Overview of Nanotoxicology in Humans and the Environment; Developments, Challenges and Impacts

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Contents

Abstract This chapter provides an overview of the potential human health and environmental impact of nanomaterials (NMs). These unique materials can be produced naturally, incidentally or manufactured and can have numerous effects on human and ecological health. From the perspective of human health, the ultra-small nature of NMs can cause them to be highly reactive and promote adverse interactions at the organ, tissue, and cellular levels. Ecologically, NMs have the potential to pass into the environment at each point in their life cycle. Within the environment NMs undergo chemical, physical or biological processes that will modify their

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environmental fate and biological effects. The toxicological issues broadly covered in this chapter are discussed in further detail throughout this book.

Keywords Nanosafety · Human health hazard · Environmental hazard · (Eco) Toxicology · Regulation · Risk · Exposure

Introduction

Nanomaterials (NMs) can be produced naturally, incidentally, or by manufacturing and can have numerous effects on human and ecological health. Naturally-formed NMs include colloidal suspensions, such as humic and fulvic acids, proteins and peptides, and hydrated metal oxides, which are found in aquatic environments (Klaine et al. 2018; Lead et al. 2018; Buffle and van Leeuwen 1992; Buffle and van Leeuwen 1993). Of historical note, early work (Cameron 1915) suggested that clays, soil organic matter, metal oxides, and other minerals are important soil constituents. Modern research indicates that these constituents exhibit unique behaviours at nano-scale (Maurice 2010). Incidental releases of atmospheric NMs can occur through combustion or aerosolization (Klaine et al. 2018).

Over the course of the twentieth and twenty-first centuries, the field of nanotechnology has expanded at an exponential rate and with this expansion there has been a rapid increase in the number of novel engineered NMs being developed (Klaine et al. 2018). The annual projected growth rates for major NMs are shown in Table 1, adapted from Jankovic and Plata (2019). These new materials are having a transformative impact on research and development across numerous sectors including electronics, medicine, aerospace, construction and personal care, and are increasingly being used in nanotechnology-enabled products (Vance et al. 2015; Jankovic and Plata 2019). These new developments have been made possible due to the unique, size dependent physico-chemical properties that NMs exert. Some NMs allow for improved thermal or electrical conductivity, catalytic action, tensile strength, super-paramagnetism, controllable colloidal behaviour, and advanced optical properties. Environmental and human health studies have suggested relationships between these properties of NMs and their environmental fate, transport, and bioavailability, which may present a set of novel risks compared to larger particulate or dissolved counterparts (Lead et al. 2018).

Nanotechnology has been used since ancient times, for example, in the dichroic Lycurgus Cup of fourth century Rome which was made of glass interspersed with gold and silver NMs (Beyda et al. 2020). Photography is another application of NMs, in which daguerreotype photographs in the nineteenth century employed light sensitive silver NMs (Schlather et al. 2019). These artistic uses of nanotechnologies led the way to isolation of NMs, such as fullerenes and carbon nanotubes (CNTs) in 1985, and subsequent discovery of their novel properties (Bayda et al. 2019). Nanocomposites and nanohybrids are emerging classes of NMs, which are created by combining NM and non-NM materials or multiple NM materials, respectively (Lead et al. 2018). NMs may be generated in a powder or suspension form, or incorporated into matrices including polymers, building materials and even food stuffs.

Table 1 Non-exhaustive list of nanomaterials with highest estimated 2019 production volumes, projected growth rates for 2015–2025, and the number of technologies developed of each type based on an evaluation of technological readiness levels (Jankovic and Plata 2019)

Nanomaterial	Production (metric tons)	Projected growth rate (2015–2025)	Number of technologies developed
Aluminium oxide	6400–14,650	6–8%	16
Antimony tin oxide	180–410	7–11%	16
Bismuth oxide	52–108	8–11%	14
Carbon nanotubes	685–3500	5–9%	39
Cellulose	735–4149	21–31%	27
Cerium oxide	1177–2172	6–9%	12
Clays	30,000–68,200	3–6%	9
Cobalt oxide	6.5–11.7	5–9%	9
Dendrimers	0.54–2.97	10–20%	18
Diamonds	21.8–31.4	12–15%	9
Fibres	290–628	12–16%	9
Fullerenes	100–183	12–13%	13
Gold	2.2–4.0	7–12%	7
Graphene	7–310	26–43%	35
Iron oxide	24.5–115	19%	14
Magnesium oxide	37–75	13–16%	16
Manganese oxide	3.7–8.0	10–14%	11
Nickel	5.9–47.8	5–20%	8
Quantum dots	0.5–5.0	58%	17
Silicon dioxide	365,000–2,800,000	9–10%	11
Silver	230–560	6–10%	11
Titanium dioxide	38,500–225,000	4–11%	10
Zinc oxide	8440–47,460	6–8%	5
Zirconium oxide	1.739–42,583	3–4%	12

Direct synthesis of NMs (bottom-up) or high-power milling processes which grind bulk products down into NMs (top-down) are two generic approaches to synthesis, and will have substantial effects on environmental footprint, NM yield, use, production costs, and waste generation (Baraton 2002; Yokoyama and Huang 2005; Klaine et al. 2018; Jankovic and Plata 2019). Surface modification, or coating, is further used to influence NM stability, binding, or chemical functionality (Angel et al. 2013; Lead et al. 2018). Studies indicate that synthesis, suspension and coating methods for NMs can each influence toxicity and environmental behaviour (Klaine et al. 2018).

Characterization and metrology of NMs in the laboratory have advanced significantly since the early 2000s. While NM analysis in complex environments including aquatic, terrestrial, and biological media remains a challenge due to strong binding between natural macromolecules and NMs and low resolution of conventional imaging techniques, a number of innovative developments have emerged to improve these bottlenecks (Lead et al. 2018). Standardized testing media have helped identify new sources of interactions between NMs and their environment (Geitner et al. 2020). Isotopic labelling of NMs has improved quantitation of NM speciation and concentration (Merrifield et al. 2017; Merrifield et al. 2018) as well as biological uptake (Croteau et al. 2011; Handy et al. 2012; Al-Jubory and Handy 2013; Croteau et al. 2014). Conjugated separation techniques such as inductively coupled plasma, mass spectrometry, and field flow fractionation have improved separation and yielded novel single-cell and single-particle analytical techniques (Merrifield et al. 2017; Merrifield et al. 2018). Physico-chemical characterization has also been standardized for determining how NM properties behave in terms of stability and biological uptake (Liu et al. 2013, 2016).

