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Review:

Measurement and characterization of engineered titanium dioxide nanoparticles in the environment*

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Abstract: Titanium dioxide nanoparticles (TiO_2-NPs) are common components used in sunscreens, cosmetics, industrial applications, and many other products. Concerning their high production and widespread applications, characterization and quantification of TiO_2-NPs in various matrixes is a topic of great interest for researchers studying their potential environmental and health impacts. Validated and easily applicable analytical tools are required to develop and implement regulatory frameworks and an appropriate risk assessment for engineered nanoparticles (ENPs). Herein, we provide a critical review of the current knowledge available on world-wide production and measured environmental concentrations as well as on available techniques to measure and characterize these ENPs in the environment.

Key words: Titanium dioxide (TiO_2), Engineered nanoparticles (ENPs), Environmental concentration, Production, Analytical method
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1 Introduction

Nanotechnology is expected to become one of the pillars of the next industrial revolution (Zänker and Schierz, 2012; Gao *et al*., 2013). A large variety of engineered nanoparticles (ENPs) will be encountered much more frequently due to a tremendous growth in their applications in various products. These applications include cosmetics and skin-care products, sporting facilities, paints, textiles, water purification and soil remediation materials, electronics, and many others. Yet a life cycle assessment of most nanoparticles (NPs) is still under consideration. The exposure of the public (e.g., workers and consumers) as well as their release into the environment is expected, as some NPs have already demonstrated their capabilities to cause harmful effects on humans and the environment (Farré *et al*., 2009; Kiser *et al*., 2012; Lin *et al*., 2012; Gottschalk *et al*., 2013; Shi *et al*., 2013). Therefore, understanding the safety, environmental impacts, and human health implications of nanotechnology-based products is of paramount importance. An appropriate risk assessment is needed, which, to some extent, requires the availability of proper analytical methods (Maynard *et al*., 2006). Until now, the measurement, characterization, and quantification of ENPs are still challenging tasks, restricting our understanding of the environmental and human health risks arising from the use of nanotechnology and related products. The properties of ENPs can differ strongly between each other and from their (chemically identical) bulk materials, and may

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vary over time or be dependent on the surrounding matrixes. Therefore, validation of analytical methods appropriate for ENPs is challenging, particularly in different matrixes, and multi-method approaches are often required to provide reliable data as well as to assess and control the limitations of different techniques. This demands that there is not only a comprehensive number of cross-scientific studies but also availability of validated and easily applicable analytical methods (Fabricius *et al*., 2014).

Titanium dioxide NPs (TiO_2-NPs) have raised considerable attention due to their rapidly increasing production and applications as well as their potential release into the environment (Robichaud *et al*., 2009; Gao *et al*., 2013). In addition, NPs are being transported to receiving waters with increasing frequency (Luo *et al*., 2011). Direct evidence of the release of synthetic NPs from urban exterior facade paints into the aquatic environment has been documented (Kaegi *et al*., 2008). Generally, TiO_2-NPs are synthesized for their anatase, rutile, or brookite structure. Each of these crystalline structures has unique properties (Macwan *et al*., 2011). The most common procedure for synthesis of TiO_2-NPs utilizes the hydrolysis of titanium (Ti) salts in an acidic solution (Mahshid *et al*., 2007). To increase photostability and prevent aggregation, TiO_2 nanomaterials (e.g., particles, tubes, and wires) are commonly coated with aluminum, silicon, or polymers (Carlotti *et al*., 2009). The produced TiO_2-NPs are widely used for applications, such as pigments, coatings, sunscreen, and cosmetic additives, and increasingly for the photocatalytic degradation of various pollutants in water, air, and soil. The wide application of TiO_2-NPs benefits from their stronger catalytic activity when compared to its bulk material. The increase in catalytic activity has been attributed to a smaller size, which results in a larger surface area per unit mass. However, these unique properties could potentially also lead to unexpected environmental hazards with possible serious effects on human health. Since 2001, most industrially developed economies have started investing into research to develop an integrated management framework for these emerging pollutants. Most previous studies on the health risk and environmental impacts of TiO_2-NPs have focused on their biological effects and toxicities. Generation of reactive oxygen species (ROS) and their inflammatory effects are considered as the main mechanisms for TiO_2-NPs toxicity. Toxicity studies mainly report a risk from TiO_2-NPs due to inhalation (inflammation and possible link to asthma). Moreover, titania has also been linked to Crohn's disease through gastrointestinal intake and it has been classified as a possibly carcinogen (Lomer *et al*., 2002; Fadeel and Garcia- Bennett, 2010; Hussain *et al*., 2011; Weir *et al*., 2012). In the environment, less is known about how TiO_2-NPs affect organisms, although it has been shown to inhibit growth of algae and plants, and bioaccumulate in *Daphnia magna*. Very recently, toxicities of TiO_2-NPs to benthic organisms were also reported (Ma *et al*., 2010; Du *et al*., 2011; Weir *et al*., 2012; Li *et al*., 2014a; 2014b). It should be mentioned that up till now, all studies are restricted to simulated environmental conditions in a laboratory. *In situ* investigations of nanomaterials in the environment are still an emerging research field. Due to the natural presence of TiO_2-NPs in the environment, one might consider that particle size is the primary toxicity factor. Despite this, recent studies have shown that particle size is only a single (and perhaps minor) factor influencing the toxicity of NPs (Weir *et al*., 2012). The risk assessment of TiO_2-NPs is still a quite difficult task. Analytical methods for ENPs lack validation, thus the physicochemical characteristics of the tested NPs can hardly be demonstrated with enough reliable information to obtain valid conclusions (Menard *et al*., 2011; Zänker and Schierz, 2012).

