

Examples Early4AdMa section on Human Health:

Indication of another hazard or increased toxicity as compared to the conventional materials?

- The answer on the case study FLG was *Yes*. The speaker also noted that it was difficult to answer. To overcome this, they used information from Safety Data Sheets on the conventional materials, comparing the ingredients to those of the new developed composite.

Does the material consist of, contain or release particles at the nanoscale.

- The answer on the case study FLG was *Yes*. It does contain FLG at the nanoscale. But it also highlighted that the risks from nanoparticles are not the same as the risk from released particles that contain nanoparticles. In the second case, the organism might not be exposed to the nanomaterial. There was a suggestion to further develop this question, perhaps, by splitting in two, to allow a response that reflects better these details.

Is this an AdMa used or likely to be used in many products and or by a wide population

- The answer on the case study FLG was *Yes*. However, the FLG will be enclosed in the battery management system, in the battery system in the car.
- There were also some redundancies on some questions, for example on consumer exposure vs a question on work exposure, the frequency of the exposure. Answering yes to those questions will lead to answering yes in other questions. Perhaps those could be further merged to avoid redundancies.

Examples Early4AdMa section on Environmental Safety

Is there an indication that fate of multi-component materials differs from that of the individual components of the material?

- It was difficult to answer because the different components may have different fates. In this case study the epoxy-FLG was considered as the main component. Since the FLG content was so low, the environmental fate was driven by the epoxy, it was suggested to be more specific about the question on the component.

Questions on accumulation persistence, mobility, potential uptake.

- The answer was based on microplastics literature, as all particles are epoxy and therefore considered microplastics. When looking at the question from the graphene perspective, it leads to the same environmental fate

Early4AdMa Section on regulatory frameworks

- As it was discussed in previous presentation, there are issues with producing stable dispersions which might hamper experiments. The concentration of the FLG is extremely low, so the toxicity may be driven by the matrix. However, there is some complexity that may be introduced because the FLG is unevenly dispersed in the matrix. For this reason, it was decided to answer Yes. Acknowledging that there is no official definition on advanced materials. So, the AdMa could be allocated to another class of material, such as nanomaterials since in the case of FLG the

provisions apply. This raises the question on whether legislation or guidance lacks provisions that address AdMas.

Early4AdMa Section on Sustainability

Questions on energy, water, land consumption, and global warming potential on the different stages of the life cycle.

- These are difficult to answer without a Root cause analysis (RCA), which is known to be difficult to implement at early stages. Furthermore, the results might stay uncertain regarding energy and water consumption at early stages. Another aspect that was noted is the lack of guidance on threshold for high land consumption.
- Other question was on the waste generated during manufacturing, production, transport and use since this was not available for the pilot-scale case study. It was decided to answer *Yes* even though it was a case study where no waste is generated. Another clarification would be useful for short-lived versus long-term applications. Finally, we also find some redundancies on questions addressing problematic substances.

In summary, the transdisciplinary collaboration is essential to answer the questions of Early4AdMa Step 5. Based on the use of Early4AdMa for the MACRAME case study, results are that the materials are neither safer nor more sustainable. It was suggested to further refine some of the questions and merge those that seem redundant as well as further develop the guidance for users. Finally, based on the lessons learned from this case study, the Early4AdMa approach might be more suitable to single materials rather than composites.

Sustainability Aspects of Graphene-based Materials evaluated within the scope of SSbD - Fiorella Pitaro (EMPA, Switzerland)

Fiorella Pitaro talked about some sustainability aspects of graphene-based materials evaluated within the scope of Safe and Sustainable by Design. Graphene is often associated with sustainability, mainly due to its potential to contribute to a more sustainable future. The Graphene Flagship claims that all 17 UN Sustainable Development Goals can be addressed by graphene. Examples include its role in drug delivery systems, water filtration, and enhancing the performance of various materials (e.g., lighter packaging, which could reduce costs and energy consumption). These examples reflect the three pillars of sustainability: social, environmental, and economic.

While promising, a more quantitative assessment is needed. Therefore, a Life Cycle Assessment (LCA) was performed. The case study presented followed the EU Safe and Sustainable by Design framework (COM, 2022). The study relied entirely on literature data and reflected the viewpoint of an external observer rather than that of a producer.

The case study was based on a material flow analysis which used market reports and forecasts, predicting a rapid increase in production volume of graphene-based materials in Europe and identifying prospective product applications. By 2030, the largest share of production is expected to be used in wind turbines. In this case study, three forms of graphene-based materials were analysed: graphene, graphene oxide, and reduced graphene oxide. The selection was based on the properties and functionality of these materials, which vary depending on the degree of oxidation.

Graphene can be used in various ways in this sector. The presentation focused on its application in wind turbine blades, which are growing in size and face harsh conditions, particularly erosion. Erosion is a major issue, potentially reducing annual energy production by up to 25%. Stronger blades and coatings are needed. Two types of coatings are commonly used: zinc-based and polyurethane-based. Graphene-based

materials are added to these coatings for their anti-corrosion properties. Additionally, graphene is added to glass fiber to reinforce plastics, making blades stronger. Although carbon nanotubes have been used similarly, graphene's structure has proven to be better since it enhances surface area contact with polymers.

The sustainability assessment required a life cycle assessment to analyze environmental impacts and identify hotspots for improvement. The standardized approach begins with defining the goal and scope. The goal was to determine whether adding graphene-based materials to wind turbine blades provides enough benefits to justify the additional production steps. The functional unit chosen was one kilowatt-hour of electricity produced by an offshore wind turbine over a 40-year lifespan. The environmental footprint was calculated using a cradle-to-grave approach, covering raw material sourcing, graphene production, blade manufacturing, turbine assembly, 40 years of use, and end-of-life (landfilling). Only elements within the system boundaries were considered.

The speaker first presented graphene production processes. Few LCA studies compare techniques, and those that do are based on lab-scale data. This study estimated scaling effects to assess impact changes. Three production techniques were examined: electrochemical exfoliation, chemical oxidation-reduction (lowest environmental impact), and chemical vapor deposition. However, comparisons are difficult due to differing functional units. This highlights the challenge of comparing production techniques, where material states and functionality must be considered. Electricity is the main impact contributor for electrochemical exfoliation and chemical vapor deposition, while chemical oxidation-reduction is impacted by the materials used. A study in China comparing oxidation-reduction and thermal exfoliation found thermal exfoliation is more sustainable in terms of environmental impact and human toxicity. However, obtaining reliable data from producers remains difficult.

Limitations in LCA inventories were noted. For example, thermal exfoliation did not account for argon or nitrogen use.

LCA modeling compared six systems: two reference blades and four innovations involving graphene. Key findings are:

- Adding graphene to zinc-based coatings allows a small amount of graphene to replace a large fraction of zinc.
- In polyurethane-based coatings, erosion resistance increased by 12%, reducing blade replacement frequency.
- In glass fibre-reinforced plastic, plastic mass was reduced by 30%, making blades lighter.

Manufacturing impact comparisons:

- Polyurethane-based coatings showed increased impacts due to graphene production, but benefits emerged during use.
- Zinc-based coatings showed decreased impacts due to zinc replacement.
- Glass fiber-reinforced plastic showed reduced impacts in most categories, though acidification and water use increased due to sulfuric acid and water in the Hummers method.

The assessment aimed to compare the environmental footprint of the entire wind turbine over 40 years, including blade replacement and erosion-related power loss. The LCA showed that adding graphene in all four applications generally reduced environmental impact.