Potential NM uses are vast and influenced by their physico-chemistry, as shown in Fig. 1, with several nanotechnologies already developed and tested. For example, the size and shape of nano-titanium dioxide (TiO_2) in anatase and rutile crystal structures gives improved photocatalytic properties over bulk TiO_2 (Chaturvedi et al. 2012).

In medicine, a range of NMs including iron oxides and quantum dots are being applied in tissue engineering, imaging enhancement and drug delivery systems (Cortajarena et al. 2014; Jankovic and Plata 2019). Within aerospace and other industries, the light weight and extremely high tensile strength of NMs such as CNTs makes them ideal for the construction of numerous components (De Volder et al. 2013). Moreover, a variety of NMs are utilised in a number of personal care products including zinc oxide (ZnO) and TiO_2 in sun cream, in addition to products such as moisturiser, foundation and hair colouring (Keller et al. 2014). Zero-valent metals, such as silver (Ag), gold (Au), and iron are commonly used for medical and environmental applications as catalysts of reactive species (Zhang 2003; Klaine et al. 2018). The production volumes and potential applications of NMs influence the risk of toxicity and environmental exposure. For example, carbon-based NM manufacturing rose from 1000 to 5000 metric tons between 2008 and 2015 (Jankovic and Plata 2019). To mitigate the risk associated with the growth of the NM industry, regulations such as REACH in Europe and TSCA in the United States have limited the direct application of NMs for environmental purposes (Royal Society/Royal Academy of Engineering 2004; Jankovic and Plata 2019).

The primary releases and subsequent inadvertent exposures to NMs occur by way of manufacturing, end-use, and disposal (Lead et al. 2018). With the high variability in production volumes and exposure sources, the expansion of the nanotechnology industry has given rise to nanotoxicology, which is a new sub-discipline aimed at understanding NM toxicology, fate, and behaviour and used to assess the human health and environmental effects of NMs. Donaldson et al. (2004) initially proposed the formation of this subcategory to, "…Address the gaps in knowledge and to specifically address special problems to be caused by nanoparticles." The 'special problems' to which Donaldson refers are the unique physico-chemical properties possessed by NMs that give them different properties compared with dissolved or larger scale particles of the same composition. Most notably, NMs have a

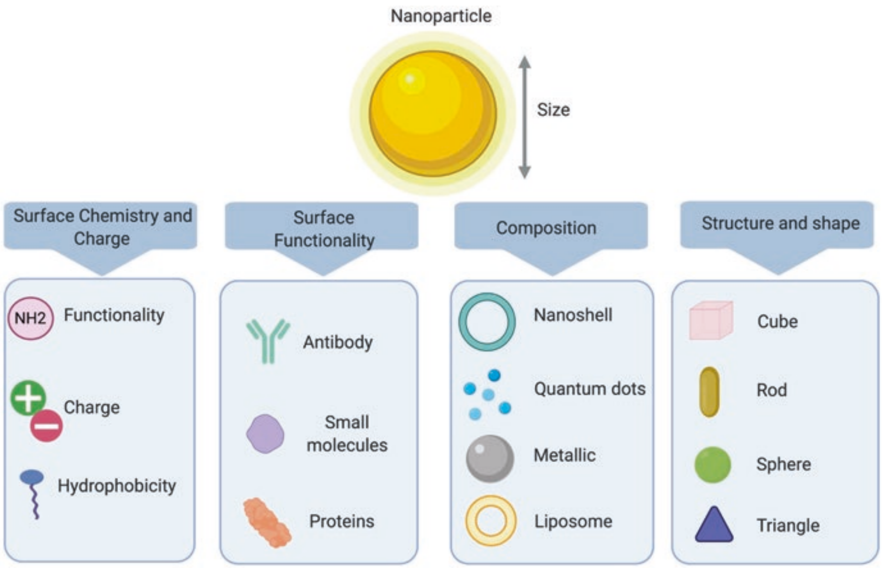

Fig. 1 Example nanomaterial physico-chemical characteristics – size, surface chemistry, charge functionality, composition and surface ligands. (Adapted from Burgum et al. 2018)

high specific surface area (SSA) and surface energy along with undercoordinated bonds which increase the unpredictability of toxicological endpoints and overall uncertainty in risk to biological and ecological systems (Sager et al. 2008; Gałyńska and Persson 2013).

Nanohazard to Human Health

Introduction

The materials evolving from the nanotechnology industry possess fundamental properties very different to their bulk counterparts. In medicine, for example, the specific surface area of these NMs offer unique bioavailabilities that can be targeted to specific sites in the human body (Burgum et al. 2018). With continued increases in usage and development of these NMs there is an inevitable, potentially significant increase in human exposure. While NM physico-chemical characteristics offer great potential in the development of new technologies, the same attributes cause concern towards potential human health hazards. This behaviour is due to the ultra-small nature that gives NMs the potential to be highly reactive within a biological environment. Moreover, this ultra-small size coupled with the geometry of NMs can result in an increased likelihood of the material entering the human body, translocating to different regions other than the portal of entry and promoting adverse interactions at the organ, tissue, and cellular levels.

Human Exposure

The population most at risk of NM exposure is the nanotechnology workforce, i.e., those responsible for synthesising the materials, and who are therefore subject to routine NM exposure, i.e., long-term, possibly low dose (chronic) exposures through daily handling of NMs. This risk is in addition to that of accidental one-off, high dose acute exposures, e.g., during cleaning operations (Ramachandran 2016). Exposure risk according to portal of entry into the body, e.g., dermal, ingestion and inhalation for the nanotechnology workforce during the production process are outlined in Table 2. NM exposure to the general public will likely be lower, through use of NM-containing consumer products or environmental exposure that may lead to low dose, long term exposure on a daily basis. In contrast, individuals exposed to NMs due to medical applications would be subject to short term, controlled exposure in the form of medical imaging and drug delivery systems via intravenous exposure (Nalwa 2014). NM exposure for medical applications will vary depending on the treatment required, varying from a one-off dose for medical imaging to extensive long-term treatment of a chronic condition (Barrow et al. 2017; Patra et al. 2018). Humans are most likely to be exposed to high production NMs (listed in Table 1) and are consequently a primary focus of nano-safety studies (Jankovic and Plata 2019).

