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PERSPECTIVE

Regulatory challenges and risk assessment of graphene-enabled products: insights for safe commercialisation in Europe

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Abstract

The development of graphene-enabled products in a variety of industrial sectors like medical devices, textiles, aerospace, or food contact materials has raised significant regulatory challenges with regards to risk assessment. The work performed under the Graphene Flagship Work Package SH11 termed SafeGraph, aimed to identify challenges while implementing regulation as well as to develop a regulatory roadmap addressing these issues. This study explores and discusses the regulatory gaps and safety assessment challenges associated with graphene-enabled products and based on regulatory requirements with a particular focus on risk assessment, exposure concerns, and potential environmental impacts. Through case studies involving skin sensors, drinking water filters, wearable electronics, and de-icing systems for aircrafts, we identified critical safety and compliance issues across various sectors. The work used four Graphene Flagship case studies as showcases to address the above markets (CHEMsens, GRAPHIL, WEARgraph and GICE). These case studies underscore the need for updated regulatory guidelines tailored to graphene's unique properties. This study provides insights into current challenges of assessing risks and proposes steps to ensure safe and sustainable commercialisation of graphene-based products, advocating for harmonised regulatory frameworks.

1. Introduction

Simple graphene was first isolated in 2004 as a two-dimensional (2D) carbon nanomaterial with remarkable properties, such as high electrical conductivity, mechanical strength, flexibility, and thermal stability [1]. These characteristics have promoted the integration of graphene into a wide range of industrial applications. However, the term graphene is currently used in a generic manner to cover several different types of graphene-related materials (GRMs) (e.g. few-layer graphene or graphene oxides). The differences between the GRM options can however be of concern when assessing their potential risks and a classification framework for GRM has thus been developed to describe the key differentiating properties [2]. In the present publication both graphene and GRM are used interchangeably.

The global graphene market is projected to grow exponentially, reaching $1.48 billion by 2025 [3]. This boom presents a challenge regarding chemicals legislation and risk assessment, as graphene can show nano-specific toxic effects depending on their physical-chemical properties, such as shape, dimension, stiffness, impurities etc [4, 5]. While GRM could offer immense benefits in some applications, ensuring its safe use in consumer and industrial products requires addressing regulatory gaps, particularly in relation to its unique nanomaterial characteristics.

In the European Union (EU), regulations such as REACH [6] (registration, evaluation, authorisation, and restriction of chemicals) and CLP [7] (classification, labelling, and packaging) were established to protect human health and the environment from risks posed by chemicals, including nanomaterials. In fact, depending on the type of product, there are specific sectoral regulations to be followed, and those containing graphene will be the focus of this publication. Worldwide, different countries differ greatly in the way they regulate GRM. This is based on the fact that several jurisdictions do not contain provisions for nanomaterials or risk assessment may be guided, initially, following exposure, such is the case of the US Toxic Substance Control Act Significant New Use Rules [8]. In general REACH is considered one of the most stringent regulations and requires full hazard assessments of chemicals (which may not be required upfront in the US) [9]. The need for a comprehensive regulatory framework for GRM becomes even more pressing when considering the rate at which graphene-enabled products are entering the market. With over 26 000 graphene-related patents registered globally [10], the rapid commercialisation of graphene-based technologies necessitates harmonised regulatory practices to streamline safe development that does not require the consideration of many guidelines. Indeed, despite the recognition of graphene as a key nanomaterial, regulations have not kept pace with its application in diverse industries, leaving manufacturers with the daunting task of navigating a fragmented regulatory environment.

In Europe, the above comes as a result of the fragmented regulatory landscape where REACH, as a transversal regulation, is hazard driven whereas sectoral regulations also take into account relevant exposure routes [11]. Worldwide efforts to update testing guidelines and guidance to graphene are ongoing under organisations such as ISO229 [12], American society for testing and materials (ASTM) [13] or the organisation for economic co-operation and development (OECD) WPMN. In general, adaptation of testing guidelines and guidance to nanomaterials is on-going (including graphene) however progress has been slowed down due to a lack of funding from OECD Member States. To speed up this process, a priority list was created by industry and regulators to indicate which guidelines and guidance are most relevant and should be adapted first, namely the Malta Priority List [14]. The list included transversal guidelines like dispersion, which may be used across different testing approaches [15].

