NanoImpact 6 (2017) 69–80

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.journals.elsevier.com/nanoimpact

Biokinetics of nanomaterials: The role of biopersistence

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ARTICLE INFO

Article history:
Received 30 September 2016
Received in revised form 25 February 2017
Accepted 6 March 2017
Available online 22 March 2017

Keywords:
Biokinetics
Dosimetry
Extrapulmonary organs
Granular biopersistent particle without known significant specific toxicity (GBP)
Inhalation

ABSTRACT

Nanotechnology risk management strategies and environmental regulations continue to rely on hazard and exposure assessment protocols developed for bulk materials, including larger size particles, while commercial application of nanomaterials (NMs) increases. In order to support and corroborate risk assessment of NMs for workers, consumers, and the environment it is crucial to establish the impact of biopersistence of NMs at realistic doses. In the future, such data will allow a more refined categorization of NMs. Despite many experiments on NM characterization and numerous *in vitro* and *in vivo* studies, several questions remain unanswered including the influence of biopersistence on the toxicity of NMs. It is unclear which criteria to apply to characterize a NM as biopersistent. Detection and quantification of NMs, especially determination of their state, *i.e.*, dissolution, aggregation, and agglomeration within biological matrices and other environments are still challenging tasks; moreover mechanisms of nanoparticle (NP) translocation and persistence remain critical gaps. This review summarizes the current understanding of NM biokinetics focusing on determinants of biopersistence. Thorough particle characterization in different exposure scenarios and biological matrices requires use of suitable analytical methods and is a prerequisite to understand biopersistence and for the development of appropriate dosimetry. Analytical tools that potentially can facilitate elucidation of key NM characteristics, such as ion beam microscopy (IBM) and time-of-flight secondary ion mass spectrometry (ToF-SIMS), are discussed in relation to their potential to advance the understanding of biopersistent NM kinetics. We conclude that a major requirement for future nanosafety research is the development and application of analytical tools to characterize NPs in different exposure scenarios and biological matrices.

Contents

Abbreviations: ABB, air-blood barrier; AM, alveolar macrophage; BALF, bronchoalveolar lavage fluid; BBB, blood-brain barrier; CRM, confocal Raman spectroscopy; DEE, diesel engine emissions; DEP, diesel exhaust particles; GBP, granular biopersistent particle without known significant specific toxicity; ICP-MS, inductively coupled plasma mass spectrometry; IBM, ion beam microscopy; LALN, lung associated lymph node; MWCNT, multi-walled carbon nanotube; NM, nanomaterial; NOAEC, no observed adverse effect concentration; NP, nanoparticle; PAA, polyacrylamide; PAH, polyaromatic hydrocarbons; PCLS, precision cut lung slices; PEG, polyethyleneglycol; PIXE, proton-induced X-ray emission; PMN, polymorphonuclear neutrophilic leucocytes; PSP, poorly soluble particle; RBS, Rutherford backscattering spectrometry; RES, reticuloendothelial system; TEM, transmission electron microscopy; TG, technical guideline; ToF-SIMS, time-of-flight secondary ion mass spectrometry.

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http://dx.doi.org/10.1016/j.impact.2017.03.003

1. Introduction

The growing production and use of nanomaterials (NMs) in diverse industrial processes, construction, and medical and consumer products is resulting in increasing exposure of humans and the environment. Humans encounter NMs from many sources and exposure routes, including ingestion of food (Szakal et al., 2014), direct dermal contact through consumer products (Gulson et al., 2015; Vance et al., 2015), and by inhalation of airborne NMs (Donaldson and Seaton, 2012). Environmental exposure on the other hand derives mostly from material aging and waste (Mitrano et al., 2015; Neale et al., 2013). Detecting NMs and understanding their kinetics and transformation are of paramount importance to assess their potential hazards and risks for humans and the environment. With respect to risk assessments, knowledge about the influence of biopersistence on the biokinetics and environmental fate of NMs is required for establishing meaningful categorization approaches.