There are a limited number of epidemiology studies that have assessed the effect of NM exposure on humans. Those that are available are primarily focused on the nanotechnology workforce. For example, Shvedova et al. (2016) assessed the gene expression profiles of workers having direct contact with multi-walled CNT (MWCNT) aerosols, with an estimated exposure concentration of 14.42 μg m^{-3} within the worker's breathing zone, for at least 6 months. The study revealed that MWCNT exposure resulted in up-regulation of genes involved in a pro-inflammatory response (e.g. IL-6, CSF2, IL-8) indicating potential for the material to cause

Table 2 The potential risks of inhalation, dermal and gastrointestinal tract entry into the body following occupational exposure to NMs during various synthesis processes (http://ec.europa.eu/health/ph_risk)

Synthesis process	Particle formation	Inhalation risks	Dermal/ingestion risks
Gas phase	In air	Reactor leakage Product recovery Post-recovery processing and packaging	Airborne workplace contamination Product handling Plant cleaning/maintenance
Vapour phase	On substrate	Product recovery Post-recovery processing and packaging	Dry workplace contamination Product handling Plant cleaning/maintenance
Colloidal/attrition	Liquid suspension	Product drying Processing/spillage	Workplace spillage/contamination Product handling Plant cleaning/maintenance

pulmonary and cardiovascular complications in humans. A larger epidemiological study recruited 227 workers that physically handled NMs and 137 that did not handle NMs (Liou et al. 2012). The investigation highlighted that workers who handled NMs had decreased levels of antioxidant enzymes superoxide dismutase (SOD) and Glutathione peroxidase (GPX) compared to workers that did not handle the material, thus signifying that cellular oxidative stress increases when working with NM exposure. Wu et al. (2014) undertook a study to measure levels of fractional exhaled nitric oxide (FENO) in 241 workers handling nano-TiO_2. All of the workers investigated had increased FENO levels compared to the control group, showing that continued exposure to aerosolised TiO_2 over time periods up to 5 hours, up to 8 times per week (exposure concentrations not calculated) could potentially result in persistent lung inflammation. These two studies highlight that the nanotechnology industry is beginning to understand the potential risks NMs pose in an occupational setting (Schulte et al. 2019). However, there is a significant need for longitudinal epidemiological investigations with clear exposure characterisations of NMs to more comprehensively understand their potential adverse health effects (Schulte et al. 2019). With this in mind it should be noted that the vast majority of nanotoxicology studies are animal or in vitro based, and conclusions or hypothesises on NM health risk are based on these data rather than human and epidemiological studies to date.

Inhalation

NM entry into the body via the respiratory tract is widely deemed to be a primary route of entry into the human body following occupational exposure (Oberdörster et al. 2005; Geiser and Kreyling 2010). Aerodynamic size is key when considering where an inhaled material will deposit in the respiratory tract, which includes the extra thoracic, upper bronchial, lower bronchial, or the alveolar regions. In simple terms the distance a material is able to penetrate into the lung by diffusional transport is increased with decreasing particle size (Heyder 2004). The ultra-small size of NMs (<100 nm) suggests that a large fraction of them will be deposited within the alveolar region, presuming there is no increase in primary particle size due to agglomeration. The mechanism of deposition is also determined by size, for example a material of ~1 μm in diameter will undergo gravitational sedimentation and inertial impaction, whereas below 100 nm diffusional deposition is the major mechanism (Tsuda et al. 2013).

In vivo studies have confirmed that Ag NPs of 15 nm diameter were found in 3.5-fold greater numbers in the rat alveolus compared to 410 nm Ag NPs (Braakhuis et al. 2014). In silico models have further supported this concept. For instance, application of a multiple-path particle dosimetry model to the nasal inhalation of a 100 nm NM at a concentration of 1 μg m^{-3} in humans showed the greatest deposition to be in the alveolar region of the lung in comparison to a 1 μm particle which deposits mostly in the head and neck region (Manojkumar et al. 2019). This region of the lung is highly vulnerable to NM retention due to the absence of the mucocilliary elevator and slow clearance by alveolar macrophages that consequently provides the potential for adverse direct and/or indirect NM-interaction with the alveolar epithelium (Maynard and Downes 2019). Key to alveolar macrophage NM-interaction is the initial influence of lung surfactant which is comprised of phospholipids including dipalmitolphosphatidylcholine (DPPC), proteins (SP-A, SP-B, SP-C and SP-D), and numerous neutral lipids (Veldhuizen and Haagsman 2000). Not only do lung surfactant components potentially alter NM surface chemistry via the formation of a NM-corona, but the opsonization function of SP-A and SP-D enhances the ability of alveolar macrophages to phagocytose a foreign material present in the lung (Ruge et al. 2012). Due to the small size and/or shape of NMs clearance by alveolar macrophages may not be possible, resulting in a higher rate of exposure to alveolar cells. NM shape is also a vital consideration; high aspect ratio NMs such as carbon nanotubes or nanofibers may result in frustrated phagocytosis, as the macrophages are unable to fully entrap the material. The result of frustrated phagocytosis is chronic inflammation in the lung tissue causing an inflammatory cascade, immune cell recruitment, and excessive production of reactive oxygen species (ROS) that can cause tissue injury (Cheresh et al. 2013).

Ingestion

The gastrointestinal tract (GI) offers a route for NM entry into the body following intentional consumption, leaching from food containers, deposition onto food, or secondary exposure from inhalation. The GI tract offers a very large surface area of ~200 m^2 for potential NM interaction, similar to the alveolar region in an adult human. Broadly, the GI tract consists of the oesophagus, stomach, duodenum, small intestine, large intestine, and anal canal. Potential NM interactions within these regions include absorption (which allows translocation to the blood and other organs), interaction with the cells comprising the GI tract, or effects on components such as the mucus layer and the microbiome (Bergin and Witzmann 2013). The gut microbiome has become a key area of study due the potential bactericidal toxicity effects of NMs such as Silver NPs (Li et al. 2019). It should be noted that the number of studies that have focused on assessing the effect of NMs on the GI tract is relatively small in comparison to those focusing on the respiratory tract. It can be argued that this lack of focus is due to the low rate of NM passage through the epithelial barrier that has been recorded to occur *in vivo*, although the strong focus on lung studies is also impart due to the historical development of the nanotoxicology field by lung toxicologists (Munger et al. 2014; Van Der Zande et al. 2012; Kreyling et al. 2017c). However, investigations in this open field are beginning to highlight that even a low level of NM absorption in the gut epithelium can result in heavy accumulation over time, ultimately resulting in potential systemic exposure (Kämpfer et al. 2020; Da Silva et al. 2020). NM absorption may potentially occur along the entire GI tract although due to its thick mucus membrane, surrounding connective tissue, and muscular tissue, absorption is highly unlikely to occur in the stomach (Bergin and Witzmann 2013). The acidic environment of the stomach (pH