Notably, it has been proposed that TiO_2-NPs could serve as a sentinel, or tracer, for other nanomaterials, especially those of similar size and aggregation behavior due to their long-term use in commercial products (Kiser *et al*., 2009; Luo *et al*., 2011). By measuring and characterizing TiO_2-NPs in the environment, we can facilitate understanding the potential transporting and fates of widely used engineered nanomaterials. In this review, we cover the production, possible concentration in different matrixes, and common or potential methods for characterization and measurement of engineered TiO_2-NPs in the environment, aimed at enhancing our knowledge on how to measure and characterize engineered TiO_2-NPs.

2 Occurrence of engineered TiO_2-NPs

2.1 TiO_2 production

The global production of TiO_2 already reached 5.70 million tons in 2008 with a growth rate of 4.3%

(Chen, 2010). Its production is the highest production among all nanomaterials (Windler *et al.*, 2012). In China, the production increased from 0.43 million tons in 2001 to 1.28 million tons in 2007, which made China the second largest producer after USA. Nowadays, the global production of TiO_2 is predicted to be near 10 million tons, and it is expected to continue to increase until at least 2025 with greater reliance being placed upon nanosized TiO_2 (Landsiedel *et al.*, 2010). Nearly 70% of all TiO_2 produced is used as a pigment in paints, but it is also used as a pigment in glazes, enamels, plastics, paper, fibers, foods, pharmaceuticals, cosmetics, and toothpastes (Weir *et al.*, 2012). The production quantities of TiO_2-NPs in China and in the rest of the world are shown in Table 1. Large variations in production are observed between different countries/regions, which can also be partly attributed to the different methods which are used to assess the production quantities, some of which have a limited accuracy. For TiO_2-NPs in Europe, production ranges between 11–1000 tons were reported (Piccinno *et al.*, 2012). However, some experts estimated the annual European TiO_2-NPs production to be above 10000 tons. Generally, TiO_2-NPs are manufactured worldwide in large quantities for use in a wide range of applications.

Table 1 Production quantities of TiO_2-NPs in China and the rest of the world

Country/region	Production (ton/year)	Reference
China	1300	Gao *et al.*, 2013
Europe median (25/75 percentile)	550 (55–3000)	Piccinno *et al.*, 2012
USA range	7800–38000	Hendren *et al.*, 2011
Switzerland	435	Schmid and Riediker, 2008
Worldwide median (25/75 percentile)	3000 (550–5500)	Piccinno *et al.*, 2012