In conclusion, LCA is valuable for identifying environmental hotspots and improving processes throughout the lifecycle. However, the criticality of graphite as a raw material was not discussed. Key sustainability contributors are energy/electricity requirements and chemicals used in production. LCA data reliability varies, and industrial data is hard to obtain. Functionality is crucial—material replacement and blade lifespan extension contribute to sustainability. End-of-life and recyclability of graphene remain unexplored.

Regulatory challenges/questions (focus on legal requirements) - Eric Bleeker (RIVM, Netherlands)

The talk began with a reminder that in 2013, the OECD adopted the Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials (OECD, 2013), confirming that existing regulatory frameworks are suitable for nanomaterials—provided they are adapted to account for the specific properties of manufactured nanomaterials. This led to certain changes and adaptations in regulations concerning nanomaterials. A key question for more complex materials, such as graphene, is whether these adaptations are sufficient for the broader family of graphene-related materials.

The speaker emphasized that the purpose of the talk was not to establish a definition for these materials. Instead, he presented a summary of existing definitions for nanomaterials, based on Rasmussen et al. 2024. This illustrates complexity of agreeing on harmonised regulatory definitions and reveal differences between regulatory approaches:

- *Global agreement* that nanomaterials have at least one dimension at the nanometre scale (between 1 and 100 nanometres) ›
- *Differences between regulatory definitions:*
  - – Consideration of agglomerates and aggregates (i.e. one or more particles)
  - – Origin of the material (manufactured, natural or incidental)
  - – Metrics used (number/mass of particles)
  - – Threshold (the fraction of nanometre-scale particles that is required for the material to be considered a nanomaterial)
  - – Whether the evaluated material must exhibit nanometre-scale-related properties

Nevertheless, definitions in a regulatory context are required, as they determine specific requirements.

As an example, the speaker referenced European legislation—REACH—where “A nanoform is defined as a form of a natural or manufactured substance containing particles, either in an unbound state, as an aggregate, or as an agglomerate, where 50% or more of the particles in the number size distribution have one or more external dimensions in the 1–100 nm range”. This definition also includes, by derogation, fullerenes, graphene flakes, and single-wall carbon nanotubes with one or more external dimensions below 1 nm”. Graphene flakes explicitly fall under this definition, meaning nanospecific requirements apply. In addition, based on this definition, additional requirements may apply to the physical-chemical parameters of nanoforms (e.g., dustiness). The characterization of a nanoform includes its name, particle size distribution, surface chemistry, shape, and surface area.

The 2022 new EU recommendation on the definition of nanomaterials (EC, 2022) specifically mentions to include a material if “[...] (c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm [...]”., confirming that graphene materials are included in this definition, although this 2022 definition is not (yet) included in REACH legislation.

However, graphene is not merely a carbon compound—it represents a broad range of different 2D material forms. The Graphene Council developed a classification framework with 19 parameters (see: https://www.thegraphenecouncil.org/page/GCF; ISO/TS 9651:2025). Among these, particle size distribution addresses dimensional aspects, while surface chemistry, functionalization, and oxygen content are also relevant. Surface area, crystallinity, elemental composition, and bulk density are generally included in the chemical identity of substances under REACH. Other parameters, such as particle charge, may influence further testing.

A report (ECHA, 2022) commissioned by the European Observatory for Nanomaterials (EUON) emphasized the importance of detailed information and characterization. This is already the case for dosimetry, but other endpoints—such as the role of impurities—are still lacking.

From a regulatory perspective, the question is whether method adaptations are needed, or whether awareness of these factors is sufficient when applying existing methods. The Graphene Council demonstrated that some methods are applicable (e.g., OECD Test Guidelines No. 431 (*In Vitro* Skin Corrosion) and 439 (*In Vitro* Skin Irritation). However, challenges remain—for example, dispersion in liquids, where the energy applied may alter the graphene structure. In such cases, dispersion may be present at the start of a test but diminish after 24 hours, complicating exposure descriptions.

Other testing challenges arise when examining physical effects. Some studies have shown that Daphnia accumulate carbon nanotubes in their intestines, leading to blockage and death by starvation—a physical rather than chemical (toxic) effect. Therefore, it is important to distinguish between chemical and physical effects.

The question remains: do we need further adaptations to Test Guidelines, or will adapted Guidance Documents suffice? In conclusion, there is a continued need to identify whether new Test Guidelines or Guidance Documents are required to meet regulatory demands. Experience has shown that for nanomaterials, most dispersion-related issues in aqueous systems can be addressed with a single guidance document covering a range of aquatic tests. Several guidance documents are currently in development to address specific effects, so there is no need to rush to adapt every individual Test Guideline.

Given the diversity and complexity of 2D materials, challenges remain in properly characterizing them. Another consideration is whether a mixture toxicity approach is appropriate, or whether it is more pragmatic to assess each material individually. As these varied 2D materials increasingly enter the market, it is essential to evaluate how prepared regulatory systems are to manage them. A pragmatic yet reliable strategic approach is needed to keep pace with innovation.

Methodological challenges and gaps physico-chemical characterisation - Jörg Radnik (BAM, Germany)

Jörg Radnik presented an overview on methodological challenges and gaps for the physico- chemical characterization based on his experience in developing standard methodologies within IEC and ISO, which have developed several measurement standards. The speaker presented a list of standards for the structural characterization of graphene, and graphene oxide as sheets and in particle form, and mentioned that other documents are on the way to become standards.

Regarding the classification framework, ISO has developed a Classification Framework [ISO/TS 9651:2025] but it was noted that it was not developed from the toxicological nor regulatory perspective.

The speaker updated participants on the methods available for graphene and their use in the ISO Classification Framework. The speaker shared lessons learned from the Graphene Flagship and shared the lessons learns from that case study. Several materials were used, for each case some endpoints or measurements were needed. Special emphasis was made on the particle form or Graphene Flakes. Several methods have proven useful for the characterisation of graphene:

Structural characterisation: microscopy (optical, AFM, SEM, TEM), Raman spectroscopy

Chemical characterisation: XPS

Key methods in graphene and other 2D Materials characterisation: AFM, SEM, Raman, XPS

However, most methods are also highly sophisticated, time consuming and/ or resource intensive. There are several discussions underway to develop other methods to assess, for example, the oxygen content (oxygen to carbon ratio) or for measuring functionalization.

The speaker identified several methodological challenges for the physical-chemical characterisation of Graphene, highlighting the following ones:

- First challenge: To define the physico-chemical key parameters that influence the biological and environmental activity.

  Defining key parameters to understand the biological and environmental activity of the materials is crucial. To achieve this, a critical analysis of existing reliable biological and environmental behaviour data is required. However, this raises further questions on what "reliable data" are. To summarise, the challenges are i) critical analysis of reliable existing data (e.g. Use of Large Language Models); ii) to identify the gaps; and iii) to fill the identified gaps.

- Second challenge: To analyse graphene-related 2D materials in various matrices.

  This is particularly challenging for biological matrices (Graphene is a carbon-based material, and biological matrices are carbon-based). There is a need to look for key physicochemical properties. For example, when the important property is a powder, the question will be how the powder or flakes behave in different matrices. More could be learned from ECHA's Survey[3] on state of the art of carbon-based nanomaterial detection and quantification in environmental and biological matrices. In addition, there is value in learning from other fields with experience in carbon-based advanced materials. The Graphene Council mapped the landscape for graphene commercialization (Barkan T. et al. 2024). One of the findings is that large volume applications of graphene are produced and treated as trade secrets, so often not appearing in patent reviews or advertisement, which makes it difficult to track products containing graphene and thus hinders material traceability. Therefore, it is easy to underestimate the amount of graphene available and where it will go. The patent distribution reveals, for example that energy storage is one area of applications, but when submitted as a chemical, it refers to graphene as additive in different chemical products (polymers and paintings). Establishing reliable protocols for detecting such small percentage of graphene related 2 D materials (GR2M) (< 1 %) with physico-chemical methods remains a major challenge.

