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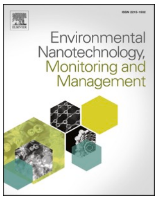

Environmental considerations and current status of grouping and regulation of engineered nanomaterials

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ABSTRACT

This article reviews the current status of nanotechnology with emphasis on application and related environmental considerations as well as legislation. Application and analysis of nanomaterials in infrastructure (construction, building coatings, and water treatment) is discussed, and in particular nanomaterial release during the lifecycle of these applications. Moreover, possible grouping approaches with regard to ecotoxicological and toxicological properties, and the fate of nanomaterials in the environment are evaluated. In terms of potential exposure, the opportunities that arise from leveraging advances in several key areas, such as water treatment and construction are addressed. Additionally, this review describes challenges with regard to the European Commission's definition of 'nanomaterial'. The revised REACH information requirements, intended to enable a comprehensive risk assessment of nanomaterials, are outlined.

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1. Introduction

Nanotechnology can offer benefits for the environment, e.g. in the fields of energy and resource efficiency, environmental remediation or water purification and for consumers (e.g. functionalized textiles and polishing agents) (Guerra et al., 2018). At the same time, the application of engineered nanomaterials (NM) in these areas creates new challenges for regulation and also for environmental considerations. NMs are intentionally designed and prepared materials at the nanoscale.

Since 2018 there has been a particular progress of nanotechnology application in water treatment, separation processes, food and food packaging, as well as in different areas of construction industries (Westerhoff et al., 2018; Voigt et al., 2019; Bott and Franz, 2019; Jones et al., 2015). Moreover, the increased application of NMs in products for everyday life has raised new questions of chemical and product safety (Wagener et al., 2016; Störmer et al., 2017; Hischier et al., 2015). For some high-tonnage materials, such as synthetic amorphous silica or carbon black, nearly the entire production volume is covered by the definition of NM, thus contributing to increased regulatory relevance of the topic without any changes to the market situation. (Wigger et al., 2018). Though the introduction of NMs into the environment via industrial and consumer products is increasingly understood, issues such as the ability and regulatory need to analytically differentiate NM from natural or incidental ones, remain unsolved (Hochella et al., 2019).

However, some fundamental problems in the regulation of NMs such as the update of testing methods to address nano-specific needs do still exist (Leeuwen and Vermeire, 2007). Since January 1st, 2020, NMs are specifically addressed by the amended annexes of the European chemicals regulation REACH (registration, evaluation, authorisation, restriction of chemicals) (European Commission, 2018; European Parliament, 2006). Substances that fulfil the European Commission's recommendation for a definition of the term "nanomaterial" (EC NM Definition) are nanoforms under REACH (European Commission, 2011). Other countries such as the USA have not yet introduced a regulatory definition of nanomaterial. The new information requirements for nanoforms of substances that are subject to registration under REACH address specifically (I) characterization of nanoforms or sets of nanoforms, (II) the chemical safety assessment, (III) registration information requirements and (IV) obligations for downstream users (see Fig. 1) (European Commission, 2018). In order to enable the generation of the necessary data for NMs, the OECD has revised some of its existing test guidelines (TG), e.g. for inhalation toxicity (OECD, 2018a, 2018b) and developed a new TG for dispersion stability testing (OECD, 2017). Rasmussen et al. give an overview of the updating of the OECD TGs to address nano-specific issues (Rasmussen et al., 2019a).

While in Europe the legislation for cosmetic products and parts of the legislative framework for food (e.g. novel food) have their own definitions of a NM, the regulation for food contact materials does not have a definition of NM, leading to some uncertainty for industry and market surveillance (European Commission and the Parliament, 2009; European Commission, 2012; European Parliament and Council, 2015). REACH (2006) does not list 'nanoform' under its definitions, but the amended annexes (2018) include a definition that is based on the European Commission's recommendation of 2011 for a definition of the term "nanomaterial" (European Commission, 2018; European Commission, 2011). Also other legislation, such as the Biocidal Products Regulation (The European Commission, 2012) and the Medical Devices Regulation (European Parliament, 2017), bases its nano-definition on the EU NM Recommendation. The EU NM Definition, and consequently also the definition of nanoform, is based on size only. This is in line with the ISO definition of the so called "nanoscale" (i.e. size range of 1 nm to 100 nm) (Rasmussen et al., 2019b).The European Commission has reviewed the EC NM Definition (refs in comment), and is currently considering its revision (Rauscher et al., 2015; Roebben et al., 2014; Rauscher et al., 2014).

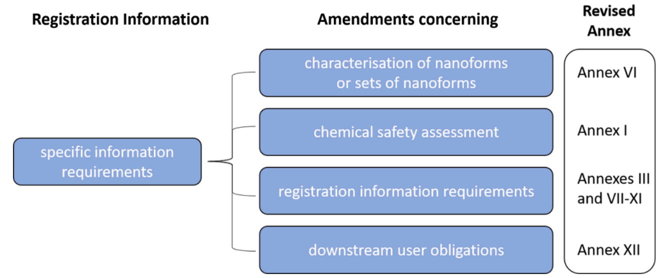

Fig. 1. Specific REACH requirements to be fulfilled by companies producing or importing nanoforms, set out in the amended annexes to REACH.

In this paper findings regarding ecotoxicological properties and considerations about the fate of NMs in the environment will be discussed. Currently the regulatory assessment of ecotoxicological effects of NMs is hampered by the application of a wide variety of test designs, leading to incomparable data. This includes the preparation of the test dispersions, the applied test media, organisms, and endpoints. To overcome some of these issues, a possible testing approach aiming to group NMs is discussed. It concerns aquatic and terrestrial effects and includes the identification of relevant properties and should lead to comprehensive and homogenous data (Hund-Rinke et al., 2018; Kühnel et al., 2019). Due to the large number of NMs, grouping and read-across of NMs for regulatory purposes has gained increasing attention and is the subject of several projects such as GRACIOUS, a project funded within the EU's Horizon 2020 programme (EU Project: GRACIOUS - Framework for Grouping of Nanomaterials within the H2020 www.h2020gracious.eu).