Therefore, 'SafeGraph' was developed under the 'Graphene Flagship' to review and evaluate the complex regulatory landscape associated with graphene products. 'SafeGraph' utilised four case studies to illustrate the regulatory challenges encountered when bringing graphene-enabled products to market. The selected case studies represent those sectors most prolific regarding use of graphene, e.g. consumer products such as textiles or wearables and aeronautics. Such sectors do not contain yet specifications for the nanosize. The medical device sector and food and feed sectors were selected to showcase the demands of regulations which contain specifications for nanomaterials (e.g. graphene). The work performed focuses on EU regulations as they represent one of the most stringent regulations worldwide. Each case study represents a sector with unique regulatory requirements and distinct safety concerns. The first case study, 'CHEMsens' [16], focused on medical devices through the development of a skin sensor, integrated into a plaster for biomonitoring stress biomarkers in sweat. This case study was used as an example to highlight the complexities of achieving compliance with the medical device regulation (MDR) [17], which requires detailed safety data and adherence to REACH. The second case study named 'GRAPHIL' [18], developed a grapheme oxide-based drinking water filter using polymeric hollow fibre membranes with graphene. This case study falls under the regulation for food contact materials [19], emphasising the need for exposure-driven risk assessment, particularly in ensuring good water quality and avoiding the migration of the nanomaterials. The third case study, 'WEARgraph' [20], focused on integrated textile-based wearables that can also be used for energy conversion and storage. This case study was selected to illustrate the regulatory gap in the textile industry for specific provisions regarding nanomaterials like GRM. The fourth case study, 'GICE' [21], sought to advance in the development of graphene-based ice protection technologies to be integrated in helicopter rotor blades. This case study has been used to investigate the potential sustainability improvements of graphene-based de-icing systems for aircrafts.

2. Methodology

The results presented in this study were produced following a stepwise approach as: (1) mapping the regulatory landscape of the selected case studies, (2) dissecting the identified regulations, directives and legislations regarding provisions for nanomaterials, (3) identification of end point requirements (physicochemical characterisation, hazard characterisation and exposure assessment), (4) recommendations regarding methodologies to address those, (5) testing where possible with 'SafeGraph' materials following latest recommendations from OECD and EU projects, (6) collection of results, (7) identification of gaps based on 'SafeGraph' testing approaches and literature reviews. 'SafeGraph' partners evaluated 15 regulations, legislations and directives which were identified as relevant for industry prior to product market launch in the selected sectors, those were as follows: regulation (EC) No 1272/2008—CLP of substances and mixtures, Regulation (EC) No 1907/2006—REACHs, Directive 98/24/EC—risks related to chemical agents at work, the MDR 2017/745, Directive 89/391—OSH 'Framework Directive', directive 2019/1831 (occupational exposure limit (OEL) values), directive 2004/37/EC (carcinogens or mutagens at work), Regulation 1007/2011 on fibre names and related marking of the fibre composition of textile products, EU regulation 765/2008) for launching products on the EU market, RoHS directive 2002/95/EC (EU legislation restricting the use of hazardous substances in electrical and electronic equipment). Directive 2004/108/EC Electromagnetic Compatibility, regulation (EC) No 1935/2004, regulation (EU) 2019/1381, directive (EU) 2020/2184 on the quality of water consumption and regulation (EU) 2023/988 on general product safety. Other documents evaluated were the Guidance document for the Conformity Assessment and Certification of Complex products, ISO 10993, ISO/TS 80004-13, ISO 14040 and ISO 14044. Testing approaches regarding safety followed OECD testing guidelines and guidance recommendations, where available.

In the context of environmental exposure assessment, current analytical methods for quantifying engineered nanomaterials and distinguishing them from naturally occurring nanomaterials are insufficient [22]. The lack of techniques capable of specifically detecting and differentiating GBMs from other carbon-based materials in environmental samples poses a further challenge [23]. The predicted environmental concentration thus serves as the best available estimate for environmental exposure assessment [24, 25]. In the referring study a material flow analysis model was used, based on the complete life cycle of applications containing GBMs, to account for the full movement of these materials through Europe's anthroposphere and into the environment.

The general life cycle assessment (LCA) method described in the ISO 14040 and 14044 documents can be used without many changes to support the evaluation of the environmental sustainability for GRMs (as shown in Munuera *et al* [26] or Beloin-Saint-Pierre & Hischier 2021 [27]). Only two adaptations would improve the relevance of LCA studies: (1) using impact assessment methods that consider the effects of GRM on human health and (2) specific descriptions of their uses with descriptions of how physical properties of GRMs might affect their use in devices.

3. Current challenges and identified gaps to address sector specific regulatory requirements

The rapid commercialisation of graphene presents several challenges, particularly when trying to ensure regulatory compliance. In this section we present the challenges encountered while trying to fulfil the different regulations required for our case studies to achieve successful market launch in the EU. The first challenge encountered was represented by a significant gap in the alignment of regulations for nanomaterials like graphene and GRM across various sectors. For example, the definition of what nanomaterials are varies between REACH and other sectoral regulations, such as food contact materials (FCMs) or cosmetics. Besides, the new EU recommendation for a definition of nanomaterial [28] has not been taken up by any regulations so far (as of April 2025), so it has not been legally enforced. This discrepancy leads to varying data requirements, creating hurdles for manufacturers who need to ensure that their products meet all necessary safety standards.

Regarding GRM, a harmonised definition is essential to ensure consistency in safety assessment, quality control and regulatory compliance. Currently, however, the only definition published is that by ISO/TS 80004-13:2007, whereas REACH, EFSA or FDA lack definitions. Besides a harmonised definition, the Graphene Council (even if not a regulatory body itself) is advocating for a harmonised classification system for graphene [29].