2.2 Measured environmental TiO_2-NPs concentrations

Measured environmental TiO_2-NPs concentrations have been reported for the workplace, surface water, wastewater treatment plants (WWTPs) effluents, biosolids, and sediments (Table 2) (Luo *et al.*, 2011; Gottschalk *et al.*, 2013). In this context, a workplace is defined as a particular environment in which workers are exposed to NPs with the high likelihood of adverse health effects. Concentrations of atmospheric TiO_2-NPs emitted from nanomaterial production processes have been measured using direct-reading methods like a condensation particle counter (CPC), scanning mobility particle sizer (SMPS), and diffusion charger (DC) in some particular workplaces. The CPC is a powerful tool to quantify really small NPs concentrations in a workplace. The SMPS is widely used for investigating particle-size distribution, and it comprises an electrostatic device with a differential mobility analyzer (DMA) for size distribution and a CPC for particles counting. The DC is an instrument for monitoring surface areas in real time, responding to particles smaller than 100 nm (Duarte *et al.*, 2014). Lee *et al.* (2011) used a SMPS and a CPC to assess the exposure at workplaces manufacturing nanosized TiO_2. A particle-number concentration for TiO_2 of 11418–45889 particles/cm^3 was detected with a size distribution of 15–710.5 nm during the growth reaction. In contrast, the particle-number concentration of TiO_2 ranged from 9512 to 16337 particles/cm^3 in European construction industries, where a self-cleaning coating (that contained TiO_2 as an active nano-component) was sprayed on windows (van Broekhuizen *et al.*, 2011). Also, an Aerasense NP monitor (NanoTracer), a portable aerosol sampler of Philips Aerasense (Eindhoven, the Netherlands) was used to measure particle concentrations at various workplaces. This NanoTracer provides real-time information about the number concentration (particles/cm^3), number-averaged particle diameter, and surface area. It detects the concentration of NPs (NPs/cm^3) within a range of 10–300 nm, simultaneously with the mean particles diameter over a time interval of 16 s or, in the fast mode, only the number of NPs per cm^3 over a time interval of 3 s (Marra *et al.*, 2010). van Broekhuizen *et al.* (2012) observed TiO_2-NPs concentrations within a range of 0.005–0.021 mg/m^3 in different manufacturing workplaces using the NanoTracer.

The release of engineered TiO_2-NPs into the environment has been demonstrated to some extent via the measurement and characterization of TiO_2-NPs in surface water, wastewater treatment plant effluents, biosolids, and sediments (Table 2). A TiO_2 concentration (almost completely colloidal or nanoparticulate) of surface water from UK averaged 2.1 μg/L in a range of 0.55–6.48 μg/L measured by subsequent filtration, cross-flow ultrafiltration, and inductively coupled plasma mass spectrometry (ICP-MS) (Neal *et al.*, 2011). In wastewater treatment plants in Arizona, Colorado, California, Maryland, Iowa, and New York (USA), the TiO_2 concentration ranged <5.0–15.0 μg/L in the effluents and 1.8–6.4 g/kg in the biosolids, measured using a combination of filtration, acid digestion, ICP-MS, inductively coupled plasma optical emission spectroscopy (ICP-OES), and a scanning electron microscopy+electron dispersive X-ray microanalysis (SEM+EDX) (Kiser *et al.*, 2009). Similarly, the TiO_2 concentration was about 3.2 μg/L with 305 mg/kg dry weight in biosolids in an activated sludge plant serving over 200 000 people in the UK (Johnson *et al.*, 2011). Westerhoff *et al.* (2011) also reported effluent titanium concentrations of less than 25 μg/L in 10 representative WWTPs, measured by a combination of filtration, acid digestion, and ICP-OES. Via rota-evaporation, dialysis, and lyophilization as well as high resolution transmission electron microscopy and energy dispersive X-ray analysis, the Ti was found to be present in the size fraction of 4 to 30 nm in diameter. By using ICP-MS after ammonium persulfate digestion, Khosravi *et al.* (2012) found total Ti concentrations of 1.6 and 1.8 μg/L in wastewater effluents and 317.4 mg/kg in sewage sludge from Canada. Moreover, the TiO_2-NPs concentration was found to be ≤2.74 g/kg in surface sediment from Xiamen Bay, China (Luo *et al.*, 2011). Unfortunately, TiO_2-NPs concentrations in soil have not yet been measured, even though a large quantity of TiO_2-NPs could ultimately end up in soils, as biosolids are often used as agricultural land amendments (fertilizers).