- Third challenge: To clarify what the impact and relevance of small amounts in a (consumer) product can be in risk assessment.GR2M is used in a broad range of applications (such as paintings, constructions, textiles, tyres) where a small mol% of GR2M is needed to have an impact on the properties (e.g.: resistance, stability, wettability). Knowing that less than 1% could be included in a consumer product, how we evaluate the impact and relevance from a toxicological standpoint. There is no clarity on the possible consequences for health and safety, despite knowing that such a percentage is sufficient to have a significant impact on the product. Those questions should be answered.

The conclusions from this talk were that physico-chemical characterisation of graphene related 2D materials is progressing but more is to be done. Further work is needed to understand the structure-activity relationships which is needed to define key physico-chemical characteristics for the risk assessment of GR2M. Finally, joint efforts with the carbon-based advanced materials community are necessary to leverage the available knowledge.

[3] See Ex-Ante notice – ECHA/2024/LVP/0002. Negotiated procedure for low value service contract for a Survey on state of the art of carbon-based nanomaterial detection and quantification in environmental and biological matrices (ECA.80743) ECHA/2024/LVP/0002-ExA)

Methodological challenges and gaps human health - Marco Pelin (Universita degli Study di Trieste, Italy)

The OECD TGs related to human health cover a wide range of *in vitro* and *in vivo* toxicity methods, addressing oral toxicity, inhalational toxicity, skin toxicity, genotoxicity, and other health-associated parameters. Therefore, it is very difficult to generalize the limitations and drawbacks of applying these guidelines to graphene. However, some generalizations can be made, and the presentation provided examples. For instance, the lightweight nature of graphene-based materials means that the concentrations and doses suggested by these guidelines are sometimes too high. Another issue is dispersion stability when these materials are tested in liquid form rather than powders but as dispersions, leading to dosimetry problems associated with aggregation and agglomeration. The optical and quenching properties of these materials can lead to misclassification. Additionally, this is a broad range of materials, meaning different materials have different properties, as previously explained. Consequently, it is crucial to complete physicochemical characterization in parallel with the toxicological analysis.

The presentation focused on skin irritation and skin sensitisation.. This work framed the efforts of the Graphene Flagship project and other European projects in which the University of Trieste has been involved. The speaker presented an overview of all the OECD Test Guidelines covered in their study addressing the main adverse outcomes at the skin level, such as skin irritation, corrosion, and sensitization:

- TG 442C: *In chemico* skin sensitization (Direct peptide reactivity)
- TG 442D: *In vitro* skin sensitization (Keratinocytes activation)
- TG 442E: *In vitro* skin sensitization (Dendritic cells activation)
- TG 439: *In vitro* skin irritation
- TG 431: *In vitro* skin corrosion
- TG 442B: *In vivo* skin sensitization (LLNA assay)

The simplest models—skin irritation and skin corrosion prediction—were addressed using Test Guidelines 439 and 431, respectively. Both use a commercially available reconstructed human epidermis model, where materials are directly exposed on the surface of the epidermis grown at the air-liquid interface, applied as powders at different doses and exposure conditions depending on guideline requirements. In both cases, prediction is based on tissue viability evaluated by the MTT assay[4]. The study found two main limitations: the doses suggested could be too high for these materials, leading to overload, and there are possible interferences with the MTT assay.

Two types of few-layers graphene flakes were tested: one skin irritant and one non-irritant. An irritant material, reduced graphene oxide, was also tested at different doses. Results were compared between the MTT assay, and the WST-8 assay, which is known to produce fewer artifacts and interferences. Based on the results, it was concluded that OECD TG 439 for skin irritation can be adopted for these materials without modifications. Given the similarity between the prediction models for skin irritation [OECD TG 439] and corrosion [OECD TG 431], both guidelines were adopted for a wide range of graphene-based materials, including carbon-based materials such as carbon black and multi-wall carbon nanotubes. For skin irritation, none of the materials reduced tissue viability to levels that would predict irritation, unless they were prepared with toxic surfactants as exfoliation agents and/or these surfactants were not sufficiently removed from the final material. In addition, none of the materials reduced tissue viability to levels predicting mild or high corrosiveness, demonstrating that these guidelines can be adopted and yield important results for these materials (Carlin et al., 2023).

[4] MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Thiazolyl blue tetrazolium bromide.

For skin sensitization, the prediction model is more complex, involving four key events of the adverse outcome pathway (AOP). The first event—covalent binding to skin proteins—is evaluated by guideline 442C. The second and third events—keratinocyte and dendritic cell activation—are evaluated by *in vitro* guidelines (TG 442D and TG 442E). The fourth event—lymphocyte activation—is evaluated by *in vivo* guideline 442B. Results showed that TG 442B can be adopted without modifications (Sosa et al., 2022). However, TG 442C cannot be adopted due to technical limitations and the specific characteristics of these materials. TGs for the second and third events can be adopted with caution or with procedural modifications. All data have been reported in a manuscript (Carlin, 2025). In particular, guideline 442C, using the DPRA assay, evaluates the reactivity of test substances toward cysteine-rich peptides via HPLC analysis. Known limitations hinder adoption for graphene-related materials, such as: i) substances that absorb significantly at 220 nm (HPLC wavelength), ii) water-soluble substances that cannot be stably dissolved in acqueous buffers at 100 mM and precipitate in solution, iii) substances that spontaneously oxidize cysteine. Graphene-related materials are known to oxidize cysteine, leading to false positives. Thus, these guidelines cannot be adopted for graphene materials. For the second key event—keratinocyte activation—evaluated by TG 442D using the KeratinoSense™ model, potential limitations include interferences with the MTT assay and luciferase measurement. Graphene oxide, reduced graphene oxide, and graphene nanoplatelets were studied. The MTT assay underestimated cytotoxic potential compared to other assays. The MTS[5] assay was selected for cytotoxicity evaluation, and two washing steps were introduced to minimize interferences. Results suggested these materials do not activate keratinocytes. For the third key event—dendritic cell activation—evaluated via differentiation markers measurement on THP-1 monocytes by flow cytometry after 48 hours, limitations were found with the Propidium Iodide Uptake assay due to high concentrations and fluorescent quenching in addition to aggregates that may clog the flow cytometer. The guideline allows alternative viability assays, such as the Trypan Blue Exclusion Test. Results showed mild cytotoxicity for graphene oxide, graphene nanoplatelets and reduced graphene oxide, not allowing the computation of CV75[6], used to calculate the correct concentration range for treating cells to measure the differentiation markers. Hence, as stated by the guideline, the concentration range was established based on dispersion stability, evaluated by UV-Vis spectroscopy, with a concentration of 7.8 µg/mL as the basis for dose range testing (2.6–9.4 µg/mL). None of the materials increased differentiation marker expression to levels predicting dendritic cell activation.

Since the materials did not activate keratinocytes or dendritic cells according to two of three *in chemico*/*in vitro* approaches in OECD TG 497, they were concluded to be non-skin sensitizers. This was confirmed by OECD TG 442B via the Local Lymph Node Assay. No limitations were reported for TG 442B, which already includes buffers and solvents for stable dispersion of powders. No evidence of lymphocyte activation was found, confirming the absence of skin sensitizing properties.