1.5–3.5) can cause NM dissolution, resulting in the release of dissolved material or non-soluble derivatives, along with aggregation through surface charge neutralization (Kämpfer et al. 2020). Key to the ability of NM interactions with cells of the GI tract is mucus penetration; typically the sticky network of mucin fibres prevents the penetration of foreign materials by steric obstruction and adhesion (Liu et al. 2015). Trapped material is subsequently removed from the tissue either quickly or within a few hours depending on location with the GI tract. Small, negatively charged NMs have been shown to penetrate through mucus more easily than those that are large and positively charged (Wang et al. 2011). This behaviour is based on the principle that, the smaller the particle, the increased likelihood that it is able to pass through the mucus mesh spacings between mucin fibres. Comparison of mucus penetration by different materials established that NMs such as carbon nanotubes CNTs (~210 nm in length) become trapped by adhesive interactions, whereas ZnO NPs (<50 nm in diameter) rapidly penetrated mucus layers (Jachak et al. 2012). Once the barrier has been penetrated, NMs are able to interact with the GI tract epithelium. For example, within the small intestine the epithelium layer is comprised of goblet cells, enteroendocrine, and microfold (M) cells (which are located over Peyer's patches) embedded in a layer of columnar epithelial cells (Fröhlich and Roblegg 2012). It is understood that interaction and uptake by these different cell types is highly dependent on NM size (Unfried et al. 2007) For example, NMs within the size range of 10–50 nm are able to penetrate the epithelial cells (Powell et al. 2010). Alternatively, NMs within the size range of ~50–200 nm are typically in the uptake range of M cells as the NM maybe able to interact with the mechanism used to traffic endogenous calcium phosphate particles into the Peyer's patch immune cells (Powell et al. 2015; Da Silva et al. 2020).

Dermal Penetration

Although arguably not the most significant route into the body, the skin does certainly offer the largest surface area for potential NM contact. Skin exposure may be the result of deposition of an airborne NM, unintentional contact, or intentional application via NM-containing personal care products. The skin is comprised of three major layers; the epidermis, dermis, and subcutaneous layer. The outer layer of the epidermis is termed the stratum corneum, made up of keratinised dead cells, and is the main barrier against penetration (Proksch et al. 2008). A number of investigations into NM human skin penetration via topical application show penetration no deeper than the stratum corneum. This was shown to be the case when 17 nm TiO_2 and 30 nm ZnO NPs only penetrated the stratum corneum and accumulated in hair follicles (Baroli et al. 2007). However, there is evidence that penetration past this initial skin layer is highly probable. A study of 40 nm polystyrene NP penetration in murine skin models showed entry through the hair follicles, into the surrounding dermis, and ultimate passage to draining lymph nodes (although it was noted that mouse skin is thinner than human) (Vogt et al. 2006). Various studies have also reported the correlation between skin damage and increased permeability.

For example, an ex vivo study of Ag NM human skin penetration showed increased permeability through the stratum corneum in damaged skin compared to intact skin (Larese et al. 2009). Similarly, UV damaged porcine skin exhibited increased, although limited, penetration in comparison with the non-damaged model (Miquel-Jeanjean et al. 2012; Monteiro-Riviere et al. 2011). Like all other portals of entry and modes of toxicity, the potential and degree of skin penetration will be dependent of NM properties. The stratum corneum is abundant in cationic filaggrin, and would therefore be more susceptible to penetration by small, anionic NPs (Jatana and Delouise 2014). Due to the increasing prevalence of NM-enabled cosmetic products and the risk of skin exposure in a workplace scenario, the potential of NMs to cause skin sensitization is also an important consideration. It is well known that conditions such metal allergy, e.g., from jewellery or clothing, are major causes of allergic contact dermatitis, an inflammatory disease categorized as delayed-type hypersensitivity (Yoshihisa and Shimizu 2012). Although the exact mechanism of metal allergy is unknown it is believed that metal ions penetrate the skin, promoting an inflammatory response and ultimately $CD4^{+}$T cell activation that causes a characteristic allergic reaction consisting of skin lesions at the site of contact (Saito et al. 2016). NMs also can induce skin sensitization in a similar manner. For example, the local lymph node assay (LLNA) in rabbits has been utilised to demonstrate the ability of <25 nm TiO_2 NPs to induce skin sensitization after topical skin treatment (Park et al. 2011). In recent years NM skin hazard assessment, particularly when centred around cosmetic product assessment, has had to move away from in vivo techniques such as the LLNA due to the ban on the use of animals in cosmetic testing in the European Union (Regulation (EC) No. 1223/2009). This ban has led to the development and use of in vitro reconstructed skin models, such as EpiDerm™ and Straticell, that represent a first point of contact following exposure of a cosmetic product and for skin sensitisation assays (Evans et al. 2017; Choi et al. 2014; Wills et al. 2016).

Ocular Exposure

Despite being in direct contact with the external environment, NM contact with the eyes is often an overlooked potential hazard (Zhu et al. 2019). The eyeball possesses a series of anatomical barriers that prevent the contact of material with the ocular surface, such as blinking and tear film (Pastore 2019). NMs pose a challenge to this protection as their small size may permit close contact with the ocular surface. Subsequent attachment to the cornea and penetration then allows entry into the posterior of the eye (Xu et al. 2013). Although studies evaluating the risks posed by NMs to the eyes are limited, a number of investigations have been undertaken. For example, the effect of 20 and 80 nm gold NPs on mouse retinas over a 72-hour period demonstrated a significant increase in oxidative stress, as measured by Avidin D staining (Söderstjerna et al. 2014). Moreover, an investigation by Sriram et al. (2012) showed that 22.4 and 42.5 nm Ag NPs increase ROS production in bovine retina cells. A recent review by Zhu et al. (2019) has further highlighted ocular toxicity studies based on NMs used in industrial and environmental locations. The article also stresses that there is a limited number of nano-safety studies that place emphasis on ocular exposure risk and states that the area of study is relatively neglected in comparison to other points of NM exposure.