The aim of this review article is to give insights into different environmental considerations of applications of NMs and their safe use as well as progress in the areas of grouping and regulation.

2. Application of nanotechnology in construction and environmental considerations in house coatings

NMs are used for various purposes in construction and buildings. In 2020 more than 800 products for construction and based on nanotechnology (https://product.statnano.com/industry/construction; http://www.nano.elcosh.org/index.php?module=Browse&type=Category; Lippy, 2015) have been listed worldwide. Fig. 2 shows some examples especially in the field of nano-coatings, concrete reinforcement and heat insulation. All the applications shown are used either by consumers or on an industrial scale.

These applications are of interest here due to the nano-scale materials used, and to their properties associated to the nano-scale. In general, NMs show a high reactivity due to their high surface area which is relevant in processes such as photo-catalysis and odor absorption. Very

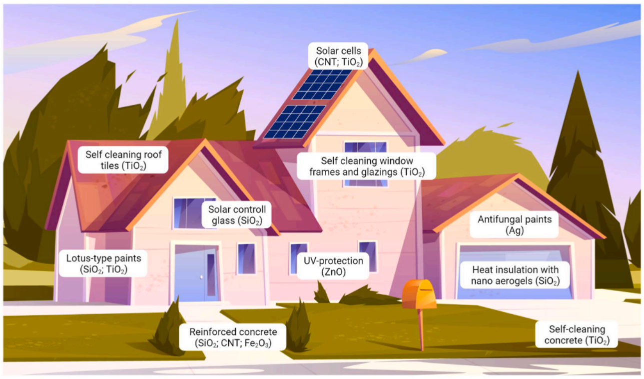

Fig. 2. Examples of nanotechnology enabled functionalities in construction. Picture retrieved and modified from *Freepik.com*.

Table 1
Examples of NMs and typical uses in construction/buildings.

Material	Use in	Function	Reference
SiO_2	Concrete	Durability	(Teixeira Silvestre, 2015)
	Ceramic/ Aerogels	Fire resistance, heat insulation combined with light transmittance	(Lee et al., 2010)
	Windows	Antireflective	(Jones et al., 2019)
	Paints	Durability	(Krystek et al., 2018)
TiO_2	Concrete	Rapid hydration, self-cleaning	(Hanus and Harris, 2013)
	Windows	Antifogging	(Jones et al., 2015)
	Solar cells	NMs in Grätzel-cells	(Hadnadjev-Kostic et al., 2020)
	Paints	Photocatalysis	(Pacheco-Torgal, 2019)
CNT	Concrete	Durability	(Krystek et al., 2018)
	Ceramics	Thermal properties, effective heaters	(Teixeira Silvestre, 2015)
	Sensors	Health monitoring in construction	(Hanus and Harris, 2013)
	Solar cells	Conductivity	(Shukrullah et al., 2020)
Fe_2O_3	Concrete	Increased compressive strength	(Norhasri et al., 2017)
Ag	Paints	Biocidal activity	(Kumar et al., 2008)
Cu	Steel	Weldability, corrosion resistance	(Jones et al., 2019)
Pores	Various	Heat insulation, absorber, catalysis	(Jelle et al., 2015)

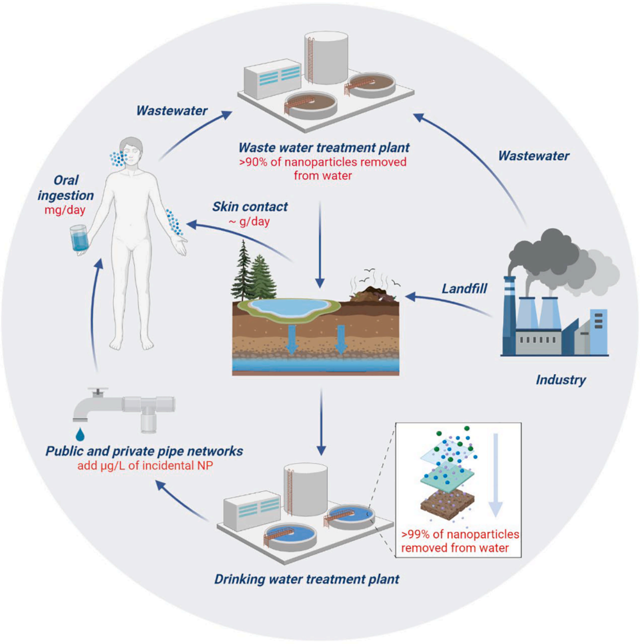

Fig. 3. Illustration of human ingestion levels of NMs from water, removal rates for NMs at wastewater and drinking water treatment plants, and order of magnitude estimates for NMs in various water sources. *Created with BioRender.com.*

small particles show very low light scattering and, hence, can be used for transparent functional coatings, which are widely applied in glazing, electrochromic and antireflective films, solar control films or coatings on wood (Nikolic et al., 2015). Thin films, as well as coatings, paints, and surfaces based on nanotechnology, have functionalities similar to classical coatings but require much less resource input, making them very promising applications of NMs. This is used in corrosion protection, easy to clean surfaces, scratch resistant coatings, antimicrobial functionalities, etc. (Krystek et al., 2018). To some extent this also levels the higher price tag of NMs compared to classical materials. Furthermore, there are porous systems which utilize their nanopore size for heat insulating materials or the infiltration of pores, e.g. for hydrophobic treatment of concrete by functional components (Karthick et al., 2018). The classical use of nanostructures is relevant during strength formation in concrete or by adding nanoparticles to ultra-high performance concrete in order to generate improved mechanical strength and chemical durability (Mohajerani et al., 2019).

Table 1 shows typical NMs and their use in construction. Examples comprise oxides, e.g. SiO_2 and TiO_2, metals (nanosilver), and materials such as carbon nanotubes (CNT) or graphene that so far have not found widespread application. Further details concerning the use of NMs and related functionalities, as well as considerations concerning health and safety can be found in for example Haas et al. or Al-Bayati et al. (Haas et al., 2012; Al-Bayati and Al-Zubaidi, 2018).