To summarise, it was concluded that Graphene materials are generally not skin sensitizers, opening doors for technological applications. Test Guidelines for skin irritation, corrosion, and *in vivo* sensitization can be adopted as they are. However, TG 442C cannot be adopted, TG 442D can be adopted with procedural modifications, and TG 442E can be adopted after careful concentration range evaluation.

Methodological challenges and gaps environment - Jose Maria Navas (INIA, CSIC, Spain)

Jose Maria Navas spoke about the *Methodological and Regulatory Challenges for Environmental Testing*. The information presented aligned with the OECD Early4AdMa system—an early awareness framework—which includes, among other things, a set of questions related to physicochemical properties, safety,

[5] MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium).

[6] CV75: The estimated concentration showing 75% cell viability.

environment and health, and sustainability. The safety assessment must consider that potential issues could arise throughout the life cycle of advanced materials.

Early4AdMa includes several sub-topics, such as physicochemical properties, hazard, fate, and exposure upon environmental release. These questions are directly related to OECD Test Guidelines, which are internationally agreed tools for the safety assessment of chemicals and to which some apply to nanomaterials with or without limitations. They address regulatory requirements. In the environmental context, three areas are covered by Test Guidelines:

- Section 1: Physicochemical Properties
- Section 2: Effects on Biotic Systems (ecotoxicity)
- Section 3: Environmental Fate and Behaviour (degradation and bioaccumulation)

OECD Test Guidelines were originally developed for soluble chemicals. Over the years, the question has been to what extent they are applicable to nanomaterials, and for the purpose of this workshop, whether they are applicable to materials such as graphene. This question has been pivotal for the work within OECD. Already in 2009, a thorough review on the applicability of TGs for nanomaterials was conducted. In the case of physicochemical properties, the 2009 review highlighted that only four of the 23 existing TGs at the time were applicable to nanomaterials. The majority were applicable with limitations, and three were not applicable at all. Regarding methods for biotic effects, it was concluded that only basic toxicological practices were adequate for testing nanomaterials. Several needed guidance on sample preparation, delivery, measurement, dosimetry and it was recommended to develop such guidance. For protocols available to assess environmental fate and behaviour, it became clear that some TGs were not applicable, some were applicable but with limitations or specific conditions, and again, guidance was recommended for using TGs when testing nanomaterials. These recommendations triggered several OECD projects, such as:

- OECD Guidance Document 317 on Aquatic and Sediment Toxicological Testing of Nanomaterials (OECD, 2021)
- OECD Guidance Document 318 for Testing Dissolution and Dispersion Stability of Nanomaterials, and Use of the Data for Further Environmental Testing and Assessment (OECD, 2020b)
- OECD TG 318 on Dispersion Stability of Manufactured Nanomaterials in Simulated Environmental Media (OECD, 2017a)
- *(Under preparation)*
    - New TG addressing dissolution rate of nanomaterials in aquatic environments
    - TGP Project 1.5: Guidance Document on Determination of Solubility and Dissolution Rate of Nanomaterials in Water and Relevant Synthetic Biological Media
    - TGP Project 3.10: New TG on Dissolution Rate of Nanomaterials in Aquatic Environments

Regarding their applicability to graphene materials, a preliminary assessment showed that GD 317 includes two references to graphene; however, the content does not provide specific advice for this type of material. In GD 318, graphene is not mentioned at all. Nevertheless, the speaker highlighted areas where we can expect similarities in addressing graphene vis-à-vis nanomaterials, as well as areas requiring specific considerations when addressing graphene materials, summarized as follows:

Similarities in the Approach from Nanomaterials to Graphene:

- Test dispersion preparation in liquid media
- Stock dispersion
- Dispersion in test media
- Ensuring stability of test dispersion in liquid media throughout the assay
- Interaction with organic matter present in media
- Sediment or soil spiking
- Conduct of the test

- Opacity
- Water renewal

Particular Needs for Graphenes:

- Analytical limitations for quantifying GFMs in tissues and media with high organic content
- Opacity in liquid media at high concentrations
- Problems observing organisms
- Problems when light does not reach organisms (e.g., algae or plants)
- Interferences with test readouts

The OECD Early4AdMa questionnaire was used to address the environmental section, and the responses highlighted limitations in the applicability of OECD TGs to graphene materials. The study focused on the applicability of two Test Guidelines for environmental safety assessment: TG 203 (fish toxicity assay) and TG 201 (cyanobacteria growth inhibition test). The case study was conducted under the framework of the Graphene Flagship, using GR2M.

Several challenges were identified when performing environmental fate and life cycle assessments. It was possible to identify challenges in using these two TGs to generate reliable results. This means that research and development related to these guidelines can reveal limitations in their applicability to graphene family materials, but also procedures to overcome such limitations.

OECD TG 203: Acute Toxicity in Fish

- *Generating a dispersion. It will be generated as in the case of NMs, but there is a problem for the detection and quantification of GO. Solution: simultaneous use of absorbance and dynamic light scattering (DLS).*
- *Maintaining dispersion conditions for 96 h (the influence of fish in aquaria must be taken into account, so that assays were performed to observe stability of the dispersion without and with fish*) *Solutions*: Turbines (similar to flow-through system, although not sufficient), or turbines and natural organic matter (NOM) (suggested in GD 317, in this case, humic acid 50 mg/L were used))
- *Quantifying GO concentration in aquaria. As in the case of the detection and quantification of GO in the initial dispersion, GO concentration maintenance in the water column was assessed by the simultaneous use of absorbance and DLS*

There are several challenges to consider when testing graphene family materials and some will be similar to those of manufactured nanomaterials. Challenges that are specific to graphene include analytical limitations for quantifying these materials in tissues and media, opacity in liquid media at high concentrations, and characterizing and maintaining dispersion stability in aquarium water. These lead to different problems such as ability to observe the organisms, and light penetration, which affects algae or plants and causes interference with test results.

There are ongoing issues regarding the applicability of test guidelines to manufactured materials, especially graphene-related materials, due to difficulties in obtaining stable dispersions in aquatic media. To respond to the environmental section of Early4AdMa, it was noted that the questions are conditioned by the ability to generate appropriate results using test guidelines.

Under the Graphene Flagship framework, several assays were performed on different graphene materials (GO, reduced graphene oxide (RGO)) and at different concentrations. The stability of graphene materials was strongly dependent on material composition and ionic content of the liquid solution. To overcome this, the substance in suspension was allowed to sediment or this sedimentation was accelerated by centrifugation. The assay was then performed with the material remaining in the water column. Although

this concentration was not the highest, it allowed for measurable levels and enabled the assay to evaluate environmental fate and exposure.

One important challenge was detecting graphene family materials in tissues. This can be addressed using TEM; RAMAN; Confocal microscopy; Confocal laser scanning microscopy; Absorbance; X-ray Photoelectron Spectroscopy (XPS); AFM; SEM; Thermal Gravimetric Analysis (TGA); Total Organic Carbon analysis. A different challenge is quantifying graphene materials in tissues and substrates with high organic content, such as soils or sediments. Available methodologies are difficult to implement or extremely expensive. Currently, there is no viable method to appropriately evaluate the accumulation of graphene family materials, meaning TG 305 -bioaccumulation in fish (OECD, 2017b) is not applicable. It is difficult to quantify environmental exposure and levels of these materials in natural waters, sediments, or soils, which are inherently high in carbon content.

Finally, another aspect of environmental safety assessment is the life cycle of advanced materials and products containing them. Studies estimating the toxicity of RGO-enabled polyamide 6 (PA6) overcame difficulties in obtaining stable dispersions of abraded materials and RGO by combining vortex and bath sonication for different periods of time.