Translocation from Portal of Entry

There is substantial evidence to suggest that inhaled NMs are capable of distributing from the exposure site to secondary organ systems which include, but are not limited to, the central nervous, hepatic, renal, and cardiovascular systems (Kermanizadeh et al. 2015). Initially NM translocation was not considered a major issue. However, early in vivo nanotoxicology studies demonstrated translocation of radioactive NPs from the lungs, into the blood, and eventually the brain (Nemmar et al. 2001; Oberdörster et al. 2004). An in vitro assessment of the translocation potential of silicon dioxide (SiO_2) and TiO_2 NPs of varying sizes and charge demonstrated that both materials, regardless of characteristics, could translocate across a human bronchial epithelial barrier constructed on a Transwell membrane (George et al. 2015). However, increased translocation rate correlated with decreased NP size and a negative charge. Neither material disrupted the epithelial barrier integrity, suggesting transcytosis of the internalised NPs as a transport mechanism. A similar model comprised of the same cell line showed that carbon nanotubes substantially disrupt the epithelial barrier during translocation (Derk et al. 2015). This form of penetration has also been demonstrated in vivo. CNT (150–200 nm) inhalation in rats showed that the material translocated through the lung and was eventually transported to various organs (Czarny et al. 2014). Size is clearly a key factor in NM translocation. Studies that use an array of differently sized NMs in the majority of cases identify the smallest NMs as having the greatest translocation potential (Kreyling et al. 2017a, b, d). For instance, comparison of Au NP translocation in rats indicated that the smallest particles (of identical shape and composition) (13 ± 12 nm) were able to translocate out of the lung tissue to the blood, liver, spleen, brain, and testes, whereas larger particles (105 ± 42 nm) were only found in the blood rather than secondary organs (Han et al. 2015). Consideration of the ability of an NM to undergo translocation through the body is vital given that this parameter dictates subsequent toxicity at point of entry, and the potential for multi-organ toxicity (Raftis and Miller 2019).

Biological Impact

Ultimately, the primary interactions of NMs in a biological environment occur at the cellular level and involve cellular structures, surfaces and biochemical components (Rothen-Rutishauser et al. 2019). Nanotoxicology studies typically focus on the evaluation of one or more toxicological endpoints, e.g., cytotoxicity, pro-inflammation and/or genotoxicity. Information on the ability of a test NM to undergo cellular uptake and its localisation within the cell is key in understanding its toxicological fate. Upon interaction with the cell surface, there is the potential for a NM to enter the cell by a number of mechanisms, e.g., phagocytosis, micropinocytosis, caveolin-dependent endocytosis, clathrin-dependent endocytosis, receptor mediated endocytosis, non-specific endocytosis, and passive diffusion, as shown in Fig. 2(i) (Conner and Schmid 2003). Figure 2(ii) shows an example of the uptake of dextran-coated iron oxide NMs in macrophage-like cells derived from the THP-1 cell line. It should be noted that NM uptake may not be limited to one of these mechanisms, i.e., multiple different forms of uptake may be involved for a single NM type (Behra et al. 2013). The ability of a NM to undergo cellular uptake will be dependent on its physico-chemical characteristics, along with the changes to these properties adopted by the material in the biological environment. For example, alteration of surface charges and corona formation can occur as a result of proteins and other macromolecules coating the NM surface (Monopoli et al. 2011).

The Oxidative Stress Paradigm and Its Role in Genotoxicity

The oxidative stress paradigm is key in NM toxicology and plays a central role in promoting genotoxicity (Evans et al. 2019b). Briefly, the term oxidative stress refers to a cellular redox imbalance between reactive oxygen species (ROS), e.g., super oxides ($O_2^{\bullet -}$), hydroxyl radicals ($^{\bullet}OH$), and antioxidants (e.g. SOD), which in a cell's natural state is maintained in homeostasis (Zhang et al. 2016). Many NMs are capable of interacting with oxygen-containing molecules, causing the formation of ROS. For example, ions released from transition metals can react with hydrogen peroxide via Fenton chemistry creating hydroxyl radicals ($^{\bullet}OH$) (Valko et al. 2006):

$$\mathrm{M}^{n+} + \mathrm{H_2O_2} \rightarrow \mathrm{M}^{(n+1)} + {}^{\bullet}OH + OH^{-} \left(\text{where M represents transition metal}\right)$$

The formation of ROS in this manner presents the possibility of inducing DNA damage due to the ability of $^{\bullet}OH$ to readily react with DNA and DNA precursors, resulting in the formation of DNA lesions (Singh et al. 2009). A further example of NM oxidative stress potential is catalysation of ROS formation at the NM surface due to immobilised free bonds. For example, quartz NMs have been shown to promote ROS production due to surface $SiO^{\bullet}$ and $SiO_2^{\bullet}$ moieties (Huang et al. 2010). Oxidative damage to the cellular genetic machinery within a single cell is defined as primary indirect genotoxicity, which is distinct from direct genotoxic mechanisms where an exogenous agent enters the nuclei and directly interferes with the structure and function of DNA. However, evidence of direct induction of genotoxicity by NMs within the literature is limited and is consequently not regarded as a major mechanism of damage (Doak et al. 2012). Aside from primary genotoxicity mechanisms, the ability of a NM to damage DNA can also be mediated by other cell types at the tissue level. This is a prominent mechanism of DNA damage induced by