The benefits of improved material properties and resource efficiency including reduced environmental pollution have to be balanced against the barriers for application of NMs in construction, e.g. cost and legislation issues, safety concerns, and lack of long term experience especially in the very conservative construction industry.

For any particular NM-based product, such as coating for facades, a product-related life cycle approach can be performed. For a comprehensive benefit and risk assessment, the following aspects can be covered based on product life cycle thinking: I) a survey (see below) among producers of NM- and nano-paints; experiments for II) exposure (weathering and release), and for III) identifying possible adverse effects (*in vivo* and *in vitro*, which are not part of the study and not described here); and calculations for IV) life cycle assessment to measure the environmental performance of NM-based facade coating. A survey among producers of NM and NM-based facade coatings indicated that the NMs most frequently used in facade coatings in Europe were SiO_2, and TiO_2. The most frequently mentioned potential benefits were UV-protection, water, and dirt repellency (easy to clean), and antimicrobial properties (Hincapié et al., 2015).

The exposure can be investigated with different weathering and release experiments, for example using panels coated with nano-SiO_2-based or NM-free paints and exposure to accelerated weathering cycles. With this experimental design, the total release into water was reported to be 2.3 % of the total SiO_2 content, the Si was mainly released in dissolved form and only a small fraction was released in (nano)particulate form. The majority of the particulate Si was found to be still embedded in the paint matrix (Al-Kattan et al., 2015; Zhang et al., 2017). The same can be seen comparing nano-TiO_2 or NM-free paints. The release of titanium was only 0.007 % of the total titanium, which can also be seen in other studies (Fichera et al., 2019). The extraction of UV-exposed and then milled paint resulted in about 100-times increased release of titanium from the nano-TiO_2 and pigment-TiO_2 [TiO_2 not in the nano-scale] containing paint. However, the paint with without nano-TiO_2 did not show this increase (Al-Kattan et al., 2013). It was assumed that photocatalytic active nano-TiO_2 degrades the organic paint matrix (Truffier-Boutry et al., 2017). Furthermore, a recent release study during incineration showed that nano-coatings emit a higher concentration of NM during incineration compared to thermoplastic pellets containing a similar amount of NM (Singh et al., 2019). The higher specific surface area of coatings probably has the greatest impact on this effect. Nevertheless, it must be emphasized that the findings cannot be generalized for other NM and host matrices. In order to identify factors that lead to a higher emissivity of an NM more research is needed (Morgeneyer et al., 2018).

Finally, life cycle calculations revealed that the benefit of a better environmental performance of NM-based facade coatings compared to conventional facade coatings depends on a number of factors. The NM has to substitute for an (active) ingredient of the initial paint composition. Furthermore, the new composition should extend the lifetime of the paint for such a time period that the consumption of paint along the life time of a building or its maintenance is reduced (Hischier et al., 2015; Hischier et al., 2017).

3. Monitoring and safe use of engineered nanomaterials for drinking and industrial water purification

Over the past two decades the field of environmental nanotechnology has answered several important questions related to nanotechnology risks (Maynard et al., 2006), and is now transitioning to the safe use of NMs for addressing hazard of other chemicals in the environment. Based upon market usage, there is good agreement on the types of historic and new NMs in commerce (Keller and Lazareva, 2014). The field has recognized that the “system” in which NMs (e.g. water, soil, biota, polymers, air, etc.) occur influences their behavior (e.g. dissolution, aggregation, toxicity) (Hendren et al., 2015; Kidd et al., 2018). Numerous research laboratories now have analytical techniques available to measure levels of NMs in water and other systems (Hochella et al., 2019). Based upon modeling and direct measurements, estimates of human ingestion of NMs and contributions from industrial sectors, it has become possible to estimate concentrations of NMs in sewage and treated wastewater effluents that enter rivers (Fig. 3). Wastewater treatment plants remove more than 90 % of the NM from water, transferring it to sewage solids (Kiser et al., 2012; Kaegi et al., 2013; Westerhoff et al., 2013). For example, the most widely used NMs (e.g. TiO_2) occur at parts-per-billion level in wastewater effluents or rivers (Westerhoff et al., 2013; Venkatesan et al., 2018; Kiser et al., 2009). Drinking water treatment plants remove more than 99 % of nano-sized materials, leading to parts per trillion of NMs in tap water (Good et al., 2016). Consequently, despite the uncertainty of the hazards from human ingestion of NMs, based upon very low exposure to NMs in drinking water, it can be concluded that NMs pose low risk in drinking water (Westerhoff et al., 2018). Moreover, the community has developed tools to detect NMs in water. The identification of nanoplastics, which is almost always generated by break-down of larger plastic items and is thus not ‘manufactured’, remains a challenge.

As the risks of NMs to human health is evaluated to be low in drinking water, based on low exposure, the focus is shifting towards the beneficial uses of NMs to treat water. By harnessing the unique properties of NMs there are new opportunities to use nanotechnology enabled processes to purify drinking water or industrial wastewaters. NMs can be used to treat recalcitrant pollutants that conventional water treatment processes poorly remove, and which consume large amounts of conventional treatment chemicals, or require disposal of large amounts of solid wastes (Westerhoff et al., 2016). Life cycle analyses indicate the suitability of NMs in several water treatment applications (Gifford et al., 2017; Gifford et al., 2018; Falinski et al., 2018). NMs can be designed to treat water by using various parts of the electromagnetic spectrum, large and selective surface area, electrical conductance, magnetism and tunable hydrophobic/hydrophilic surface properties (Westerhoff et al., 2016; Zodrow et al., 2017). The safe use of NMs for water treatment should be based upon several guiding scientific principles, represented by the following questions: I) how can we use (novel) nano-specific properties for water purification?; II) when is using such novel nano-specific properties superior to conventional water treatment practices?; III) how can NMs be embedded into scaffolding without losing their functionality? and IV) what safety concerns exist around nano-enabled water technologies?

Tunable NM properties and opportunities to use non-chemical stimuli to activate NMs in removing pollutants has the recognized potential to enable fit-for-purpose water treatment through nano-enabled treatment devices that are small, portable, efficient and can be deployed throughout the water grid or in locations “off the water grid” such as homes with private drinking water wells (Zodrow et al., 2017).