Note that reported concentrations in aquatic and solid environmental samples are often total Ti concentrations, which have been measured after acid digestion of the sample. These results give us only an upper limit of the real TiO_2-NP concentrations, as also microparticles of TiO_2 could occur and Ti could also be associated with other particles occurring in the samples. This therefore might reflect the large analytical limitations regarding TiO_2-NPs in the environment. Therefore, more attention should go to the testing and development of analytical techniques able to measure TiO_2-NPs in the natural environment.

3 Potential methods for characterization and measurement of engineered TiO_2-NPs

Previous researchers already reviewed methods to characterize and measure ENPs in the environment (Tiede *et al.*, 2008; Hassellöv *et al.*, 2008; Stone *et al.*, 2010; Silva *et al.*, 2011; Tsao *et al.*, 2011; Weir *et al.*, 2012; Xiao and Wiesner, 2012; Zänker and Schierz,

Table 2 Measured environmental TiO_2-NPs in different environmental matrixes and various analytical methods

Environmental matrix	Concentration	Measurement method used	Reference
Workplace	11 418–45 889 particles/cm^3 for manufacturing workplace; 9512–16 337 particles/cm^3 for European construction industries	CPC, SMPS, DC	Duarte *et al.*, 2014
Surface water	2.1 (0.55–6.48) μg/L	Filtration, CFU, ICP-MS	Neal *et al.*, 2011
Wastewater treatment plants effluents	<5.0–15.0 μg/L; 3.2 μg/L; <25 μg/L; 1.6 &1.8 μg/L	Filtration, RDL, digestion, ICP-OES, SEM+EDX	Kiser *et al.*, 2009; Johnson *et al.*, 2011; Westerhoff *et al.*, 2011; Khosravi *et al.*, 2012
Biosolids	1.0–6.0 g/kg; 305 mg/kg; 317.4 mg/kg	Filtration, digestion, ICP-MS, SEM+EDX	Kiser *et al.*, 2009; Johnson *et al.*, 2011; Khosravi *et al.*, 2012
Sediment	≤2.74 g/kg	Microwave aid acid digestion, ICP-MS, SEM+TEM+EDX	Luo *et al.*, 2011

CFU: cross flow ultrafiltration; RDL: rota-evaporation, dialysis, and lyophilization

2012; Gottschalk *et al.*, 2013; Luo *et al.*, 2013; Fabricius *et al.*, 2014). Herein, a short overview is given on methods that may be used to study engineered TiO_2-NPs. For a detailed description of these methods, we refer to the specific literature (Tiede *et al.*, 2008; Stone *et al.*, 2010; Zänker and Schierz, 2012; Fabricius *et al.*, 2014). We focus on discussing the advantages and disadvantages of these methods, and possible drawbacks to be taken into account when using these techniques to study engineered TiO_2-NPs.

3.1 Pretreatment and particle fractionation-related techniques

Sample pretreatment for ENPs analysis, in general, removes coarser components using settling, mild centrifugation, and filtration through filters with relatively large pore size, as well as extraction (Benn *et al.*, 2011; Zänker and Schierz, 2012). These pretreatment techniques are supposed to have only a low impact on the occurrence and morphology of the NPs themselves.

Particle fractionation can help to achieve spatiotemporal separation of the particles, which can be used to obtain fractions of separated NPs that subsequently can be further investigated. Microfiltration and ultrafiltration are the easiest ways to perform such a fractionation task, while field-flow fractionation (FFF) is a more powerful separation method. FFF includes flow field-flow fractionation (FFFF), sedimentation field-flow fractionation, and thermal field-flow fractionation (Gimbert *et al.*, 2005; Baalousha *et al.*, 2006; Hassellöv *et al.*, 2008; Plathe *et al.*, 2010; Baalousha *et al.*, 2011; von der Kammer *et al.*, 2011). Other important methods are centrifugation and ultracentrifugation (Bootz *et al.*, 2004; Hassellöv *et al.*, 2008), size-exclusion chromatography (SEC) (Weinberg *et al.*, 2011), hydrodynamic chromatography (Tiede *et al.*, 2010), capillary electrophoresis (CE) (Celiz *et al.*, 2011), gel electrophoresis (Surugau and Urban, 2009), isoelectric focusing (Howard, 2010), manipulation between solvent phases such as cloud point extraction (Howard, 2010; Liu *et al.*, 2012), and photophoretic velocimetry (Helmbrecht *et al.*, 2011). Most of these fractionation techniques can be coupled with detectors that can trace the separated particles online.