To summarise, it is crucial to consider the entire life cycle of advanced materials and products containing them. The challenge lies in identifying appropriate methods for exposure and hazard assessment, especially due to difficulties in obtaining suitable suspensions for analysis. One of the main challenges is the lack of analytical methods that can differentiate graphene flakes from the organic background in composite materials or media.

3 Signals and knowledge gaps on safety, sustainability, and regulatory issues

Introduction

Participant were divided in five groups ensuring different expertise across all groups, while considering the type of participation (online / on-site). Each breakout group was assigned a specific topic: *Environmental Safety* and *Human Health Safety* (both combining on-site and remote participation);; *Sustainability*, *Regulatory Issues* (remote participation only) and Cross-Cutting Issues (on-site participation). The information below summarises the outcomes from both sessions per topic, including feedback from the plenary discussion. Each group met in two separate sessions to address:

- Applying E4A – focused on identifying signals and knowledge gaps.
- Recommendations for Action – aimed at formulating actionable steps.

Environmental Safety

This session was moderated by Doris Völker (UBA with Kathrin Schwirn as rapporteur (UBA, Germany)

The group discussed GRM as such, no focus on any specify type nor on a specific application was made. However, it became clear that most knowledge on the ecotoxic potential is available for graphene oxide. Thus, most questions of the Early4AdMa step 5 questions on environmental safety were responded based on knowledge on graphene oxide.

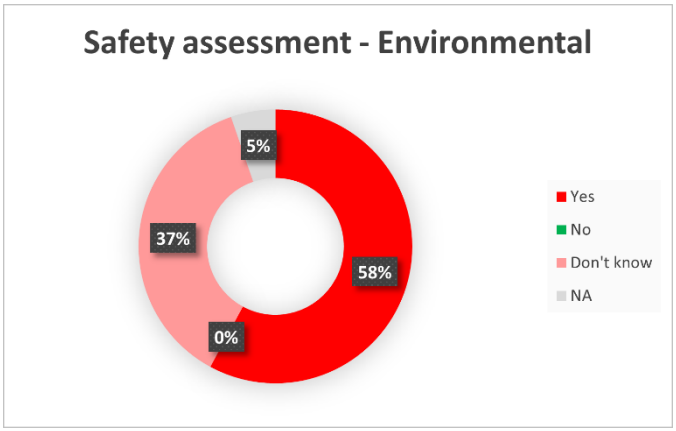
The discussion on signals for potential implications for environmental safety of GRM based on their physical chemical properties was mainly attributed to the hydrophobic character of the materials which will fundamentally influence fate and behaviour and interaction with environmental organisms and thus, ecotoxicity. Furthermore, the formation of reactive oxygen species as known for graphene oxide and the nanosized 2D morphology of GRM raise concerns regarding an ecotoxicological potential. Possible impurities or substances used as doping might introduce toxic effects as well. Based on available ecotoxicity data for graphene oxide, impact on daphnid mobility is reported as well as sublethal effects in fish, but no short-term mortality in fish. In addition, there are indications for antibacterial properties, i.e., introduced via mechanical interaction with cell membranes, which point towards a potential impact on microbial communities. GRM have the ability to absorb light. Thus, in the environment, this might impact photosynthesis depending on organisms. Due to the high surface area, adsorption of substances might be possible which on the one had could lead to a nutrient depletion in case important nutrients are adsorbed and thus, are no longer available to organisms. On the other hand, this might also lead to carrying of pollutants and by that, changing their mobility. It was highlighted that data on long term toxicity of graphene oxide and other GRM is largely missing.

Regarding fate and behaviour of GRM in the environment, still many knowledge gaps exist. Data on accumulation, persistence and mobility are missing, partly also due to the lack of appropriate test methods and analytical methods. Although, it was accepted that GRM can change in the environment, the underlying mechanisms are unknown to large extent, and it remains unclear which degradation products occur and how they impact hazard. However, it was observed that e.g., degradation products with structure similarities to polycyclic aromatics can occur. It is known that GRM are taken up by organisms and that phagocytosis is taken place, however, information on bioaccumulation or biomagnification is scarce.

For GRM many upcoming applications are expected, therefore, it is assumed that they will be produced in larger volumes in future and depending on the applications, environmental exposure over the life cycle is likely to occur. However, further information is needed to determine if direct exposure of biota is possible. Potential consumer applications identified from presentations and research projects are for instance inks, composites, car waxes and tyres, water purification, textiles, foot contact materials, or face masks. Based on the group´s opinion, the most likely sink for GRM in the environment are soil and sediment.

Based on the discussions of the breakout group many questions of step 5 of the Early4AdMa were responded with a "*Yes*" (indicating a signal), some with a "*don't know*". An overview on the distribution of the answers "*Yes*", "*No*", "*don't know*" and "*not applicable*" to the questions of step 5 on environmental safety of GRM is given in Figure 1.

Figure 1. Responses to the environmental safety questions on GRM within step 5 of the Early4AdMa



For GRM, biggest concern for environmental safety relates to the lack of understanding on their fate and behaviour in the environment as well as their interaction with environmental organisms. It is unknown based on which parameters of the material as well as based on which environmental conditions, degradation and transformation as well as corona formation will occur and how that might impact the hazard. A further concern are the existing analytical challenges which do not allow for reliable detection and quantification. Thus, the question is if the currently available methods for analytics show the right picture to e.g., quantify exposure conditions and thus, e.g., derive reliable effect concentrations in ecotoxicity tests. Many of the existing studies on ecotoxicity of GRM do not sufficiently report sample preparation and dosimetry. Thus, uncertainty remains regarding the real exposure situation and the observed effect concentrations. Sample preparation remains a challenge, e.g., regarding the use of sonication which may introduce defects into the material structure. Finally, the limited applicability of OECD TGs to determine ecotoxic effects and environmental behaviour to GRM remains an area of concern as well.

Drawing conclusions on the environmental safety of GRM is currently not possible due to many remaining knowledge gaps. Even though some freshwater ecotoxicity data are available for graphene oxide, data

gaps remain regarding effects on terrestrial and marine organisms, long term effects, bioaccumulation and fate and behaviour in general. Even less data is available for other GRM, such as graphene, reduced graphene, few layer graphene and functionalised graphene.

Recommendations for follow up actions

Based on this analysis of concerns and gaps regarding environmental safety of GRM, the group recommended follow up actions with following priority:

- OECD WPMN should review and revise the OECD GD 317 on aquatic and sediment toxicological testing of nanomaterials for the need for specific guidance for GRM. Such a revision should also include specific guidance on how to perform testing for interference.
- Of great importance is the development of proper analytical methods to detect, characterise and quantify GRM in test systems and complex matrices which should be taken forward by research, supported by funding agencies.
- The OECD Guidance on Sample Preparation and Dosimetry of Manufactured Nanomaterials, which is currently updated, should be supplemented by OECD WPMN with advice on sample preparation specific for the different GRM.
- As many data gaps remain for reliable environmental safety assessment of GRM, industry and research should focus on closing these gaps. Next to hazard information, this includes also research on environmental fate (e.g., transformation, mobility). In addition to that, OECD test methods to address the specific endpoints should be amended or newly developed, if necessary as well as validated by OECD, regulators, academia, and industry, supported by funding agencies.
- As long as there are no valid and accepted guidance for sample preparation, nor agreed procedures for interference testing, a list of minimum reporting requirements (e.g., energy input used for sample preparation) in scientific publications should be required by journals.