In the context of nano-enabled treatment applications, nano-structured ceramic membranes are one example of the use of NMs in water treatment. Since separation processes are the most energy consuming processes in industry there is a great demand for alternative and more eco-friendly methods. Filtration using porous membranes is a simple, pressure driven separation process which has a low energy consumption. Membranes made of ceramics have many advantages regarding stability (chemical, mechanical, thermal) and flux in comparison to polymeric ones. Ceramic membranes are mainly prepared in tubular geometry. Filter elements with 19 channels and a length of 1.2 m resulting in 0.25 m^2 membrane area are state of the art. Inside the channels of the tubes, which have large pore sizes of 3 μm and high open porosity, successive thin layers of decreasing pore size can be prepared (Richter et al., 1997). Filtration occurs from core to shell side of the tubes. For colloidal and polymeric sol–gel techniques, nano-structured membrane layers of 50 nm thickness and below 1 nm pore size have been reported (Puhlfürß et al., 2000). With this nano filtration (NF) membrane separation of dissolved molecules (with a molecular weight above 450 Dalton) and polyvalent ions from water under harsh conditions (pH, temperature, pressure, and organic solvents, etc.) is possible. Several applications in the textile, food, chemical industries etc. have been in use for years (Riedel and Chen, 2013). Some examples are reconditioning of cleaning solutions such as Cleaning in Place solutions for PET-bottle washing (pH 13–14, T = 60 °C) or of waste water from the textile industry (pH 3–12, T = 20 °C-90 °C, H_2O_2) (Voigt et al., 2001). Furthermore, diafiltration of chemically modified sugars from synthesis in n-methylpyrrolidone or recovery of catalysts for organic synthesis such as Pd-(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) in toluene with organophilic NF is possible (Duscher et al., 2012).

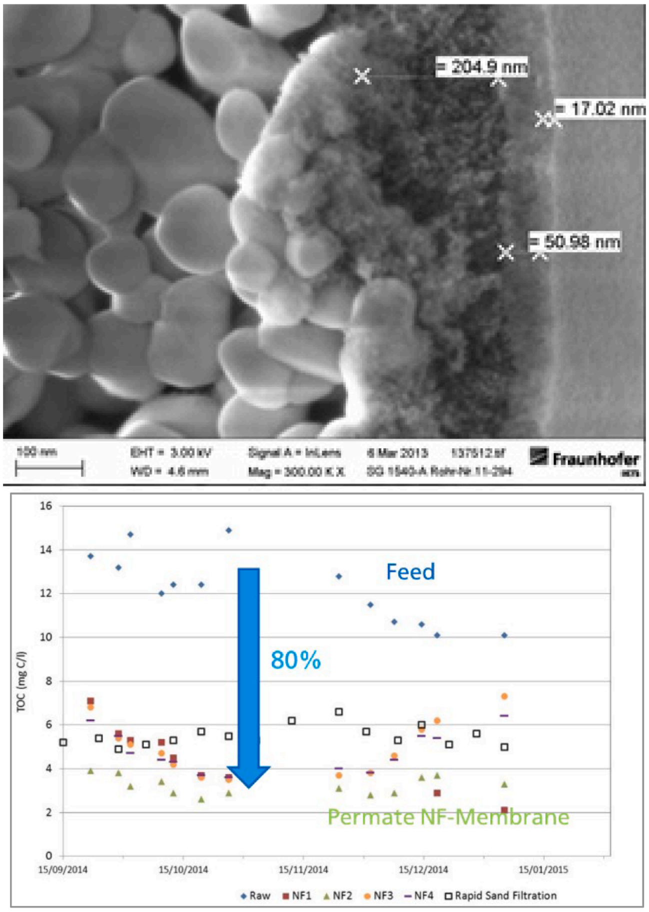

Fig. 4. SEM image of the cross-section through a nanofiltration membrane on a ceramic support of 1.25 m^2 membrane area (upper) and reduction of content of total organic carbon (TOC) in surface water treatment with this kind of membrane (lower).

However, large-scale applications of ceramic NF membranes in water treatment are hindered by the high production costs of ceramic NF-membranes. Significantly reduced costs were achieved by development of ceramic NF-membranes with 163-channel elements of 1.25 m^2. With a cut-off of 400 Dalton and a membrane layer thickness of only 17 nm the membranes could be successfully tested for drinking water production from surface water over a time period of half a year (Fig. 4). All contaminants of the water were considerably reduced by the membrane: natural organic matters (NOMs) by 80 % compared to the original feed, down to very low value of 3 mgC/l, SO_4^{2-} by 25 % and micro pollutants by 15 % – 92 % while a constant flux of 20 – 25 l/(m^2h) was achieved. In additional tests for the treatment of process water from oil sand extraction processes the total organic carbon was reduced by more than 95 % and divalent ions by up to 80 % while a constant flux of 15 l/m^2h was achieved.

By improving the polymeric sol–gel process the pore size of the NF-membrane could further be reduced. This allows the separation of molecules with a molecular weight above 200 g/mol (Zeidler et al., 2014). An additional increase of the specific membrane area of the ceramic NF elements up to 4.5 m^2/element and testing in desalination applications are topics of current research (Voigt et al., 2019).

As water purification technologies develop, the scientific and regulatory communities need to be aware of the public acceptance of nanotechnology. In a large survey of the general public in the United States of America it was observed that approximately 90 % of the survey respondents had little to no prior knowledge of NMs and their use in consumer products. Furthermore, respondents were more concerned about using NMs where there is higher potential for direct exposure. The public was more likely to use products based on nanotechnology to treat drinking water when they had more information about nano-safety, legislation and why nanotechnology was applied to improve the efficiency or lower the cost of the point-of-use devices (Kidd et al., 2020).