Second, the lack of standardised testing methods for GRM is a critical issue. Current hazard and exposure assessment methodologies may be inadequate for evaluating the unique properties of GRM. Without such standardised methods, regulatory bodies face challenges in accurately assessing the risks associated with graphene and GRM.

Another significant challenge is the absence of guidelines for the detection and quantification of graphene in complex matrices at low concentrations with relatively high carbon content originating from natural organic matter such as biological tissues or humic acids in environmental samples. As graphene is increasingly incorporated into consumer products, the risk of its release into the environment or human exposure grows. Novel detection techniques like SERS, have been developed [14], which can be used e.g. for migration testing or environmental monitoring, but widespread adoption and standardisation of these methods remain necessary to ensure regulatory compliance.

Lastly, environmental concerns are becoming more prominent as graphene and GRM use expands [30]. Current environmental hazard assessment frameworks do not adequately address the potential eco-toxicological impact of graphene and GRM, particularly in aquatic ecosystems. There is an urgent

Table 1. Methods identified as relevant to cover for regulatory needs regarding intrinsic properties of GRMs together with limitations encountered for graphene.

Method	Measured properties	Status for GRM
OECD TG 125	Particle size distribution	Applicable, recently developed
Electron microscopy	Morphological characterisation: shape and aspect ratio	Applicable for graphene
X-ray diffraction	Crystallinity	Applicable for graphene
Brunauer–Emmett–Teller (BET)	Specific surface area (powder form)	Applicable for graphene (powder)
Small angle x-ray scattering (SAXS)	Specific surface area (suspensions)	Ongoing development for graphene suspensions
OECD TG 124	Volume specific surface area	Applicable for graphene, used for powders
OECD TG 318	Dispersion stability in environmental media	Applicable for graphene, environmental media

Table 2. Methods identified as relevant to cover for regulatory needs regarding extrinsic properties of GRMs together with limitations encountered.

Method	Measured properties	Status for GRM
OECD 318	Dissolution rate in biological and environmental media	Methods under development
OECD 318	Stability, aggregation, and agglomeration	Relevant for graphene, methods available
Electrophoretic mobility	Zeta potential	Used as a proxy for surface charge in graphene
Reactivity tests (e.g. biological, photoreactivity)	Reactivity in various environments	Not fully standardised, some methods available
ISO 20814:2019	Photocatalytic activity	
ISO/TS 19006:2016	Intracellular ROS production in macrophage cell line	
ASTM E3351-22	*In vitro* nitric oxide production	
Dustiness	Dust released from nanomaterial handling	Methods being adapted for graphene in the EU project called MACRAMÈ [31]

need for regulatory bodies to adapt existing guidelines to include nanomaterials and their potential environmental effects.

3.1. Physicochemical characterisation

Physicochemical characterisation of graphene and GRMs was a requirement in all sectoral regulations addressed in 'SafeGraph', and various limitations have been encountered while trying to meet the regulatory requirements as enumerated below (tables 1 and 2).

Minimal data requirements: for regulatory purposes, specific information is needed on the number-based particle size distribution, surface functionalisation, morphology, specific surface area, and chemical composition of nanomaterials, including graphene. Most available methods are applicable to graphene, although small angle x-ray scattering (SAXS) is under development for specific surface area of graphene suspensions.

Methodological challenges: existing methods for determining physicochemical properties like particle size and surface area are often inadequate for GRM. Some test guidelines (TGs), such as OECD TG 110, are not applicable, leading to the development of new guidelines like OECD TG 125.

Surface functionalisation and shape: methods are available for surface chemical analysis, but challenges remain in harmonising the types of surface modifications and geometric dimensions of GRM. For example, determining shape and aspect ratio requires advanced microscopy methods.

Extrinsic properties: properties like solubility, dustiness, and dispersibility are crucial for understanding the behaviour of GRMs in different environments (e.g. water bodies). Some methods need further development and standardisation.

Future methodological developments: additional guidelines and methods are under development for characterising GO in complex environments.

Expertise from Contract Research Organisations (CROs): at present it remains a challenge to identify commercial (certified) laboratories which can perform complete physicochemical assessments. A full assessment is also expensive and requires highly trained personnel. Since physicochemical characterisation may be accepted without Good Laboratory Practices a solution may be to seek expertise from Research Laboratories rather than CROs.

3.2. Hazard assessment

'SafeGraph' examined the current limitations and regulatory gaps in the hazard assessment of GRMs, focusing on their testing and evaluation in compliance with EU regulations, particularly REACH. Specific concerns were identified and necessary adaptations suggested to accurately assess the risks posed by these nanomaterials.