With regard to human exposure, inhalation is considered the most relevant route for consumers and workers alike. Nano-sized respirable particles will access the alveoli, the location of gas exchange and generally the most vulnerable part of the lungs. A small fraction of NMs may cross biological barriers, such as the air-blood barrier (ABB) of the lung. Translocation of NMs was shown to be dependent on material and aggregate size (Kreyling et al., 2009). This was demonstrated by translocation of NMs to secondary organs such as the liver, heart, spleen, or kidney, subsequent to pulmonary uptake (Choi et al., 2010; Kermanizadeh et al., 2015; Kreyling et al., 2013; Moreno-Horn and Gebel, 2014). Kreyling et al. (2013) concluded that the extent of NM translocation is rather low. For risk assessment, knowledge about exposure including total uptake of NMs and retained multiple organ burdens, as well as tissue localization, and responses is necessary. Basic studies on the biokinetics of polymer nanoparticles (NPs) used in therapeutic applications have revealed size, surface characteristics, and shape as important parameters for their biodistribution *in vivo* (Petros and DeSimone, 2010). While liposomes were found to be rapidly cleared by extravasation or renal clearance if their size ranges between 5 and 10 nm, these mechanisms were not effective at entity sizes above 10 nm (Torchilin, 1998; Vinogradov et al., 2002). Larger entities of ~ 100–200 nm on the other hand, are cleared by the reticuloendothelial system (Petros and DeSimone, 2010). From these findings, a narrow size range of 10–100 nm was concluded to be optimal to achieve enhanced permeability and retention for particulate drug carriers (Petros and DeSimone, 2010). Particle binding and uptake by macrophages is largely influenced by opsonization, the adsorption to the particle surface of protein entities capable of interacting with specific plasma membrane receptors. In addition to opsonization, the interaction between particles and blood protein may lead to further effects such as interference with the blood-clotting cascade, a process that may lead to fibrin formation and anaphylaxis because of complement activation. Prevention of opsonization and complement activation may reduce particulate uptake by macrophages (Moghimi et al., 2001). Neutral vesicles were found to poorly activate the complement system (Chonn et al., 1991; Devine and Bradley, 1998) and to circulate longer in rats when compared to equivalent anionic examples (Senior and Gregoriadis, 1982). The impact of protein binding observed in the case of therapeutically used polymer particles is meanwhile recognized for all materials including NMs for which the term “biomolecular corona” was established, reviewed by Monopoli et al. (2012). Elements of such a corona acquired upon the first contact with the physiological environment might prevail on the particle surface during the onward transport of the material as has been shown for polymeric NPs (Cedervall et al., 2007) and silica (Tenzer et al., 2011). Moreover, the corona might impact a particle's capability to cross biological barriers (Monopoli et al., 2012). Corona formation is influenced by the ratio between surface area and protein concentration (Cedervall et al., 2007; Monopoli et al., 2011). The radius of curvature is considered as another key parameter (Cedervall et al., 2007; Dobrovolskaia et al., 2009; Lundqvist et al., 2008; Tenzer et al., 2011; Zhang et al., 2011). In studies with amorphous silica NPs, particle size impacted the quantity of 37% of all proteins identified, including toxicologically relevant candidates (Tenzer et al., 2011). Inhaled silica NPs acquire a corona during their passage through the respiratory tract lining fluid that is different from the one acquired by the same particles in plasma or whole blood. Investigations of the involved proteins indicate opsonization in preparation of particle phagocytosis and clearance from the lungs (Kumar et al., 2016). Currently most studies on corona formation are carried out with plasma, therefore they are of limited use for inhalation toxicology. In addition, first results indicate that biomolecule absorption from bronchoalveolar lavage fluid (BALF) may equalize particle surface properties (Whitwell et al., 2016).

Under real-life conditions, the majority of airborne NMs appear in agglomerated form. Such agglomerates behave like larger particles with respect to lung deposition, and hence it is crucial to understand where and when (*e.g.* in the product formulation, during aerosolization, or in the lung lining fluid) agglomeration occurs (Aalapati et al., 2014; Konduru et al., 2014; Methner et al., 2010; Morfeld et al., 2012; Pauluhn, 2009b; Seipenbusch et al., 2008; Srinivas et al., 2011). Even agglomerated NMs have almost the same high surface area as primary particles; they induce stronger effects per unit mass than larger microparticles. A contentious issue is the potential deagglomeration of NMs. One side argues that currently there is no evidence and that it is unlikely with respect to the underlying knowledge of physical behavior that NMs deagglomerate in biological milieus (Creutzenberg et al., 2012a; Levy et al., 2012; Preining, 1998). The other side counters that deagglomeration in the lung may occur for some, but not necessarily for all NMs (Mercer et al., 2013; Oberdörster et al., 1992a), keeping in mind the many possible, yet untested, NMs.

In addition to agglomeration, particle dissolution is increasingly recognized as a fundamental parameter influencing inhalation toxicity due to the reduction of particle size and related changes of dissolution kinetics (Pauluhn, 2014a). Since dissolution of metal oxide NMs *in vivo* varies widely, it has to be critically evaluated in each case whether the metal component detected in secondary organs following inhalation arrived there as the original NM or if the original NM dissolved in the lungs or distal to the ABB and then the ions translocated. Recently developed analytical methods allow for a sensitive detection of both particulate and dissolved fractions, which is important but rarely reported.

So far, there has been no valid evidence that NMs show hazards that are different from bulk materials (Donaldson and Poland, 2013; Gebel et