4. Grouping of engineered nanomaterials for industrial and regulatory purposes

The physico-chemical (PC) properties of NMs can be precisely fine-tuned to meet the needs of the various applications, and this results in a vast number of NM variants. The PC properties of nanomaterials determine their functionality but also affect their biological kinetics (uptake, absorption, distribution, excretion) and toxicity. Thus, each variant requires characterization of its PC characteristics and properties, and a proper kinetic and (eco)toxicity assessment, rendering hazard and risk assessment time-consuming and costly. Accordingly, in the last decade, the development of grouping approaches for NMs has attracted huge interest and several NM grouping concepts have already been published, sharing some commonalities but also showing differences as summarized by (Giusti et al., 2019) (Giusti et al., 2019).

Grouping and read-across can be applied for different purposes, most commonly they are applied for regulatory purposes to justify waiving specific tests or to fill in data gaps. Different European chemical legislation allow for grouping and read-across (Mech et al., 2019). For chemicals in general the concept of grouping is well defined and established, being *"the general approach for considering more than one chemical at the same time"* (ECHA, 2008 and OECD, 2014). Chemical categories are usually established on the basis of coherent trends in PC properties that result in trends in (eco)toxicological and/or fate properties. If several consistent trends can be identified within a category, the underlying category hypothesis is assumed to be valid. If the number of chemicals is limited, the analogue approach can be used instead. In that case, trends in properties may not be apparent but, based on structural similarity, read-across may still be applied. Once a category has been established or analogues have been identified on the basis of a specific grouping hypothesis, existing data can be linked to members of the group and data gaps may be filled by, e.g. read-across, trend analysis or by establishing quantitative structure–activity relationships (QSARs).

Grouping of NMs is however still challenging and accordingly only a low number of NM grouping case studies have been published (Aschberger et al., 2019; Wohlleben et al., 2019; Lamon et al., 2018). Defining an NM is much more complex than for chemicals in general and requires information on many more properties related to chemical identification and physical characterization. Moreover, it remains challenging to identify the key properties that drive a specific toxicity, which is the basis for grouping (Ribeiro et al., 2017; Drasler et al., 2017). Establishing NM grouping remains laborious and conventional structure–activity relationships based on one or few properties are, generally speaking, not applicable to NMs (Landsiedel, 2016). Surface area has proven to be a promising alternative to mass-based hazard grouping for both acute and chronic pulmonary toxicity, which can be attributed to the fact that many toxicological effects of biopersistent NMs are initiated at the bio-nano interface (surface area) (Maynard and Kuempel, 2005; Schmid and Stoeger, 2016; Cosnier et al., 2021). It has been shown that this allows for discriminating relatively benign NMs such as carbon black (e.g. Printex 90) and amorphous SiO_2 from more toxic NMs such as ZnO, NiO or crystalline SiO_2 (quartz) based on surface area as dose metric (and hence mass-/volume-specific surface area). This was not possible for mass (Schmid and Stoeger, 2016).

From an industrial point of view, NMs are commercialized in various grades that are optimized by factors including composition, size, shape, and coating for specific applications (Wigger et al., 2018; MEEM, 2015). The scope of the different reporting and registration schemes in the EU, USA and Canada include both nanoforms and non-NMs of the registered substance. Hence, there could be a need to evaluate how far data for the different grades can be used for assessment purposes for other grades. (Oomen et al., 2018; Burden et al., 2017). Additionally, there is necessity to ensure the safe use of innovative NMs early during R&D, ideally based on alternative methods, and read-across may provide a means of minimizing testing.

The project nanoGRAVUR funded by the German Federal Ministry for Education and Research (2015 to 2018) developed a framework for grouping of NMs. A number of frameworks and reviews that focused on individual endpoints or general methodologies for grouping (Hund-Rinke et al., 2018; Oomen et al., 2018; Arts et al., 2015; Arts et al., 2014; Oomen et al., 2015; ECHA, 2017; Drew et al., 2017; Kuempel et al., 2012) had been developed or were under development in parallel with nanoGRAVUR, which addressed grouping in the perspective of occupational, consumer and environmental safety. Different groups may result for each of the three distinct perspectives or purposes of grouping. The indicators are harmonized between the three perspectives and are structured as follows:

- Tier 1 is based on intrinsic PC properties (what they are) or GHS (United Nations Globally Harmonized System for classification and labelling of chemicals[1]) classification of the non-nano form, if available (human toxicology, ecotoxicology, physical hazards);
- Tier 2 is based on extrinsic PC properties, release from nano-enabled products, *in vitro* assays (where they go; what they do);
- Tier 3 is based on case-specific testing, potentially *in vivo* studies to substantiate the similarity within groups or application-specific exposure testing.

The methods developed by nanoGRAVUR fill several gaps highlighted in the ProSafe reviews (Steinhäuser and Sayre, 2017), and are useful to implement both the REACH concept of nanoforms as well as the United States Environmental Protection Agency (U.S. EPA) concept of how to distinguish discrete forms (European Commission, 2018). Case studies include families of Fe_2O_3, SiO_2, CeO_2, organic pigment, ZnO, Cu, TiO_2 (nano)forms. Benchmark NMs and benchmark nano-enabled

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[1] 1 https://unece.org/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

products are essential to achieve reproducible groupings across different laboratories with slightly differing equipment (e.g. for dustiness, sanding, dispersion stability, reactivity). Benchmark materials span the dynamic range of each property (often about three to five orders of magnitude), and thus help to assess the relevance of any dissimilarity between different nanoforms. For all properties investigated, decadic bands could be derived as appropriate level of biological relevance, and be compared for which properties are most susceptible to different (nano)forms (Koltermann-Jülly et al., 2018; Hellack et al., 2017).

The GRACIOUS project funded by the European Commission' Horizon 2020 programme developed a Framework which facilitates grouping of NMs or nanoforms (NFs) in a regulatory context and as a support to innovation (Stone et al., 2020). The Framework provides an initial set of hypotheses for the grouping of NFs which take into account the identity and use(s) of the NFs, as well as the purpose of grouping. Initial collection of basic information allows selection of an appropriate pre-defined grouping hypothesis and a tailored Integrated Approach to Testing and Assessment (IATA), designed to generate new evidence to support acceptance or rejection of the hypothesis. The IATAs also guide acquisition of the information needed to support read-across. Users can also define their own hypothesis (and IATA for testing the hypothesis) with support of the Framework. Methods and case studies for grouping and read across are currently being further developed in the project, which also introduces proposals for purpose-specific requirements for ensuring a certain level of certainty and similarity. Selected results are collected in a special issue (Stone, 2021).