An overarching demand is seen in building up knowledge and expertise in testing fate and effects GRM in contract laboratories, in companies, and during education. Policy should establish a foundation for this. In addition, industry and research should collect data and provide information on uses of GRM and their release to the environment during life cycle.

Human Health Safety

This session was moderated by Agnes Oomen (RIVM - Netherlands) with Delphine Bard (HSE- United Kingdom) as rapporteur.

Physicochemical properties

GRMs can generally be considered as a nanomaterial, as one dimension in the pristine form is often smaller than 100 nm. Due to their physical structure, these materials can show new or enhanced properties, like electroconductivity or thermal conductivity, as compared to other carbon-based materials. There are indications for some persistency, although graphene oxide may degrade faster than graphene. Degradation (in organs) may change the material into amorphous carbon. The large surface area may implicate that the material is reactive. Unless functionalised or containing impurities, there is no indication for the release of toxic ions or molecules. The GRMs are considered unlikely to trigger frustrated phagocytosis, as these materials are so thin that they are not rigid. In contrast, impurities in the form of graphite platelets may be rigid, though it is unknown if these platelets can induce frustrated phagocytosis.

Hazard

Although progress has been made, e.g. by the Graphene Flagship and other projects, information on additional hazard or increased toxicity of GRM as compared to the conventional material(s) is often difficult to get and interpret. This is related to technical challenges. The properties of the material tested are not always (well) reported, i.e. including information on number of layers, lateral size, defects and impurities. Dispersing GRMs, especially the graphene and reduced graphene oxide forms, in aqueous media is highly challenging. This is required for many *in vitro* assays and some *in vivo* exposure routes such as oral and intravenous (IV) administration. Using high dispersion energies as is the case with probe sonication, damages the GRMs, so that the test results are not representative of the starting material. A dispersion protocol relevant for GRMs, or 2D materials in general, is expected to lead to more harmonised testing results. In addition, guidance on how to characterise a dispersion containing GRMs may be helpful, as 'simple' methods based on light scattering like DLS assume particles to be spherical. It is also unclear which conventional material is appropriate for comparing GRM (for example graphite or carbon materials in general).

Graphite platelets may have potential carcinogenic, genotoxic, or mutagenic effects due to their greater thickness and rigidity compared to GRM. However, there are currently no indications of such effects for GRM, though long-term studies are lacking. The reactivity and immunotoxicity potential are considered the most relevant drivers and should be considered when assessing hazard endpoints for GRMs. Hazard from constituent chemicals for non-functionalised GRMs are not expected, unless they originate from impurities. For functionalised GRMs, these additional constituents need to be considered.

Kinetics

There are some indications for uptake after inhalation exposure and uptake by cells in *in vitro* assays. However, there is very limited information, and differences between forms are expected. Better analytical methods for detection of GRM in complex matrices are needed. No information is available on transport across barriers like blood-brain, blood-testis and placenta. GRM may not be as persistent as poorly soluble nanometals, but (Newman et al.,2020) observed a half-life of slightly less than 1 month in spleen, suggesting that some accumulation may be possible in case of daily exposure.

Exposure

Inhalation exposure is considered most relevant for GRMs. Exposure for individual consumers is anticipated to be generally low due to the low amounts of GRM used in products and because release is generally not expected in normal use. However, in occupational settings and depending on the situation, e.g. sawing in composite materials, exposure may be possible. Furthermore, some sprays contain graphene (car care, tyre shining). It may also be used in lubricants (e.g. for bicycle chains etc.). In occupational settings, risk assessment should consider the dustiness of GRM. While large airborne agglomerates may be generated during handling, their low density means they could still be inhaled. Data on exposure is very limited, and measuring airborne GRM is challenging. As GRMs are increasingly used in products, occupational exposure, exposure to consumers and exposure at end-of-life is expected to increase. GRMs are often used in pastes and slurries that are dried in ovens before application in products. To cover these occupational settings, often in SMEs, there is a high need to derive an Occupational Exposure Level (OEL) for these materials.

Recommendations for follow up actions

Potential follow-up actions:

- Encourage that a (provisional) Occupation Exposure Limit (OEL) is derived for GRMs. This includes a method to determine exposure in the workplace.

- Develop guidance on dispersion preparation and characterisation of GRMs and/or 2D materials in general.
- Evaluate the applicability of (nano-specific) TGs and GDs for GRMs.
- Encourage that experimental studies report on the physicochemical properties and dispersion of the material.
- Encourage the use of positive controls and the availability of benchmark or standard materials.
- Encourage the development of better analytical methods for detection in complex matrices.
- Encourage that information gaps are filled: information on dustiness, chronic toxicity, toxicokinetic behaviour and release.
- Encourage gaining insight in the differences in exposure, toxicokinetics and hazard between different forms of GRMs.

Sustainability

This session was moderated by Eric Bleeker with Samia Ouhajji as rapporteur (RIVM, Netherlands).

Raw materials and resources

Graphite is a critical raw material and is used as resource to produce GRM.

Manufacturing, production, transport and use

The manufacturing processes of GRM (*e.g.*, Hummers' method and exfoliation) require considerable amounts of electricity and water. However, a direct comparison of environmental impacts should be based on the amount of material required to achieve a specific function in a given application. For example, if 1 kg of GRM provides 10-100 times greater functionality than an alternative material in a given application, the higher resource use per kilogram may be offset by the reduced total material required. The overall impact on global warming potential per unit of function delivered may be similar to or even lower than that of the alternative or conventional material. Proper comparison over the lifetime is necessary.

GRM is typically used in applications that have a "longer" lifetime, such as construction, batteries, sporting goods, electronics, etc. The production might then use more energy, but the product could last longer, resulting in an overall net gain. Some examples:

- Battery management systems containing graphene outlive those containing benchmark (metal-based) materials.
- For wind turbines, the additional environmental impacts from the production of GRM (considered in the LCA) are offset during the entire life cycle.

Other applications should be checked on a case-by-case basis.

End-of-life (recyclability and reusability)

Not much is known about the recycling of GRM. Recycling issues will depend on the degree of integration of GRM in the product (*i.e.*, how well could/should it be separated again for re-use?).

Data gaps

Many (potential) applications of GRM are still only available on lab-scale and extrapolation to industrial scale is difficult. Therefore, the environmental impacts of graphene industrial production plants and products containing graphene cannot be assessed with certitude. Also, information on end-of-life management is lacking. This applies to all materials in their early stages and is not specific to GRM.

Recommendations for follow up actions

- Manufacturers should invest in more sustainable production methods (less water and electricity) with higher yields.
- Manufacturers should think of replacing toxic chemicals and solvents by implementing safe-and-sustainable-by-design.
- Innovators and producers/manufacturers should take their respective responsibilities on end-of-life/recycling.
- Regulators should provide incentive for sustainability assessments.
- The participation of manufacturers in the sustainability assessments is important to clarify issues related to the production or for recycling processes. Experts from various backgrounds should be represented (e.g., innovators, manufacturers, risk assessors, life-cycle assessors, regulators).

Regulatory Issues

This session was moderated by Elisabeth Heunisch, Rapporteur: Anna Pohl (BAuA, Germany).

The international experts participating in this breakout group discussed worldwide regulatory issues towards graphene and GRM. Signals and knowledge gaps were assessed following the Early4AdMa questionnaire (Figure 2) and recommendations for actions to support regulatory preparedness were formulated and prioritized.