Under REACH, hazard assessment for nanomaterials must be more comprehensive than those for conventional materials, as nanomaterials and their nanoform have unique physicochemical properties that influence their behaviour in biological and environmental systems. For instance, recent research demonstrated that standard tests used to assess skin irritation and corrosion (OECD TG 439 and TG 431) have been found applicable to GRMs when used in solid form [32, 33] but other tests, such as those for skin sensitisation, are less straightforward. While the OECD TG 442D and 442E guidelines can be applied to graphene with a few modifications, TG 442C has been deemed unsuitable due to technical difficulties with the unique characteristics of graphene [34]. Regarding skin sensitisation, the OECD TG 442B able to measure, *in vivo*, the fourth key events of skin sensitisation adverse outcome pathway, which has been successfully adopted for GRMs without encountering limitations [35, 36].

Genotoxicity and mutagenicity testing is a required endpoint in several regulations, and here we found that challenges such as GRM aggregation can affect the accuracy of tests like the micronucleus assay (OECD TG 487) and the chromosomal aberration assay (OECD TG 473). These limitations have been mitigated by introducing controlled cell agitation during testing [37]. Additional modifications are required for toxicokinetic assessments, as the current guidelines (OECD TG 417) are not directly applicable to GRM, with new guidelines expected in 2025.

Environmental hazard assessments are particularly complex for GRMs due to their tendency to aggregate and alter their properties in aquatic environments. Standard tests for water-soluble chemicals, such as those outlined in OECD TG 201, TG 202, and TG 203, must be applied carefully when testing water-insoluble nanomaterials like graphene. Particularly, TG 201 requires precautions to properly implement the standard protocol because of the natural tendency of GRM to agglomerate, and then sediment, when in mineral aqueous media [38]. There is also still a need for methodological advancements to ensure accurate risk assessment, as the use of turbulence during testing to maintain stable dispersions might not always suffice. Methods for risk assessment are listed in table 3.

3.3. Exposure assessment

The exposure assessment of graphene and GRM poses significant challenges due to the absence of standardised detection methods and the complexity of assessing nanomaterials in various environments. Occupational exposure studies have shown that airborne concentrations of graphene particles remain low during the manufacturing and handling processes. Spinazzè *et al* [39] showed that the lung deposited surface area concentration (LDSA), which is an expression of the deposition probability in the lung, was up to 63 μm^2 cm^{-3} for a typical worker's profile, i.e. engineers exposed for 8 h to graphene. For comparison, the LDSA was 30 μm^2 cm^{-3} in the case of non-exposed office workers. Depending on the workplaces and tasks, the measured particle number concentration was up to 6600 particles cm^{-3} (given as 8 h time weighted average [8 h TWA] exposure), equivalent to a mass concentration of 3.9 μg m^{-3}. Spinazzé *et al* also mentioned in their monitoring study that these results are below the reference level at 40 000 particles cm^{-3} [39]. Lee *et al* estimated, based on data from a sub-chronic inhalation toxicity study, an OEL for graphene at 18 μg m^{-3} [40]. However, long-term studies are still required to establish binding OELs specifically for graphene [41]. Preliminary data indicate that graphene is unlikely to pose immediate risks due to acute toxicity effects under controlled industrial conditions, but a more comprehensive evaluation is necessary for regulatory compliance and, in particular, for long-term exposure and toxicity effects.

In terms of consumer exposure, current applications include suspensions of GRM in sprays or embedded GRM in solid matrices, such as wearable electronics and medical devices, the latter solid options significantly reducing direct exposure risks. However, the potential release of graphene under varying environmental conditions (e.g. changes in pH, temperature, or UV exposure) requires thorough investigation. Recent studies have demonstrated that mechanical stress, weathering, and aging can significantly affect GRM release rates from consumer products. Particularly concerning are applications like food packaging materials, where direct contact with consumables occurs under varying physicochemical conditions.

Environmental exposure assessments have revealed advances in detection methodologies, though significant data gaps remain. Recent developments in analytical techniques, such as Raman, electron microscopy, or Brunauer–Emmett–Teller (BET), have improved our ability to detect and characterise GRMs [42]. Moreover, confocal microscopy has been demonstrated as an effective tool for high-resolution characterisation and *in-situ* monitoring of

Table 3. Methods identified as relevant to cover for regulatory needs regarding hazard assessment of GRMs together with limitations encountered for GRM.