Some previous studies used microfiltration and ultrafiltration to perform TiO_2 particle fractionation, resulting in overestimation of their levels in wastewater treatment plants due to the inclusion of the larger fractions of colloids (Kiser *et al.*, 2009; Johnson *et al.*, 2011; Westerhoff *et al.*, 2011). Ultracentrifugation was previously also used to separate TiO_2 particles with a very high inherent size resolution (Kaegi *et al.*, 2008); but this technique seems inadequately represented in environmental NP analysis. Ultracentrifugation is not free of systematic errors (hydrodynamic non-ideality and particle-particle interaction due to differential settling). However, it does not suffer from the artifacts of chromatographic or chromatography-like techniques, such as interactions between the analyte and the stationary phase and shear degradation (SEC), or problems arising from preconcentration, dilution in the channel, particle-membrane interactions, and washing of the particles, which results in re-equilibration because of a change in chemistry (FFF) (Zänker and Schierz, 2012). In spite of having relatively cumbersome and complicated features, FFF is probably the most promising fractionation technique for TiO_2-NPs. Similarly, the other separation methods, like manipulation between solvent phases (e.g., cloud point extraction and CE), experience problems, such as being very time-consuming, possessing methodological, and handling difficulties, as well as elevated costs (Fabricius *et al.*, 2014). Therefore, an easy to handle, sufficiently available, and moderately expensive tool is needed to separate TiO_2-NPs.

3.2 Techniques for particle detection and characterization

Many physicochemical properties of ENPs need to be measured to facilitate the understanding their behavior and fate, as well as associated (eco)toxicity. The following methods measure and characterize particles based on their inherent properties (i.e., particle size, size distribution, shape, concentration, surface charge, and surface hydrophobicity).

3.2.1 Particle detection and characterization

Particle-size information (hydrodynamic particle diameter) can be obtained through dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS) (Domingos *et al.*, 2009; Brar and Verma, 2011). DLS is a very powerful tool for studying monomodal particle populations of relatively narrow particle-size distributions. However, DLS seems to contradict the size-characterization results according to the more invasive ultracentrifugation technique (Dreissig *et al.*, 2011). Thus, DLS results always need to be scrutinized thoroughly for their accuracy and plausibility tests should be performed.

Static light scattering (SLS) is another light-scattering technique (Wyatt, 1993), which measures the intensity of the scattered light of NPs suspension according to its dependence on the scattering angle. This technique provides information about the particles' molecular weight, radius of gyration of the particles, and particle conformation. As a relatively new method of light scattering, NP-tracking analysis permits the determination of particle-size distribution and, to some extent, particle-number concentration (Gallego-Urrea *et al.*, 2010; Farkas *et al.*, 2011; Zänker and Schierz, 2012). This technique is less prone to masking problems because of its physics. However, it has been widely criticized because too many adjustments and settings have to be chosen by the operator, possibly resulting in too biased results (Farkas *et al.*, 2011; Gallego-Urrea *et al.*, 2011; Zänker and Schierz, 2012). Similarly, information about particle-number concentration and average size can be obtained by laser-induced breakdown detection (LIBD), which is a colloid detection method that uses plasma formation in the focus of a pulsed laser beam (Walther *et al.*, 2004). LIBD is a highly specialized method that was only recently made available through the Cordouan technologies company. Thus, investigators can attempt to use LIBD to measure the TiO_2-NP contents in solutions since it has already been tried to measure the particle contents in water (Latkoczy *et al.*, 2010).