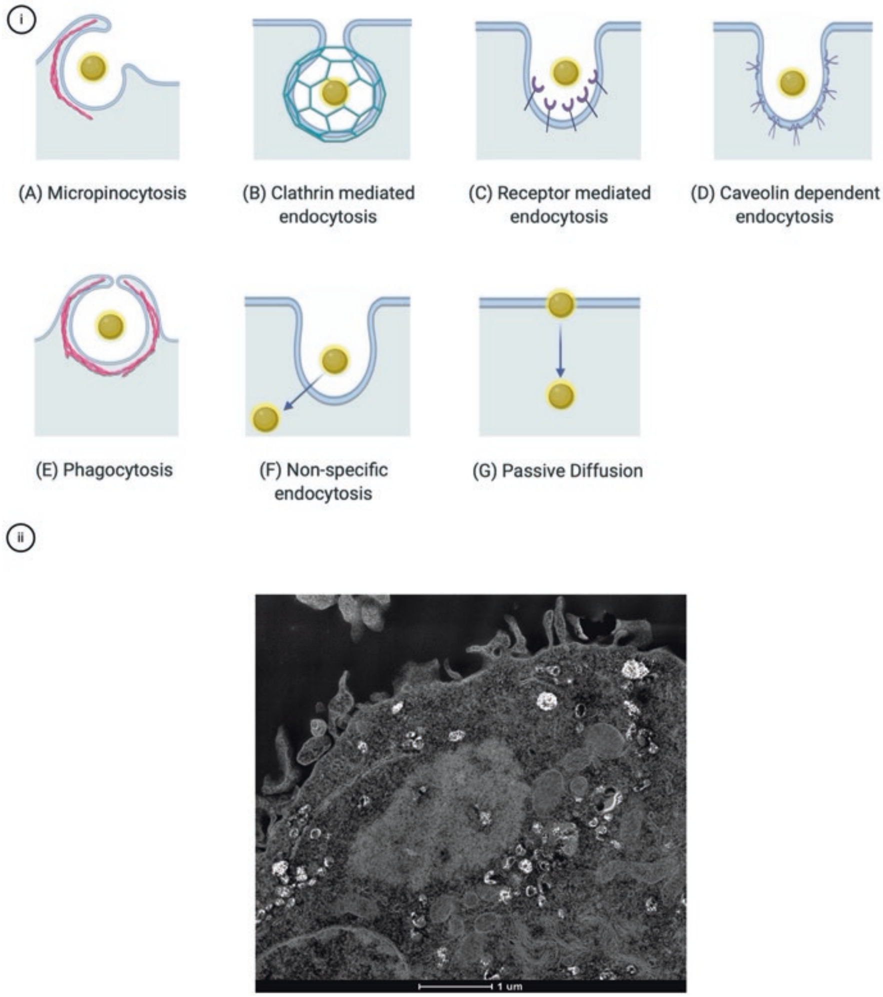

Fig. 2 Active and passive NM cellular uptake mechanisms – (i) Potential mechanisms of NM cellular uptake – (A) Phagocytosis (B) Micropinocytosis (C) Caveolin dependant endocytosis (D) Clathrin mediated endocytosis (E) Receptor mediated endocytosis (F) Non-specific endocytosis (G) Passive diffusion; (ii) Scanning electron microscopy image (STEM) displaying example of iron oxide NM (<10 nm) up take by dTHP-1 cell

NMs, whereby secondary genotoxicity is induced by a chronic pro-inflammatory response that is triggered by immune cells which internalise the invading material. This response subsequently results in oxidatively damaged DNA in surrounding tissues (Evans et al. 2017, 2019a).

Pro-inflammatory Response

The activation of immune cells results in the secretion of various inflammatory mediators, such as cytokines, chemokines, histamines, prostaglandins, ROS, and reactive nitrogen species (RNS). In a balanced biological system, this inflammatory response is vital for pathogen recognition and removal. However, NMs have the potential to disrupt this balance. The potential immunogenicity of a NM will be dependent on a number of factors related to its physico-chemical characteristics, the moieties it presents in regard to cell surfaces interactions, and its ability to undergo cellular uptake (Dobrovolskaia and Mcneil 2016). As discussed in section "Human Exposure", the vast majority of human epidemiology studies that have been undertaken have focused on NM exposure in the workplace with pulmonary inflammation as an outcome. Clear inflammatory markers have been identified in the lungs of workers persistently exposed to aerosolised NMs (Liou et al. 2012). Moreover, a key study by Poland et al. (2008) demonstrated that high aspect ratio NMs behave in a similar manner to asbestos in the lung, causing frustrated phagocytosis and its associated adverse toxicological implications. Consequently, NM immunogenicity potential has been assessed extensively with particular emphasis placed on NMs that are liable to be inhaled, including the NMs highlighted in Table 1. For example, 4–6 nm rutile TiO_2 has been shown to promote immune cell recruitment and cytokine production in the lungs of rats in addition to the onset of cardiac oedema (Nemmar et al. 2008). MWCNT and ZnO NPs can cause increased inflammation and neutrophil recruitment in the lungs of 18-month old mice (Luyts et al. 2018). Moreover, a recent 90-day study by Chu et al. (2019) reaffirmed the ability of carbon black NPs to cause extensive lung and systemic inflammation in rats. Various in vitro NM immunological studies have also been undertaken. For instance, Muller et al. (2010) utilised a lung co-culture model to demonstrate the ability of 20–30 nm TiO_2 NMs to promote an immune response along with increased ROS production. Furthermore, CNT have been shown to promote inflammatory cytokine production and increased ROS in lung epithelial cells in vitro (Fu et al. 2014). Indeed, ROS production and the oxidative stress paradigm is central in most toxicological endpoints associated with NMs.

Summary

The increasing risk of human exposure to NMs has rapidly facilitated the need for hazard and exposure assessment in relation to their effect on human health. While the toxicology of bulk materials is typically influenced by their composition, NMs possess unique physico-chemical properties that in addition to composition determine their ability to enter the human body and their bioreactivity at the organ, tissue, and cellular level. How NMs truly affect human health is not completely understood, but the continually developing field of nanotoxicology is providing evidence into the potential health risks these unique materials pose. In addition to human health impact, the wider environmental impact of these materials also needs to be considered.

Impacts of NMs on Environmental Health

Exposure to NMs via Discharges and Transformation Processes

At each point in their life cycle, NMs can pass into the environment. NMs can be directly used in the environment for processes such as remediation and can also be discharged via wastewater treatment plants and in industrial effluents from manufacturing sites. From industrial discharges, NMs can enter atmospheric, aquatic, terrestrial, or sedimentary ecosystems (Zhang and Elliott 2006; Biswas and Wu 2005; Selck et al. 2016; Holden et al. 2016; Sun et al., 2017). Possible discharge routes are shown in Fig. 3.