Issues towards sample preparation and analytics

Knowledge gaps towards sample preparation and analytics were discussed and issues were identified for the analysis of the characteristics of GRM as pristine material, for the sample preparation and for the analysis of graphene in complex matrices. Main reasons for these issues are the absence of guidance on specific preparatory steps and required modifications of existing protocols. Mainly agglomeration and subsequently dispersion issues are challenging the existing sample preparation methods. Best practice guidance on dispersion of different GRM is needed. In order to create guidance, one should test different GRM in different media under different conditions.

Furthermore, it became evident that a clear, harmonised terminology (GRM, GFM, GR2M, pristine material, tools etc.) is essential.

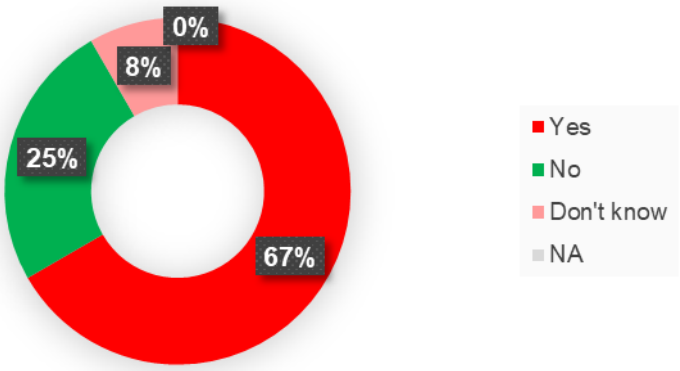
Tests to identity and characterize graphene are required since GRM properties differ between different manufacturers and from batch to batch. Variants for GRM can lead to different exposure profiles and hazard. Hence, directions should be available to match data generated for the identity and the (hazard) test. Standards for characterization of GRM are ISO standards and are behind a paywall. In addition, reference materials/benchmark materials are missing for the further comparability of methods and results. As complex matrices food, test materials, composites and released fragments were identified.

Issues towards the applicability of regulatory frameworks

The participating experts concluded that GRM are within the scope of current chemical or sector specific legislations, mainly by being considered as a chemical and a nanomaterial. The applications enabled by GRM may fall in other legislations and there might be regulatory gaps. The information requirements available for chemicals as well as for nanomaterials do not address the specificity of 2D materials. Therefore, a minimum data set for 2D materials is not available (lateral dimensions and number of layers should be assessed). In addition, other critical assessments like Raman and XPS should be performed and characterizing with the right techniques and in the right matrices is required. Better tools such as OECD Test Guidelines and Guidance Documents (on hazard characterisation and physicochemical

properties) are required to enable the enforcement of regulatory frameworks. The OECD TG 125 is not explicitly validated for plate-like/sheet-like materials. Methods for dispersion, dispersion stability, dosimetry, for measuring the rigidity, tests for similarity and test for mechanical stability in respective matrices (e.g. break-down) are yet to be developed. In addition, read-across is not valid from CNTs to GRM. Information on what drives the hazard of GRM should be generated and understanding the characteristics as exposed (during the life cycle) versus the pristine material is pivotal. Information on exposure models is missing and information and guidance for exposure assessment for different products that have GRM incorporated along the life cycle is required.

Figure 2. Applicability of Regulatory Frameworks based on the Early4AdMa Tool



Recommendations for follow up actions

The follow-up actions were identified by the participating experts. Besides prioritization, timing of the different actions is important to be considered as some of them depend on each other. It was also mentioned the need to develop descriptors to be able to group GRM in a more representative way to support safety assessment. The actions are listed below and identifies relevant stakeholders that could take this up:

1) Test exposure models and exposure test strategies for 2D materials (OECD's WPMN)
2) Research on what drives toxicity and determine relevant characteristics for grouping and read across (safety researchers, regulators, industry)
3) Develop reference materials associated with specific properties (similar to the way it was done for CNTs) (e.g. metrology institutes, IAM4EU)
4) Development and adaptation of TGs/GDs applicable for GRM (e.g. dispersion, characterisation, sample preparation, dosimetry, OECD TG 125, …). It is also important that guidance is applied for the other TGs. (WPMN, WNT, industry, regulators, IAM4EU)
5) ISO has produced the terminology and characterisation standards, and encouraged to adopt this (WPMN, WNT, ISO)
6) Document to establish a minimum data set for describing the identity of 2D materials. Properties like lateral dimensions and number of layers should be assessed. (regulators, researchers)
7) Requirements for reporting toxicity data, including those for the minimum data set for the identity on the materials tested (regulators)

8) Research on the difference between pristine materials and the forms released during the life cycle and how this may influence the toxicity profile (safety researchers)

9) One pager / appendix in the guidance to clarify for industry what is expected by the regulators (regulators)

Cross cutting issues

The discussion was moderated by Blanca Suarez-Merino (NIA) and Steffi Friedrichs (AcumenIST) as rapporteur.

Challenges and concerns related to .GRM

Advanced Materials such as GRM represent innovative solutions to address current environmental and health challenges and, within Europe, represent building blocks towards the implementation of Green Deal Goals and corresponding policies and regulations contained within. However, due to their complex composition and lack of a definition, they challenge current regulations. The speed at which these materials are being developed represents one further challenge to regulators, who struggle to prepare themselves and adapt current regulations to capture the unique nature of some of such materials. In the case of GRM, the *One Substance One Assessment approach* was seen as a concern, since GRM represent an umbrella term to cover for different types with different toxicity profiles. It was discussed that collecting toxicity data from just one type of GRM could easily misrepresent other types. At the same time, the extent of variation permissible before distinguishing between two groups of GRM remains a critical issue that requires careful consideration and decision.

It was also highlighted that generally, even if discussions mentioned Advanced Materials, speakers refer to nanomaterials (as it is the case of GRM). However, a large group of Advanced Materials are represented by composites, and either mixture toxicity may apply to those, or one may be referring to articles rather than substances (with their corresponding regulatory obligations). In any case, it was also important to highlight that there are also sectoral regulations in place to take care of safety of products based on expected use (e.g.: cosmetics, medical devices, food contact materials, etc.).

In the absence of a definition of an Advanced Material (difficult to accomplish due to a temporal factor linked to them), it is however impossible for any regulation to take up an undefined term, and it may be wiser to name Advanced Materials using applicable and well-defined terms where possible (e.g. polymers, nanomaterials), so relevant regulations and information requirements could then be identified.

Further concerns were identified regarding the misinterpretation that wider use does not imply wider exposure, and, even if a particular Advanced Material is used to develop a product, that does not mean that the same material will be released, it is very likely that it will be transformed during the manufacturing process. So, testing the initial toxicity may be irrelevant compared to what the user will be exposed to. In this regard, it is advisable to evaluate which tests make sense when dealing with these types of materials, and, characterisation of the released fraction, rather than the pristine material, may be more relevant from a safety perspective.

Important data gaps related to graphene related materials (GRM)

Although the OECD WPMN has made significant efforts to address the challenges of testing GRM—first by identifying these challenges and then by developing and adapting methodologies—several gaps persist, including the ability to detect carbon-based materials within a carbon background.

One further urgent gap which needs to be addressed is to develop descriptors to be able to group GRM in a more representative way to support safety assessment. During the discussion, reference was made to the proposed descriptors from the Graphene Council (see https://www.thegraphenecouncil.org/page/GrapheneStandards), some of those, however, are difficult to address experimentally, as well as costly. Data should therefore be provided in the Technical Data Sheet (TDS). It was also mentioned that ISO developed Technical Specification (TS) which defines terms for graphene, graphene-related two-dimensional (2D) materials and other 2D materials. It includes related terms for production methods, properties and characterization. It is intended to facilitate communication between organizations and individuals in research, industry and other interested parties and those who interact with them[7].