Additionally, other interesting techniques have been used for various NPs. Fluorescence spectroscopy can provide specific particle-related data such as average particle size for quantum dots (Ju-Nam and Lead, 2008); UV-visible spectrometry can detect the particle size of gold and silver NPs (Stiles *et al.*, 2008; Amendola and Meneghetti, 2009); and O'Connell *et al.* (2002) used near-infrared fluorescence (NIRF) spectroscopy to collect structural information, such as the chiral wrapping angle, and the diameter distribution of single-walled carbon nanotubes (SWCNTs).

Most particle fractionation methods can be coupled to the aforementioned measurement and characterization methods. Here, ultracentrifugation and FFFF provide information about the particle's sphere-equivalent hydrodynamic diameter (Stokes diameter); sedimentation FFF can provide the equivalent volumetric diameter; and CE generates the size-to-charge ratio. The limitations of the individual methods can be overcome via the use of a combination of techniques, like FFFF and LIBD (Thang *et al.*, 2000; Baik *et al.*, 2007). The high sensitivity of LIBD counteracts the detection problems often caused by FFFF due to sample dilution, while FFFF eliminates the limits of LIBD in determining particle-size distributions by separating the particles (Zänker and Schierz, 2012). The coupling of FFFF and single-particle ICP-MS is another promising approach (Mitrano *et al.*, 2012).

Coupling may not be limited to one or two detectors. The success of such analyses will always depend to some extent on the type of particles under study and the matrix of the sample. A coupled measurement can include determination of the concentration of the particles, their size distribution, the chemical composition, the crystal structure, the charge (zeta potential), etc. (Lespes and Gigault, 2011).

3.2.2 NPs visualization

Microscopy generates the most direct information about size, size distribution, and shape of NPs in water, soils, sediment, and biosolids. Although it is difficult to generate accurate quantitative information from microscopic techniques for large amounts of samples, they can be used to control the quality of results obtained by other techniques. Microscopy-based methods include optical approaches (confocal microscopy), as well as electron and scanning probe microscopy. The popular tools for ENP visualization are SEM, TEM, and atomic force microscopy (AFM) (Leppard 2008; Tiede *et al.*, 2008; Zänker and Schierz, 2012). Although microscopy provides relatively accurate estimations of the size and shape of an NP, complicated sample preparation steps (e.g., dehydration, cryofixation, and embedding for SEM) are often required, which can shift samples and create artifacts (e.g., agglomeration). Even in the case of the relatively noninvasive AFM, it is critical to avoid sample-preparation artifacts. Recently, WET-SEM, wet scanning transmission electron microscopy, Cryo-SEM, *in-situ* liquid TEM, and other electron microscopy techniques have been developed (Bogner *et al.*, 2005; Luo *et al.*, 2007; Grogan *et al.*, 2011; Pietra *et al.*, 2012). Herein, WET-SEM and similar techniques allow the observation of NPs in the liquid phase and reduce sample-preparation artifacts but provide lower resolution (Bogner *et al.*, 2005; Zänker and Schierz, 2012). Additionally, more sophisticated microscopic techniques that provide chemical images and that are only minimally invasive include X-ray spectroscopy with synchrotron radiation (Thieme *et al.*, 2007), laser scanning anti-Stokes Raman scattering (CARS) microscopy (Cheng *et al.*, 2002), and tip-enhanced Raman spectroscopic microscopy (Schmid *et al.*, 2008).

Some cases of microscopy were reported by Zänker and Schierz (2012), who illustrated the differences among these visual methods and their limitations. A general drawback of microscopic techniques is that it is difficult to obtain an accurate estimation of particle size distribution. One can obtain only reliable conclusions on the whole particle population of a sample when a large amount of particles can be counted, which is not often the case. Thus, there is a need for automation and development of suitable image-analysis software, which would enable the characterization of millions of particles (Domingos *et al.*, 2009; Tiede *et al.*, 2009; Zänker and Schierz, 2012).