Guidance/guideline/approach	Measured endpoints	Limitations
OECD TG 439 & 431	Skin irritation and corrosion using graphene-related materials in 3D human epidermis models	Doses used are high for graphene materials due to their low weight-volume ratio
OECD TG 442C, 442D, and 442E	Peptide reactivity, keratinocyte activation, and dendritic cell activation	TG 442C is not applicable for graphene, TG 442D requires modifications, TG 442E requires careful concentration selection
OECD TG 442B	Lymphocyte proliferation in skin sensitisation through a local lymph node assay	No significant limitations noted for graphene
OECD TG 487 and OECD TG 473	Chromosomal damage in genotoxicity studies	Material aggregation complicates visualisation of micronuclei and metaphases; cell agitation needed
OECD TG 489	DNA damage	Aggregation observed on cell membranes; agitation during cell incubation is required
OECD TG 476	Mutation block in genotoxicity testing	No specific limitations noted
OECD TG 417	Toxicokinetics	Current guideline (OECD TG 417) is under development for nanomaterials and does not apply to graphene; new TG expected in 2025
OECD TG 201, 202, 203	Toxic effects on freshwater organisms (algae, daphnids, fish)	Standard protocols need modifications for graphene; aggregation, sedimentation, and bioavailability pose challenges

graphene materials, enabling high-resolution analysis at sub-micron resolution [43]. However, analytical techniques for detecting and quantifying GRMs in complex environmental matrices such as soil and water are not yet robust (sensitivity) and accurate (selectivity) enough. Regarding exposure concentrations and for simplification, *in silico* models like dynamic probabilistic material flow analysis (DPMFA) are employed to predict release concentrations (PRCs) of GRMs into the environment. These models suggest that the PRC values of GRMs are expected to remain low until 2030. However, further experimental data and monitoring studies are necessary to refine these models, which also require further development to consider potential transformation and degradation products of GRMs over time [24, 25].

In conclusion, while the use of graphene and GRM is expected to increase across various industries, there are no graphene-related OELs in the EU. A field study evaluated gaps in exposure assessment approaches (tables 4 and 5) even though an increasing

Table 4. Gaps identified under consumer exposure.

Guidance/guideline/approach	Measured quantity	Limitations for graphene
Migration Testing for Food Contact Materials (FCMs)—EFSA	Potential release of graphene from water filters into drinking water	No standardised methods to detect or quantify graphene migrates

Table 5. Gaps identified under environmental exposure.

Guidance/guideline/approach	Measured quantity	Limitations for graphene
Exposure modelling by dynamic probabilistic material flow analysis (DPMFA)	Predicted release concentration (PRC) of GRMs into the environment	Does not potential consider or degradation processes to evaluate the environmental fate of GRMs
OECD TG 201, 202, 203 for aquatic toxicity	Toxic effects on algae, daphnids, and fish in aquatic environments	Standard tests not applicable to water-insoluble nanomaterials like graphene
Sampling and monitoring for GRMs in environmental samples	Monitoring of GRM release in soils, waters, and environmental compartments	Current methods are not sensitive or robust enough for complex environmental samples

explorative graphene safety activity is observed [4]. Future efforts must focus on developing standardised testing methodologies, long-term exposure studies, and regulatory frameworks that address both occupational and environmental risks associated with GRMs. These advancements are crucial for the safe commercialisation and responsible management of GRM and related products.

4. Identified gaps in the 'SafeGraph' case studies regarding sectoral regulations

The identified regulatory needs while trying to produce REACH-relevant safety assessment dossiers with the 'SafeGraph' case studies, allow us to identify gaps in the regulations, which will need to be further addressed. These gaps span multiple dimensions, from analytical challenges to environmental fate considerations.

In the medical device sector, the MDR has clear guidelines for regulatory compliance and an ISO standard dedicated to nanomaterials has been released (ISO10993-22). However, this standard presents limitations for hydrophobic materials like some GRMs and lacks comprehensive guidance on environmental fate assessment. Besides that, the MDR generally considers devices with nanomaterials as type II devices, which by definition need a dedicated testing scheme which may include *in vivo* studies. The safety assessment report produced for 'CHEMsens' also highlighted that the highest potential for release of graphene from medical devices is associated with devices in which:

- The graphene and GRM are intended to be released,
- Those that are composed of free graphene,
- Release/loosening of graphene present as coatings,
- Chemical breakdown or wear-and-tear processes due to (bio)degradation of medical devices,
- Grinded, polished or shaped during application,
- Graphene released during product application due to grinding or polishing.

Hence one main issue to successfully launch a graphene-based medical device on the market is to be able to evaluate the amount of graphene that may be released during use and how this would subsequently affect the patient. The development of technologies to address the release of graphene from complex matrices thus stands as a first priority. In the particular case of 'CHEMsens', and following the MDR ISO10993-22 [44], the identification of graphene and GRM in body fluids such as sweat may become a need to be addressed prior to market release.

The consideration of three other end points is required for these types of devices, namely skin sensitisation, cytotoxicity and irritation. ISO10993-22 is adapted to nanomaterials and should be followed for medical devices, however, issues such as dosimetry and exposure are not covered for hydrophobic materials such as GRM.

Our four case studies highlighted that environmental fate considerations represent a crucial aspect requiring regulatory attention. The potential transformation and degradation of GRMs in environmental matrices present unique challenges for risk assessment. Indeed, current regulatory frameworks must be evolved to address the complex behaviour of GRM in different environmental compartments, including air, water, and soil. This includes consideration of heteroaggregation processes, surface modifications by natural organic matter, and potential bioaccumulation pathways. Regarding the use of graphene in wearable electronic or electronic textiles (e-textiles), 'SafeGraph' identified 11 regulations which were relevant for textiles. None of which had specific provisions for nanomaterials. Two such regulations deal with safety, namely direction 2001/95/EC (product safety) [45] and regulation 1007/2011 [46] on fibre names and related marking of the fibre composition on textile products. Such regulations only require that products are safe, in line with the General Product Safety Regulation [47].