Sources of NM Discharges

While nanotechnology has been viewed as a solution to a number of environmental issues, such as water, soil, and air quality as well as food security (Adeleye et al. 2016; Iavicoli et al. 2017), the complex, energy intensive processes and specialized organic reagents used can outweigh the potential benefits (Pati et al. 2014). The potentially large exposures from production are exacerbated by the uncertainty due to their nano-specific behaviours. A major contributing factor to the environmental footprint of NM production is synthesis yield, with higher yields representing less waste generation and more efficient utilization of resources. Carbon based NMs generally have <33% yield while metal oxides have >90% yield (Jankovic and Plata 2019). Therefore, much of the waste stream from NM production is not NM-laden, but nevertheless can lead to large discharges to the environment as production increases. Additionally, processes and reactants used for synthesizing NMs and any sample handling can leave residual compounds on the NMs, with possible subsequent effects (Oberdörster 2004; Smith et al. 2007; Cheng et al. 2007; Federici et al. 2007; Griffitt et al. 2007; Lee et al. 2007; Oberdörster 2010).

NMs and NM-enabled products are discharged in effluent as solid, liquid, and gaseous wastes (Batley et al. 2013; Ostraat et al. 2013). Unless spilled or used directly into the environment, NM wastes are transmitted through, for example, wastewater treatment facilities, where discharge can occur from sludge to landfill or soil, or from wastewaters discharged to streams after tertiary treatment (Lazareva and Keller 2014). If untreated, NMs can then leach into groundwaters, soil, and surface waters. Sediments, especially marine sediments, are likely to be the final sink for many NMs (Lead et al. 2018). In usage, NMs can slowly be released into the environment, such as with NM-enabled sun creams, textiles, and paints (Nowack

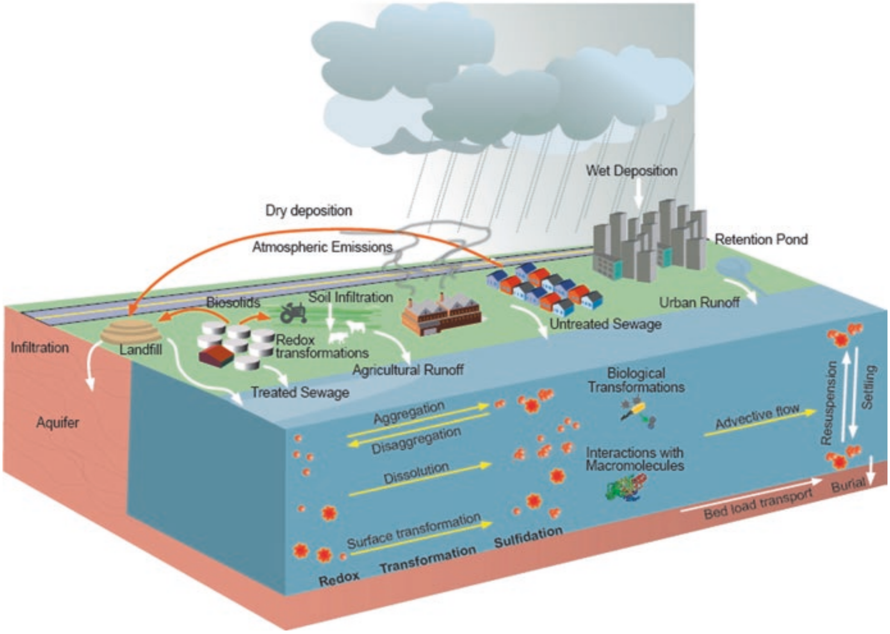

Fig. 3 The major discharge routes of NMs into the environment and potential transformations in the environment. (From Dale et al. 2015)

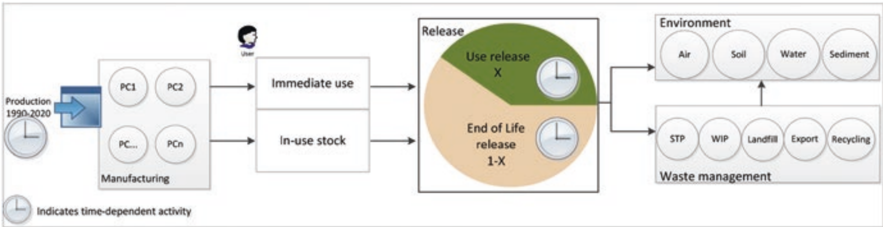

Fig. 4 A schematic of a mass flow analysis (MFA) model. This model uses data on NM production as input, with a percentage allocated to each product category an NM is embedded into. The fractions of NMs in use and in stockpiles, and those of NMs released during use and disposal determine the overall mass of NMs released in the environment. Finally, the concentrations of NMs in environmental and waste management compartments are modelled by analysing the mass of released NMs compared to the size of each compartment. (Wang and Nowack 2018)

et al. 2012). A useful tool for studying the potential environmental exposure to NM-enabled products is the mass flow analysis (MFA) model, shown in Fig. 4 (Wang and Nowack 2018). Fate and behaviour (FB) models have been employed to assess the impact of transformations to NM cores, surface coatings, and intermolecular interactions on environmental fate and behaviour based on inputs from MFA models (Dale et al. 2015; Sun et al. 2017). Some effort has gone into developing a unified approach using both MFA and FB models, which use and produce complementary datasets (Wang and Nowack 2018). Static MFA is a series of calculations based on the amounts of NMs produced annually, used to estimate the amounts released into the environment (Mueller and Nowack 2008; Gottschalk et al. 2010). Dynamic MFA considers historical production as well as the lifetime of NMs in products to calculate the amount of NMs stored in products and those released into waste infrastructure and environmental compartments (Wang and Nowack 2018). FB models require MFA data for input, and also calculate the compartmentalization of NMs. However, the functions used for these calculations are based on NM physico-chemical properties and the hydrology and geology of the study area (Markus et al. 2017; Ellis et al. 2018; Salieri et al. 2019).

Disposal of NMs occurs when a product reaches its end of life. For instance, disposal of NM-enabled products such as textiles, paints, sun cream and cosmetics, polymers, food packaging, and even food scraps likely transmit the NMs into water treatment plants, landfills or recycling centres (Mitrano et al. 2015). NMs that reach the environment after waste treatment processing are likely to accumulate in sediments (Lowry et al. 2012). NMs are also expected to be released at relatively low concentrations through their use in NM-enabled products (Lead et al. 2018). In terms of discharge, the greatest factors that influence environmental exposure are the volumes and types of NMs that are being used, for which there is scant data (Nowack et al. 2012; Holden et al. 2016). However, there is a clearly increasing trend in volumes of NMs produced and for a worst-case scenario, these gross amounts could be used as a basis for risk assessment. For example, between 2008 and 2015, carbon-based NM production rose from 1000 metric tons to about 5000 metric tons; other heavily produced NMs include SiO_2 (1,000,000 metric tons), TiO_2 (100,000 metric tons), ZnO (50,000 metric tons), zirconium dioxide (50,000 metric tons), aluminium oxide (10,000 metric tons), and CNT (3000 metric tons) (Jankovic and Plata 2019). Based on findings from an MFA model developed by Wang and Nowack (2018), the predicted compartmentalization for five types of NMs is presented in Table 3 for seven regions of Europe.