5. Environmental risk assessment and grouping concepts for nanomaterials in the environment

The section above describes the reasons and background for developing grouping and read across approaches for NMs. For the prediction of effects from NM-associated PC-properties various concepts were developed, most of which focus on human toxicity (Arts et al., 2016; Oomen et al., 2015). For ecotoxicity only a limited number of studies are available, but they do not identify any properties as main drivers for ecotoxicity or the test systems used were not relevant for regulation (Tämm et al., 2016; Patel et al., 2014).

The development of concepts using literature data is difficult as test designs vary with regard to preparation of the test dispersions, applied test media, organisms and endpoints. All these modifications can affect the results and, hence, the conclusions regarding the influence of selected PC-properties on ecotoxicological effects. There has been considerable effort spent to support the discussions on grouping regarding aquatic and terrestrial ecotoxicological effects and for the identification of relevant properties. One approach is the establishment of a comprehensive and homogenous data set. This was done by selection of 25 NMs for systematic testing. They related to seven chemical compositions (Ag, ZnO, Cu, CeO_2, TiO_2, SiO_2, Fe_2O_3) with three to five sub-types. The sub-types per NM differed in properties such as size, shape, crystalline structure, solubility, reactivity, and zeta potential. The properties of the NMs were determined in deionized water and in an aquatic test media. Aquatic and terrestrial test systems relevant for regulatory testing were used, namely OECD test guidelines 201 (algae), 202 (daphnids) and 236 (fish embryo), 222 (earthworm reproduction), and ISO 15,685 (potential ammonium oxidation activity) (OECD, 2011; OECD, 2004; OECD, 2013). The most relevant properties regarding NMs ecotoxicity were identified and grouping schemes proposed (Hund-Rinke et al., 2018; Kühnel et al., 2019; Hund-Rinke et al., 2020). Four parameters were identified as especially relevant to aquatic ecotoxicity. These are “release of toxic ions”, “morphology”, “attachment of NMs to algae” (for “stable” NMs, e.g. TiO_2, CeO_2, SiO_2) and “reactivity” (for “ion releasing NMs”, e.g. Ag, ZnO, CuO). The EC_{50} values of the various nanomaterial groups differ by a maximum of factor 10. Only for TiO_2, which was included in its photocatalytic active form and its photocatalytic inactive form, the parameter “reactivity” is additionally required for a reasonable grouping. With these criteria, NMs with the same chemical identity but e.g. different surface treatments or crystallinity but different toxicity could be allocated to different groups. For the terrestrial compartment, the only criterion suitable to distinguish the NMs was “release of toxic ions”. Differences in terrestrial ecotoxicity level between the NMs as well as between modifications of the same NM were less pronounced than for the aquatic compartment, as modifications of the same NM (e.g., doping) could not be distinguished. Only two effect groups were obvious: I) no toxicity for the rather stable oxides, and II) toxicity with EC_{50} values in the range of 1 to 1000 mg/kg for the well-known toxic ion-releasing NMs. No parameters additional to ion release and suitable to identify the ecotoxic NMs could be identified. Nevertheless, a reliable grouping of NMs with different chemical compositions was possible. It should be acknowledged, however, that the grouping concept is still preliminary at this stage, while work is ongoing. Particularly noteworthy here are the joint projects GRACIOUS and nanoRIGO funded within the EU framework of Horizon 2020 as well as nanoGRAVUR and InnoMat.Life funded by the German Federal Ministry of Education and Research.

Another important factor for consideration in environmental risk assessment of a NM are environmental exposure scenarios. Therefore, *Giese et al.* determined the annual production volumes, product applications, and associated life cycle release rates for application categories for CeO_2, SiO_2, and Ag, which are NMs with a broad spectrum of commercial uses, by a survey and research (Giese et al., 2018). Based on these data, a dynamic model for the environmental release during the full NM life cycles over a period of several decades (maximum time period 1950 – 2050) could be developed for Germany. The predicted environmental concentrations (PEC) were calculated for a scenario with a) full and immediate degradation (i.e. ionization of the tested NMs) of released NM per year and b) no degradation of released NM (worst case). Toxicity data for water organisms allowed a risk assessment for present and future concentrations of NMs in marine and fresh water (Giese et al., 2018).

Regarding environmental concentrations the modeling gave predictions in accordance with the order of production volumes for the three investigated NM: highest PECs were calculated for SiO_2-NMs and lowest for Ag-NM for different types of soil including sewage sludge treated soil, water bodies such as fresh and marine water, their sediments, and air. Here it is important to note that sludge treated soils yielded up to 40-fold higher values for the predicted concentrations of NM. The background concentrations of naturally occurring counterparts should not be neglected, as these can be naturally present in important amounts that will dominate the materials identified in environmental samples; this is the case for SiO_2 (Wang et al., 2016). The possibility to compare PECs of CeO_2- and Ag-NM with data from measurements of nano-scale particles in Bavarian water bodies revealed a high correlation of the concentration range for both types of NM and therefore supports the explanatory power of the model. Both the measured concentrations of the two nanomaterials are somewhat higher than the modeled concentrations and could, possibly, be due to naturally occurring particles of the two materials. For a risk assessment of the investigated NM (SiO_2, CeO_2 and Ag) in marine and freshwater, the overlap of the probability distributions of the PECs and the probabilistic species sensitivity distribution of the relevant water organisms can be computed (Gottschalk and Nowack, 2013). When assuming no degradation of the released NM (SiO_2, CeO_2 and Ag), the risk profiles suggest no risk for marine water organisms and a rather low risk for freshwater organisms by the end of the modeled period (2050). Under the assumptions and data used, risk seems to be negligible for CeO_2-NM over the whole period. Ag-NM, and to a lesser extent also SiO_2-NM, may represent a risk for a small fraction of very sensitive freshwater organisms.