3.2.3 Mass spectrometry

Lots of the detectors described above are not element-specific, which hampers accurate analysis in natural samples containing different types of particles with different compositions. Therefore, hyphenation of size fractionation techniques to sensitive mass spectrometers has previously been introduced. These mass spectrometers are already being used for a long time to measure elemental concentrations in solutions. They consist of an ion source (decomposing the sample and generating ions), a mass analyzer (separating the ions based on mass-to-charge ratio), and a detector system (counting the ions). Some ionization techniques do not completely decompose the compounds present in the sample and can be used for structure identification in liquid and solid biological samples. They include electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI). On the other hand, ICP sources completely decompose compounds into individual elements and are used for elemental analysis. Mass analyzers (e.g., ion trap, quadrupole or time-of-flight) cover different mass-to-charge ranges and differ in mass accuracy and achievable resolution. Most of the available analyzers are compatible with electrospray ionization, whereas MALDI is not usually coupled to a quadrupole analyzer. MS techniques have also been used in aerosol characterization, including aerosol time-of-flight mass spectrometer (ATOF-MS). An ATOF-MS consists of an aerosol introduction interface; a light-scattering region for sizing and a TOF-MS (time-of-flight mass spectrometer). MS approaches nowadays have been widely applied to measure NPs in the environment (Gray *et al.*, 2012; Liu *et al.*, 2012; Fabricius *et al.*, 2014).

Conventional MS is applicable for identifying unknown compounds and their mass concentrations, as well as their isotopic composition. If size fractionation or selection of the particles based on their size is needed prior to analysis via MS, samples cannot be injected directly into the ion source; therefore, a technique preceding separation technique is needed, such as high performance liquid chromatography. An increasingly popular combination in this respect is FFF-ICP-MS, which allows size separation of the sample with subsequent quantitative and elemental analysis of the obtained size fractions. This development is highly promising for NP analysis, as particles can be simultaneously sized and analyzed in their original environment (Tiede *et al.*, 2008). Moreover, single-particle ICP-MS (SPMS) has recently been introduced as a technique able to analyze metal and metal oxide NPs separately from dissolved ions, without the need for hyphenation to chromatographic techniques for prior size fractionation (Laborda *et al.*, 2011). Therefore, SPMS also has the ability to distinguish particles from truly dissolved species of the same element and to size the single particles.

A comprehensive summary of common and potential methods combining different MSs for separation and detection of engineered TiO_2-NPs in the environment is presented in Table 3, although these methods were developed originally to analyze metallic NPs (da Silva *et al.*, 2011). Usually, the very

Table 3 Common and potential methods for separation and subsequent detection/quantification of TiO_2-NPs (Tiede *et al*., 2008; da Silva *et al*., 2011; Zanker and Schierz, 2012; Fabricius *et al*., 2014)

Separation method	Mechanism	Size range	Coupled detection/ quantification technique
Filtration	Size fractionation	Down to 1 kDa	SEM, ICP-MS, ICP-OES
Microfiltration	Size-exclusion membrane	100 nm–1 μm	TEM, AFM, ICP-MS
Nanofiltration	Size-exclusion membrane	0.5 nm–1 nm	TEM, ICP-MS
CFU	Size-exclusion membrane	1 nm–1 μm	TEM, SEM, ICP-MS
Dialysis	Size-exclusion membrane	0.5–100 nm	TEM, SEM
SEC	Packed porous beads as stationary phase	0.5–10 nm	ICP-MS
Ultracentrifugation (UC)	Acceleration up to 10^6g	100 Da–10 GDa	SEM, TEM, EDS, XRF, ICP-MS, ICP-OES
FFF	Physical separation in an open tube based on an applied field	1 nm–1 μm	ICP-MS, ICP-OES
Electrophoretic mobility	Charge-size distribution along a gradient	3 nm–1 μm	ICP-MS, ICP-OES

first step is to pre-fractionate samples through settling, filtration or centrifugation. Based on the fact that a comprehensive characterization (e.g., size, concentration, and shape) in different matrixes is required, NPs need to be determined via separation using selected methods such as filtration, micro-filtration, nano-filtration, cross-flow ultrafilteration, dialysis, size-exclusion chromatography, FFF, and electrophoretic mobility in conjunction with appropriate coupled techniques (Table 3). Unlike gold NPs, the background of Ti in nature is much higher. Subsequently, to identify engineered TiO_2-NPs completely in the environment, several tracing techniques such as stable isotope and rare element tracing techniques are also considered to be coupled comprehensively in the future (Neal *et al*., 2011; Larner and Rehkamper, 2012).