Recommendations for follow up actions

The discussion group suggested that the development of a strategy to group GRM, so as to identify how much variability is allowed between batches, is much needed to save redundant testing, or to point out to testing if the GRM shows too much variability. Furthermore, an overview of relevant testing approaches is encouraged, since some tests do not seem to be implementable to GRM and are, at the same time, not relevant based on their predicted life cycle.

Finally, to support regulatory testing, it may be advisable to name the Advanced Material (in this case GRM) under a defined term (e.g. in this case nanomaterials, but we could be dealing with polymers, etc), so it will be easier to identify regulatory needs requirements and protocols.

[7] See: ISO/TS 80004-13:2017. Nanotechnologies — Vocabulary — Part 13: Graphene and related two-dimensional (2D) materials. https://www.iso.org/obp/ui/#iso:std:iso:ts:80004:-13:ed-1:v1:en

4 Recommendations

The recommendations developed during the workshop included:

- Harmonized terminology in the context of OECD SG AdMa.
    - Participants noted that the speaker from ISO provided an overview on terminology developed within its organisation and nuances between terms such as Graphene Family Materials (GFM), Graphene Based Materials (GBM). Graphene-Related 2D Materials (GR2M) were also presented. It was suggested to investigate ISO's key descriptors including at least defects, impurities, lateral size, thickness, elemental composition, number of layers.
    - Although there are various terms and definitions in the literature to describe these materials, consensus on terminology or the development of definitions were not discussed in the workshop. The term used during the discussion was graphene-related materials (GRM) to refer to materials that are composed of, derived from, or structurally related to graphene.
- To improve hazard and risk assessment, regulatory preparedness as well as sustainability for GRM, data gaps need to be closed. There is a need to address information gaps such on environmental safety (such as (long-term) ecotoxicity, persistence, bioaccumulation endocrine disruption, carrier for other pollutants, fate) and human health safety (such as chronic toxicity uptake/translocation, dustiness, release) and sustainability (such as extrapolation to industrial scale, end of life management) including transformation of GRM during life cycle. The amount of data available varies, e.g. depending on the type of graphene (e.g., GO vs G or RGO)
- Review the current state of art regarding the applicability of TGs and GDs for GRM. (or when they are/are not applicable) If there are not applicable, appropriate methods should be developed, and harmonisation is needed. This also includes:
    - Analytical methods to detect and characterize GRM in matrices (organic background, *in vitro* assays, organisms, environmental compartments, occupational settings, products) .
    - Development of recommendations on how to deal with interferences and impurities.
    - Harmonised dispersion protocols/sample preparation and guidance on sample preparation and dosimetry
    - Development of reference and benchmark material(s)
- A minimum requirement for information in publications should be defined. (e.g. characterisation of test material, sample preparation procedure for testing).
- Physico-chemical properties should be characterised (with appropriate techniques) and reported in hazard and exposure studies, both for the pristine material and during testing in respective media. The above-mentioned key descriptors should also be considered in the regulatory context, e.g. for

- understanding of sameness and similarity between various GRM and read-across possibilities.
- the impact of transformations during life cycle .

- Finally, regarding sustainability, manufacturers are encouraged to make the manufacturing process more sustainable (e.g. fewer toxic chemicals, less energy and water demand).

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Ms. Mar GONZALEZ	*Administrator, Nanosafety and Outreach* *ENV/EHS*

Annex 2. Agenda of the workshop

Time	Topic	Presenter/ Chair
26th November 2024		
9:00	Welcome	OECD Secretariat
9:10	Introduction	SG AdMa Chairs
9:20-10:50	Session I - Setting the Scene	Chair: Eric Bleeker (RIVM, NL)
9:20	Overview on Graphene Family Materials & their properties	Mary Gulumian (NW University, South Africa)
9:40	Graphene characterisation and terminology	Charles Clifford (NPL, UK)
10:00	Synthesis [synthesis methods and scalability; precursors, energy expenditures]	Stephen Hodge (Versarien, UK)
10:15	Relevant types and their promising (future) applications	Beatriz Alonso (Graphenea)
10:30	Discussion	Chair: Eric Bleeker (RIVM, Netherlands)
10:50	*Coffee break*	
11:20	Session II - State of the Art	Chair: Jörg Radnik (BAM, DE)
11:20	State of the knowledge on human health	Bengt Fadeel (Karolinska Institutet, Sweden)
11:40	State of the knowledge on environmental toxicity	Mona Connolly (INIA, CSIC, Spain)
12:00	Predicting environmental releases of different forms of graphene-based materials	Bernd Nowack (EMPA, Switzerland)
12:20	Discussion	Chair: Jörg Radnik (BAM, Germany)
12:50	*Lunch break*	
14:20	Session III - Applications	Chair: Blanca Suarez-Merino (NIA, BE)
14:20	Evaluation of Early4AdMa for graphene-epoxy composites with a focus on end of life	Veronique Adam (TEMAS Solutions, Switzerland)
14:40	"Sustainability Aspects of Graphene-based Materials evaluated within the scope of SSbD"	Fiorella Pitaro (EMPA, Switzerland)

15:10	Discussion	Chair: Blanca Suarez-Merino (NIA, Belgium)
15:30	Coffee break	
16:00	Session IV – Methodological and Regulatory Challenges	Chair: Kathrin Schwirn (UBA, DE)
16:00	Regulatory challenges/questions (focus on legal requirements)	Eric Bleeker (RIVM, Netherlands)
16:20	Methodological challenges and gaps physico-chemical characterisation	Jörg Radnik (BAM, Germany)
16:40	Methodological challenges and gaps human health	Marco Pelin (Universita degli Study di Trieste, Italy)
17:00	Methodological challenges and gaps environment	Jose Maria Navas (INIA, CSIC, Spain)
17:20	Discussion	Chair: Kathrin Schwirn (UBA, Germany)
17:50	Wrap up & End of the Day 1	

27th November 2024

Session V – identifying knowledge gaps and potential actions		
9:00	Welcome	Kathrin Schwirn (UBA, Germany)
9:10	Introduction to the Early4AdMa Approach	Samia Ouhajji (RIVM, Netherlands)
9:30	Introduction to the scope and context of the interactive sessions	Kathrin Schwirn (UBA, Germany)
9:40-10:10	Split into breakout groups / coffee.	

Session VI: Signals and knowledge gaps on safety, sustainability, and regulatory issues					
10:10-11:50	**Sustainability**	**Cross cutting issues**	**Human health safety**	**Environmental safety**	**Regulatory issues**
	Chairs: Eric Bleeker Samia Ouhajji	Chairs: Blanca Suarez-Merino Steffi Friedrich	Chairs: Agnes Oomen Delphine Bard	Chairs: Kathrin Schwirn Doris Völker	Chairs: Elisabeth Heunisch Anna Pohl
11:50-13:50	Lunch Break				
Session VII: Recommendations for actions to support regulatory preparedness and Safe(r)-and-Sustainable-by-Design					
13:50-14:50	**Sustainability**	**Cross cutting issues**	**Human health safety**	**Environmental safety**	**Regulatory issues**

14:50-15:20	*Coffee break*	
Session VIII: Summary from Breakout groups		
15:20	Report from the Breakout Groups Session VI & VII	Chairs & Rapporteurs
16:50	Discussion	Chair: Agnes Oomen (RIVM, Netherlands)
17:20	Wrap up & Next steps	Kathrin Schwirn (UBA, Germany)
17h30 End of the Workshop		