Regarding the safety of textiles, the main toxicological end points to be addressed were skin irritation, sensitisation and aquatic toxicity using pristine graphene as the worst-case scenario. None of the tests showed toxicity [35, 48–50]. As far as environmental exposure is concerned, release of graphene during the life cycle of a textile was identified during washing cycles and end of life.

Regulatory gaps were identified regarding the end-of-life of wearable electronics. Due to the EU Directive 2012/19/EU on waste electric and electronic equipment (WEEE) [51] member states are required to implement schemes for separate take-back and recycling of WEEE. E-textiles are not explicitly addressed by that regulation. They would be rejected at the collection points or sorted out by recycling companies unless the regulation included e-textiles or material recovery from e-textiles becomes profitable.

Regarding the use of graphene in water purification systems, GRMs are not currently approved for the use in FCM in the EU (status as November 2024), hence this should be the first step towards the use of GRM as FCM. Household water purification devices are regarded as kitchenware articles according to the regulations. The polymer-graphene composite material of the hollow fibre membranes of the purification system is undergoing the migration tests for FCM as required by the EU-regulation 10/2011 [52]. An important mechanism to ensure the safety of plastic materials is the use of migration limits. These limits specify the maximum content of substances allowed to migrate into food matrices. For the substances on the European Union list the regulation sets out '*Specific Migration Limits*'. These are established by EFSA based on toxicity data for each specific substance. As mentioned above, a novel method was used in 'SafeGraph' for migration testing of the GRAPHIL water cartridges, and no GO concentrations were found. There are also new requirements imposed by the regulation (EU) 2019/1381 [53] on Transparency and Sustainability of the EU risk assessment in the food chain to be considered if authorisation for GRMs as FCMs is to be applied for, such as the obligation to notify EFSA of laboratory studies. We recommend authorisation by the EFSA or the national competent authority as a food contact material in order to open up new and safe markets for graphene and its derivatives. This should, for example, prevent unintentional abrasion in production facilities or the migration of these advanced materials from, e.g. water filters into food.

There are no specific health or environmental safety regulations for the use of GRMs in de-icing systems for helicopter rotor blades and in the end-of-life of such vehicles. Furthermore, there are currently no specific legal regulations in Europe for the end-of-life handling or disposal of aircraft or helicopters components. Individual companies, both from the aviation industry and waste management companies, have developed their own voluntary standards and efforts are being made to improve sustainability along the entire lifecycle [54]. Recycling technologies have not yet been optimised for aircraft and no recycling process for graphene materials used in aircraft parts has been developed so far. New recycling technologies, e.g. for composite materials, are still being developed and there is no market for individual recycled components, which are generally reused, downcycled, incinerated or landfilled [54].

The connection between identified gaps and regulatory requirements highlights the need for harmonised approaches. Current regulations often fail to address the unique properties of GRMs, particularly regarding their environmental fate and transformation processes [55]. This gap necessitates the development of specific guidance documents that bridge existing regulatory frameworks with the latest scientific understanding of GRM behaviour in various environments [48, 56, 57]. GRMs can be used, for example, in wind turbine blades or as additives to drilling fluids in the oil industry, where some abraded and released fragments can contaminate soils and groundwater [24, 25]. It would therefore be necessary to assess the persistence, bioaccumulation potential, (long-term) toxicity and mobility of GRMs in the environment, for which technical guidelines and standards would be required. Graphene is also used in batteries and may be released during end-of-life processes such as mechanical shredding. Aerosol measurement methods would also be needed as a basis for workplace assessments, e.g. in battery recycling plants.

To address these regulatory gaps effectively, future frameworks must integrate standardised testing protocols with comprehensive exposure assessment methodologies [58]. These protocols should incorporate advanced analytical techniques for detecting and quantifying GRMs in complex matrices, all while considering various transformation processes and exposure scenarios. Furthermore, the regulatory framework must evolve to include specific provisions for nanomaterials, particularly addressing the unique properties and behaviour of GRMs in different applications and environmental conditions [56, 59].