3.2.4 Surface charge and surface hydrophobicity

Surface charge, expressed as zeta potential, critically influences the interaction of an NP with its environment. Surface charge measurements have been recently reviewed comprehensively by Cho *et al.* (2013). The zeta potential measurement depends on the strength and valency of ions present in the NP suspension. High ionic strength and high valency ions compress the electric double layer, resulting in reduction of the zeta potential. The pH, i.e., the concentration of hydrogen ions in the medium, greatly influences the zeta potential as well. When the suspension is acidic, NPs acquire more positive charge, and vice versa. Therefore, a zeta potential value without indication of solution pH is a virtually meaningless number. It is recommended that information on their NPs suspension be precisely described when reporting the zeta potential, including ionic strength, composition of the medium, and the pH. For comparison of results across different studies, it is conceivable to normalize the zeta potential by pC (the negative logarithm of concentration of counter-ion species) (Kirby and Hasselbrink, 2004). Generally, particles with zeta potential more positive than +30 mV or more negative than −30 mV have colloidal stability maintained by electrostatic repulsion and hydration energy (Yotsumoto and Yoon, 1993). One limitation is that in bimodal samples, the zeta potential value of larger particles dominates the scattering signal of smaller particles, similar to DLS size measurements (Murdock *et al*., 2008).

Surface hydrophobicity is a key determinant of their fate, the transport and toxicity of engineered nanomaterials. Methods for hydrophobicity fall into three categories, i.e., surface adsorption, affinity coefficient, and contact angle. Xiao and Wiesner (2012) have used these methods to characterize the surface hydrophobicity of carbon- and metal-based NPs. Nevertheless, in real samples the low levels of NPs concentrations and the presence of interfering contaminants render the determination of surface charge and surface hydrophobicity quite difficult.

4 Summary and perspectives

Analytical methods for ENPs are still under development. Until now, these methods have not been able to provide sufficiently reliable data. Moreover, processes to analyze NPs in the environment are most often laborious, expensive, and/or demand specialized and trained operators. Even though some techniques, such as FFF-ICP-MS and single particle ICP-MS, provide powerful tools for the quantification of most metal-based NPs, they also demand well-educated and highly trained operators. An ideal analytical method is needed to allow easy simultaneous determination of all physicochemical properties of an NP by real-time sampling. Although a wide range of techniques is available, the existing techniques do not yet fulfill all desirable criteria and most have considerable limitations when applied in a specific environmental medium. However, before new techniques are being developed, existing techniques have to be combined in such a way that data validation is possible, accompanied by careful sample preparation. Additionally, there is a need for reference materials and standardized protocols to use these combinations of analytical methods for determination of specific NPs in the relevant media.

Although there are already various techniques that work very well, at least in laboratory experiments, it is necessary to develop appropriate strategies using these techniques to determine engineered TiO_2-NPs in real environments. Considering the current situation of analytical methods and the large production and measured environmental concentrations of TiO_2-NPs around the world and the potential exposure from their applications to humans and the environment, it is still urgently needed to develop appropriate analytical techniques for a reliable determination of these NPs to facilitate their relevant risk assessment.

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中文概要：

本文题目：环境中工程纳米二氧化钛颗粒的表征与测定

Measurement and characterization of engineered titanium dioxide nanoparticles in the environment

研究目的：纳米二氧化钛已是防晒霜、化妆品和光催化剂等的常用成分。纳米二氧化钛的大量应用，已被证明具有潜在的环境负面影响与人体健康风险。如何分析环境中工程纳米二氧化钛的理化性质无疑是认识其潜在风险的关键课题。

研究方法：从工程纳米颗粒可用的表征与测定方法（如电镜显微方法、色谱与质谱技术等）的优缺点出发，结合稳定同位素与稀有元素示踪技术来探讨环境中工程纳米二氧化钛颗粒的分析方法。

重要结论：环境中工程纳米二氧化钛的表征与测定方法仍需深入的研究，其可靠性需要现有各种分析技术的相互验证、良好的样品预处理技术和参考物质、以及稳定同位素与稀有元素技术示踪的配合。

关键词组：二氧化钛；工程纳米颗粒；环境浓度；产量；分析方法