Despite increasing uncertainty over longer time periods the applied model gives an impression of the most probable range of NM-concentrations and potential risk in the environment. Nevertheless, the results only represent regional averages and do not take local extremes into account. Temporal and geographic variations may therefore lead to much higher risks. Further investigations should therefore consider a spatial resolution for the calculation of the potential distribution of NM in the environment.

6. Current status of registration and regulation of nanomaterials

Worldwide, the regulation of NMs is following different approaches, for example the US-EPA one-time reporting of discrete forms (EPA, 2017) or the Canadian Section 71 reporting of NMs (Morin, 2015). The Canadian approach comprises the establishment of a list of existing nanomaterials in Canada (including section 71 reporting), a prioritization of existing nanomaterials for action and action on substances identified for further work.

In Europe, NMs fall within the scope of different pieces of EU legislation, some of which address NMs explicitly, using a variety of terms, e.g. nanomaterial, engineered nanomaterial or nanoform (Rauscher et al., 2017). The legislation includes REACH (European Commission, 2018; The European Parliament and the Council, 2006), the Medical Devices Regulation (European Parliament, 2017), the Biocidal Products Regulation (The European Commission, No 528/, 2012), the Novel Foods Regulation (European Parliament and Council, 2015), and the Cosmetic Products Regulation (The European Commission and the Council, 2009). The definitions used in REACH, which addresses industrial chemicals, and in the sector-specific regulation, and in national inventories, are each different, awaiting harmonization (Ministère de l'Environnement de l'Énergie et de la Mer (Canada), 2015). When a material is identified as a NM within the scope of such a piece of legislation addressing NMs, this triggers regulatory provisions. Examples of such provisions are nano-specific requirements on the identity or on nano-related safety aspects. New information requirements for substances in the nanoform that are subject to registration under REACH entered into force on January 1st, 2020 as laid down in the amended Annexes of REACH. REACH uses the term "nanoform" and defines it as a **form of a natural or manufactured substance** which fulfils the European Commission's (EC) definition of a NM (EC NM definition) (European Commission, 2011). As stated above, the Commission is considering if the EC NM Recommendation should be revised. This means in practice that the EC NM definition has become legally binding for substances falling under REACH, with adaptations appropriate for that regulation. Following the amendment of REACH, more NMs have been registered, including nano-relevant data, under REACH. The nano-information requirements address nano-specific minimum characterization information including the substance identification, PC characterization, chemical safety assessment, and downstream user information. There is also the possibility to define sets of similar nanoforms, for which hazard assessment, exposure assessment and risk assessment can be performed jointly. ECETOC, an European industry association, has generated an online tool to support the justification of such sets from an industrial point of view (Janer et al., 2021).

The methods used for regulatory testing of chemicals are developed within the Organisation for Economic Co-operation and Development's (OECD) test guidelines programme and published under the Mutual Acceptance of Data (MAD) agreement, which is an essential component in the international harmonization of approaches to chemical safety through regulatory recognition of these test guidelines (OECD, 1981). The OECD council concluded that to manage the risks of NMs the existing international and national chemical regulatory frameworks or other management systems can be applied with the provision that specific properties of MNs have to be taken into account. Hence, based on information from the testing programme (OECD, 2017) of the OECD Working Party on Manufactured Nanomaterials (WPMN), the OECD concluded that identifying and characterizing NMs requires the use of additional PC properties compared to chemicals in general, as toxicological properties of non-NMs may not be equivalent to those for NMs (Rasmussen et al., 2016). The OECD WPMN and the Working Group of the National Coordinators for the Test Guidelines Programme (WNT) have worked closely together on the adaptation of some of the existing Test Guidelines (TGs) and on developing new TGs or Guidance Documents (GDs), which specifically address the properties of NMs. A preliminary analysis of the applicability of existing OECD TGs to NMs was made, leading to a comprehensive review, which integrates the WPMN testing programme work on developing OECD test guidelines for regulatory testing of NMs (Rasmussen et al., 2019a; OECD, 2009). In summary, the development of TGs for NMs addressing PC properties, effects on biotic systems, environmental fate and behavior, and health effects has progressed. In particular, three TGs specifically addressing NMs have been adopted: a new TG on ″Dispersion Stability of Nanomaterials in Simulated Environmental Media" (TG318) and adaptation of TGs on Subacute Inhalation Toxicity: 28-Day Study/90-day Study (TG412 and TG413). Several new TGs for PC properties are under development, e.g. "Particle size and Size Distribution of Manufactured Nanomaterials", and "Determination of the (Volume) Specific Surface Area of Manufactured Nanomaterials". The two TGs will support measuring fundamental properties of materials with particles in the nano-scale, namely size and surface area. In addition, new TGs for determining the dissolution rate of metal NMs in aquatic media and NM removal from waste water are in an advanced stage of development, and concrete proposals for more TGs were submitted to the WNT (e.g. TGs on water solubility, dustiness and aquatic transformation of NMs). The OECD has also analyzed a variety of PC endpoints and available test methods that could be used to produce an authoritative decision framework which links the relevance of certain PC endpoints to toxicological effects of NMs (Rasmussen et al., 2018).

In the EU the OECD TGs are incorporated into the Test Methods Regulation (European Parliament, 2008). Furthermore, the International Organization for Standardization (ISO) is developing standards relevant for nanotechnology which, among others, complements the regulatory test methods.

Responding to requests from numerous stakeholders expressing the need for support in the implementation of the EC NM definition (50 % or more of the particles in a material have at least one external dimension in the range 1 nm – 100 nm) the European Commission's Joint Research Centre (JRC) has prepared guidance on the practical implementation of the definition in the form of two Science for Policy reports. One of these reports provides clarifications of the key concepts and terms used in the definition, discusses them in a regulatory context, and thereby provides a common understanding of the terminology that is necessary for the implementation of the EC NM definition (Rauscher et al., 2019a). The other report provides information on the identification of NMs through measurements and addresses options and points to consider in the assessment of particulate material according to the EC NM definition (Rauscher et al., 2019b). In order to select methods which are fit-for-purpose to experimentally assess whether a material falls under the EC NM definition, certain requirements need to be met, including.