5. Industrial flowchart to guide regulatory compliance

To help or support producers and manufacturers navigate the current complex regulatory landscape for GRM, and based on the information detailed in earlier sections of this study, we have developed a guided flowchart that list key steps to follow during the path to regulatory approval (figure 1). The first step is to describe the intended use of graphene and perform basic physicochemical characterisation,

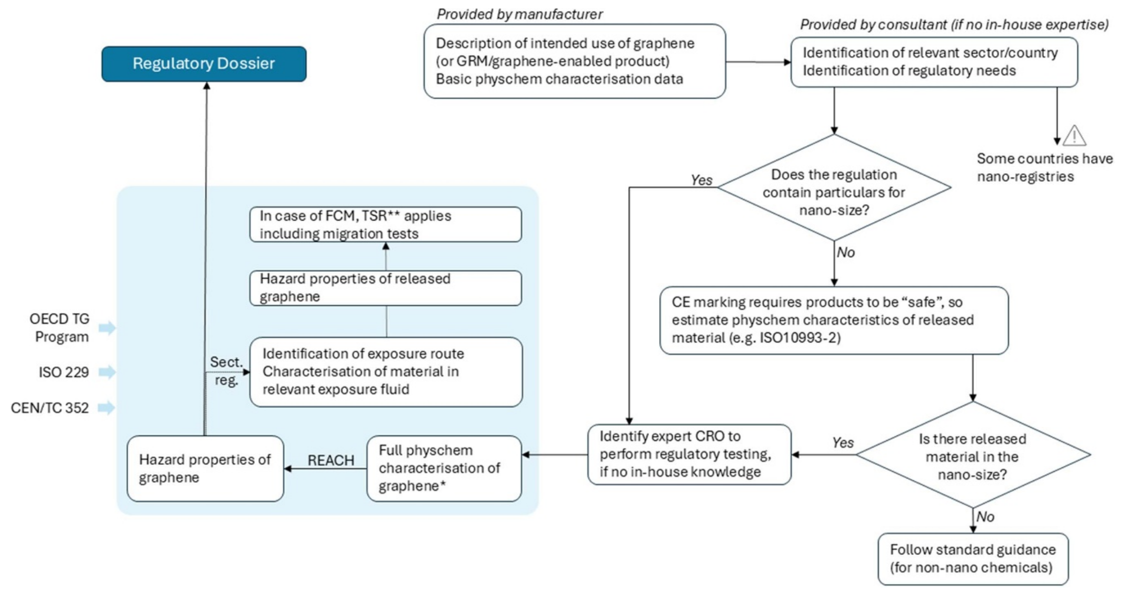

Figure 1. Flowchart to highlight key elements on the path to regulatory compliance of GRM and related products. The blue box represents regulatory testing. CRO: Contract Research Organisation. Sect. reg.: sectoral regulations. *Minimum: size, shape, crystallinity, functional groups, coating, dustiness (if powder). For more information, please refer to the main text of the conclusion section. **Transparency and sustainability regulation (regulation (EU) 2019/1381).

whereby the relevant country, sector and associated regulatory needs to be identified at this stage. To get a better market overview, some countries have their own repositories or nano-registries, e.g. France or Denmark, which means that products sold on these markets need to be registered [60]. As a second step, two paths can be followed: (1) if the regulation does not contain nano-size particulars, i.e. details on the nanoform, and the released material is not in the nano-size, the manufacturer can follow standard procedures (i.e. non-nano chemicals guidance). However, if (2) the regulation does contain particulars for the nanoform, regulatory testing should be performed to build a regulatory dossier. In this case, the OECD TGs Program, ISO 229 and CEN/TC 352 standards can be used to obtain a full physicochemical characterisation of graphene and its hazard properties. Following REACH will allow to create the regulatory dossier, as this is a hazard-driven regulation. But if the sectoral regulation is also to be followed, the manufacturer also needs to precisely identify the exposure route, characterise the material in relevant exposure fluids and the hazard properties of the released material.

6. Conclusions

One of the critical insights from 'SafeGraph' is the identification of regulatory gaps that hamper product development and market entry. The reviewed regulations require that a number of toxicological end points are addressed following in most cases OECD TGs [61] which benefit from Mutual Acceptance of Data [62]. One challenge is that current safety assessment methodologies are often inadequate for GRM, as their potential toxicity can be linked to different aspects particular to their unique physicochemical characteristics, which may or may not overlap with other nanomaterials or conventional materials. Indeed, standard testing guidelines for hazard assessment have been developed mainly for soluble chemicals, where mass drives toxicity (as opposed to other physicochemical characteristics) or for metal nanoparticles (e.g. OCED Test No. 318) and, consequently, these tests must be adapted to graphene, particularly in areas such as dispersion stability, dustiness, and toxicokinetics [14]. The unique properties of graphene, including its high surface area, layered structure, defects, small particle size, and potential for agglomeration, demand customised testing protocols that go beyond those used even for other types of nanomaterials [63].

Moreover, exposure-based risk assessments, as required according to the FCM and MDR regulations, present additional challenges. Detecting and quantifying graphene in complex matrices, such as body fluids, drinking water, or other environmental samples, is difficult due to the lack of robust and standardised analytical methods for the detection and quantification of nanomaterials. These challenges are addressed by developing methodologies to detect graphene at ultra-trace concentrations in aqueous samples [48]. For example, this method was used for migration testing of the 'GRAPHIL' water cartridges that contained up to 5% of graphene oxide in hollow fibres of the filter cartridge [49]. The level of migration was analysed by SERS and of graphene oxide could not be detected in concentrations above the practical limit of quantification.

In addition to these regulatory gaps, it is also important to consider the whole life cycle of GRM and their associated products (end-use) in risk assessments. As graphene and GRMs are increasingly used in everyday products, such as wearables and filtration systems, the likelihood of its release into the environment during production, use, recycling, or disposal is of growing concern. The potential environmental impacts of graphene, particularly in aquatic ecosystems, is still the focus of ongoing research [64]. No conclusive understanding has been reached, underscoring the need for more comprehensive ecotoxicological studies and the adaptation of existing environmental risk assessment frameworks to nanomaterials.

7. Next steps and outlook

Moving forward, several key steps are needed to ensure the successful commercialisation of GRM. The first priority is to harmonise regulatory frameworks across sectors to establish a unified definition of graphene, ensuring consistency in data requirements for safety assessments. To this end, further collaboration between regulatory bodies, such as the OECD and ISO/CEN, is necessary to ensure that these frameworks are adopted globally. Ideally, good grounds for discussion take place at annual meetings where all stakeholders are present, such as the Annual OECD WPMN, which includes Member States and industry stakeholders and where on-going projects are discussed.

Second, standardised testing methodologies must be developed to account for graphene's unique properties and should be taken into account in actions such as the Malta Initiative Priority List [14], following up from the NanoHarmony [65] and Gov4nano [66] EU projects among others.

Actions for funding are currently on-going directly by Member States with the European Commission and may be taken up by the recently created Innovative Materials Initiative [67].

The adaptation of OECD TGs, such as those for skin sensitisation and genotoxicity, to accommodate GRM is an important step forward. However, more work is needed to develop testing protocols that address dispersion stability, surface functionalisation, and toxicokinetics, all of which are critical for understanding the behaviour and fate of GRM in various environments, especially in the aquatic one. Research organisations and industry stakeholders must continue to work together to fill these gaps and ensure that testing guidelines are robust enough to cover the wide range of GRM-based products entering the market.

To overcome the lack of exposure data and further exploit the ever-increasing data derived from new approach methodologies, research efforts may guide the development of OELs based on a battery of *in silico, in vitro* models corrected using *in vitro in vivo* extrapolation approaches [68].

In terms of environmental safety, regulators must focus on adapting existing eco-toxicological guidelines to accommodate the unique behaviour of nanomaterials like graphene. 'SafeGraph' highlighted the need for updated guidelines to address the environmental impact of graphene, particularly its release into freshwater and soil ecosystems. Future research should focus on understanding the long-term toxicity and long-term effects of graphene exposure on various ecosystems, as well as developing strategies for mitigating potential risks.

Lastly, LCA studies for GRM, such as the ones mentioned in the review of Munuera *et al* [26] should become an integral part of regulatory evaluations to offer information on the environmental sustainability of GRM in addition to their safety assessments. This integration could be done, as suggested in the Commission Recommendation (EU) 2022/2510 [69] by the use of LCA studies in the safe and sustainable by design (SSbD) framework, where risk assessment (step 1–3), LCA (step 4) and socio-economic assessment (step 5) should be conducted during early innovation stages. Such integrated LCA could inform on comprehensive exposure scenarios throughout the product lifecycle (i.e. from production to disposal). Furthermore, the LCA should align with safety assessment and consider the environmental transformation processes, including degradation pathways and potential by-product formation. This is not yet possible since there are still few options to consider GRM in LCA impact assessment methods and they do not consider the transformation of GRM after a release in the environment [27]. With combined safety assessments, LCA studies and socio-economic analysis, the SSbD framework can be seen as 'early-warning system' for the viability and sustainability of novel products that use GRM. It can help the managers of companies behind all the mentioned case studies of this work to find more sustainable design that will also minimise risks in the future.

Evaluating the regulatory pathways regarding the four case studies on industrial applications of GRM in 'SafeGraph' has highlighted the need for consolidation of existing regulations as well as gaps and broader concerns about the regulation of graphene and GRM across a wide range of sectors with a need to focus on soils, water and airborne interactions.

Regulatory framework updates should prioritise the development of matrix-specific testing requirements that account for the diverse applications of GRM. This includes standardisation of exposure scenarios across different use cases and comprehensive environmental fate considerations. Consumer safety protocols must be enhanced to address both direct and indirect exposure pathways, while OELs need to be established based on long-term exposure studies and real-world workplace conditions.

In general, it is important to show that a GRM is not hazardous, exhibiting persistence, bioaccumulative, toxic and mobile properties (PBT/vPvB or PMT/vPvM properties according to REACH).

In conclusion, the next steps for ensuring the successful commercialisation of graphene products will require collaboration across industry, regulatory bodies, and research institutions. Harmonising regulations, standardising testing methods, and addressing environmental concerns will be key to realising the full potential of graphene while safeguarding public health and the environment.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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