- Availability of sufficient PC information on the material
- Compatibility of the selected technique with the material
- Clarity about the purpose of the analysis
- Information about the validation status of the method
- Information on the type of raw data produced by the method
- Specific regulatory requirements to be met
- Appropriateness of the sample preparation
- Reliability of the outcome of the analysis
- Availability of necessary *meta*-data
- Suitability of the investigated size range

These requirements are discussed in detail by Rauscher et al. (2019). Furthermore, the EU FP7 project "NanoDefine" has provided a comprehensive empirical framework supporting the implementation of the EC NM definition, and published the outcome of the project in the "NanoDefine Methods Manual" consisting of general information on measurement methods and performance criteria, tools such as a material

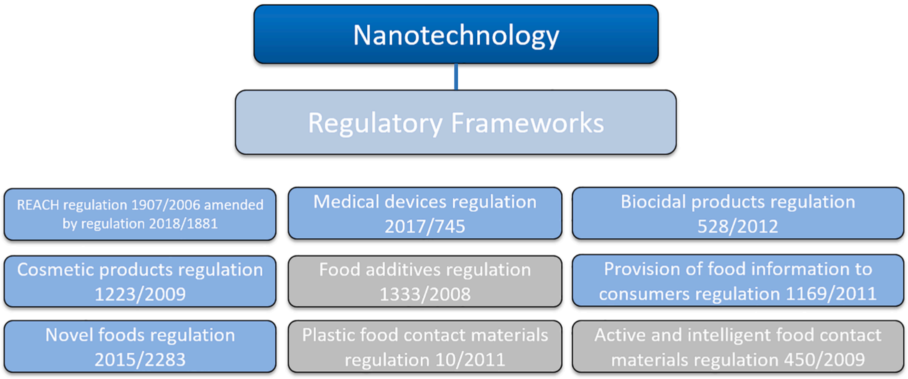

Fig. 5. Overview of selected EU legislation with relevance for NMs; Legislations including a definition of NMs are colored in blue, those without are colored gray. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

categorization system, a decision support flow scheme and an e-tool, as well as several standard operating procedures (SOPs) (Mech et al., 2020a, 2020b, 2020c).

With the JRC guidance and the NanoDefine Manual at hand it is in principle possible to systematically assess any particulate material against the criteria of the EC NM definition (Mech et al., 2020). While this is true for materials in the form of substances according to REACH ("raw materials") or at the ingredient level of a product, the assessment whether a formulation or a product on the market actually contains NMs is still an analytical challenge, which currently can be tackled only case by case.

A remaining regulatory issue is that some legislation in the EU which address NMs have their own definition of the term, e.g. the Cosmetic Products Regulation and the Novel Foods Regulation, or do not have a definition of NM at all, e.g. the Plastic Food Contact Materials Regulation. An overview of the various regulations relating to a NM definition is shown in Fig. 5. Both the Cosmetic Products Regulation and the Novel Foods Regulation include explicit provisions that the definition of a NM in these regulations shall be adjusted and adapted to technical and scientific progress and/or to definitions agreed at international level. One way to do so would be to harmonize the NM definitions in these regulations with the EC NM definition, with additional sector-specific provisions, as appropriate.

7. Conclusions

A look at current nanotechnology clearly shows its diversity and complexity. It is a key technology having remarkable progress but on the other hand the importance of formulating future directions towards resolving knowledge gaps and needs for the safe use should not be neglected. In general, the field of nanotechnology has matured and many areas of beneficial usefulness have been identified. For the future, new developments and the complexity of follow-on products and materials beyond the third and fourth generations, as well as advanced materials, will be addressed.

NMs have found successful application in different areas such as ceramic membranes for water filtration with superior properties compared to conventional filtration. Societal benefits are easily communicated in cases such as the membranes, where the nanostructure enable the main functionality of the product. Tunable NM properties and opportunities to use non-chemical stimuli to activate NMs in removing pollutants have the recognized potential to enable fit-for-purpose water treatment through nano-enabled treatment devices. In the context of NMs in construction the benefits of improved material properties and resource efficiency including reduced environmental pollution must be balanced against the barriers to application. Here, issues such as costs and regulation, concerns regarding safety, and lack of long term experience are particularly of concern in a still traditional industry.

For NM with naturally occurring variants the prediction of environmental concentrations will remain a task for modeling until reliable methods are at hand to distinguish between engineered and natural NMs. A first comparison between model and measurement of environmental concentrations suggests a correlation despite the wide range of uncertainty in modeling. For the modelling of future exposure scenarios, precise information on use models, NM quantities and kinetics and forms of NM in environmental release pathways is needed to reduce the uncertainty of decades-spanning dynamic modelling.

On the other hand, establishing NM grouping remains laborious and conventional structure–activity relationships based on one or few properties are not yet applicable to NMs. However, there are current research projects that focus on further development of the methods and case studies, e.g. the European GRACIOUS H2020 project. The OECD is supporting the regulatory assessment of nanomaterials by ensuring that relevant and applicable OECD test guidelines are becoming available for testing nanomaterials.

The regulation of NMs in the EU is increasingly taking shape, and Annexes of the general chemicals legislation, REACH, were recently amended to clarify information requirements for nanoforms. However, there are still remaining regulatory issues such as difference in legal definitions of nanomaterial across EU legislation. A harmonization of the NM definitions in the different legislation with the EC NM definition would remove many ambiguities, and was recently demanded by the EU Parliament. Ideally, that definition would be updated to technical and scientific progress and/or agreed at international level. Additionally, as previously mentioned, the assessment whether a formulation or a product on the market contains NMs, and from which source, is still analytically challenging, which currently can be tackled only case by case, if at all.

8. Disclaimer

The content expressed in this paper is solely the opinion of the authors and does not necessarily reflect the opinion of their institutions.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Wendel Wohlleben who contributed to the chapters on grouping concepts and registration of NMs is an employee of a company producing and marketing NMs.

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