Environmental Transformations of NMs

Once in the environment, NMs and NM-enabled products undergo chemical, physical, or biological processes that transform the NMs and modify their environmental fate and transport, and biological effects (Nowack et al. 2012; Lowry et al. 2012). Transformations are most likely to occur after a NM-enabled product is disposed of in the environment, rather than during controlled storage, as environmental conditions are more variable (Mitrano et al. 2015). A number of processes that cause NM aging prior to disposal in the environment were determined for silver NM cores embedded in textiles, shown in Table 4. In addition to impacting cores, Mitrano et al., found that the NM coating was also affected by transformations that affected susceptibility to further transformation (2015). These findings highlight the importance of comprehensive understanding of use cases for NMs.

These further transformation, which influences their fate, behaviour, and toxicity (Lowry et al. 2012). Transformations include agglomeration, dissolution, reprecipitation, oxidation, sulfidation, corona formation, and other processes (Nowack et al. 2012; Lowry et al. 2012; Mitrano et al. 2015). For instance, NM agglomeration has been understood within a framework of the Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory (Hotze et al. 2010), which describes aggregation for charge stabilized colloids represented as combinations of repulsive and attractive forces (Lead et al. 2018). Agglomeration is frequently observed with NMs at high

Table 3 Lists output from a MFA model for predicted concentrations of NMs in environmental compartments in European regions in 2014 (Wang and Nowack 2018)

NM	Compartment	EU	CE	EE	NE	SE	SEE	CH	Unit
Nano-SiO_2	**STP_{eff}**	65	74	51	48	23	34	12	µg/L
	STP_{sl}	4.4	5.3	2.4	4.6	2.1	3.3	6.8	g/kg
	LW	490	620	450	1500	400	200	–	mg/kg
	IW	490	620	380	470	180	5900	670	mg/kg
	BA	3.4	4.5	2.8	3.1	1.1	25	5.7	g/kg
	FA	4.7	6.1	3.9	4.1	1.5	35	7.9	g/kg
	Air	16	34	8.7	2.6	10	18	48	ng/m3
	NUS	86	170	52	28	68	92	290	µg/kg
	STS	150	390	330	240	240	110	–	mg/kg
	SW	4.3	4.4	2.5	0.22	8.6	11	4.2	µg/L
	Sed	79	79	46	4.1	180	210	75	mg/kg
Nano-CeO_2	**STP_{eff}**	37	44	25	29	19	18	4.8	ng/l
	STP_{sl}	1.8	2.5	0.89	2	1.2	1.3	2.6	mg/kg
	LW	6.5	23	3.3	41	4.4	1.3	–	mg/kg
	IW	8.4	10	8.1	7.8	4.7	150	10	µg/kg
	BA	0.55	0.85	0.66	0.25	0.32	7.1	0.9	mg/kg
	FA	0.77	1.2	0.91	0.36	0.45	9.8	1.2	mg/kg
	Air	42	100	20	6.8	35	43	110	pg/m3
	NUS	42	96	22	14	39	41	120	ng/kg
	STS	60	180	120	110	130	45	–	µg/kg
	SW	2.0	2.6	1.1	0.11	5.1	4.9	1.9	ng/l
	Sed	35	46	19	2.1	95	87	32	µg/kg
Nano-iron oxides	**STP_{eff}**	1.5	1.3	1.2	0.85	0.7	0.56	0.24	µg/L
	STP_{sl}	75	85	44	73	53	45	110	mg/kg
	LW	0.89	1.9	1.03	4.7	1.2	0.35	–	mg/kg
	IW	1	1.2	1.3	0.94	0.67	19	1.4	mg/kg
	BA	22	31	32	11	14	240	42	mg/kg
	FA	32	44	44	16	19	340	59	mg/kg
	Air	0.23	0.53	0.15	0.04	0.25	0.24	0.76	ng/m3
	NUS	0.32	0.67	0.22	0.11	0.33	0.31	1.2	µg/kg
	STS	2.7	6.6	6	4.2	5.8	1.7	–	mg/kg
	SW	86	110	58	4.7	250	180	110	ng/L
	Sed	1.6	2	1.03	0.09	4.4	3.6	2	mg/kg

Table 3 (continued)

NM	Compartment	EU	CE	EE	NE	SE	SEE	CH	Unit
Nano-Al_2O_3	**STP_{eff}**	3.6	5.1	3.5	2.6	2.5	2.5	1.1	µg/L
	STP_{sl}	240	380	160	250	220	240	620	mg/kg
	LW	9.9	20	13	41	16	4.7	–	mg/kg
	IW	9.6	17	11	9.9	6.1	140	21	mg/kg
	BA	93	190	120	64	55	870	300	mg/kg
	FA	130	260	170	88	77	1200	410	mg/kg
	Air	1.2	3.7	0.88	0.21	1.6	1.9	6.5	ng/m3
	NUS	1.3	4.1	1.2	0.51	1.9	2	8.4	ug/kg
	STS	8.2	27	24	14	23	7.9	–	mg/kg
	SW	0.31	0.53	0.22	0.02	1.1	1	0.65	µg/L
	Sed	5.7	9.3	4.1	0.33	19	17	11	mg/kg
Quantum dots	**STP_{eff}**	2.7	3.2	2.4	2.3	1.6	1.6	0.48	pg/L
	STP_{sl}	0.18	0.23	110	0.22	0.14	0.15	0.26	µg/kg
	LW	91	330	57	660	70	22	–	ng/kg
	IW	1.6	1.2	3.4	1.2	1.8	72	0.83	µg/kg
	BA	8	6.1	17	6.1	9.3	260	4.8	µg/kg
	FA	11	8.4	23	8.5	13	350	6.6	µg/kg
	Air	7.9	19	5.1	1.5	8.4	10	22	fg/m3
	NUS	8.4	18	5.8	3	9.1	9.9	27	pg/kg
	STS	6.2	17	16	11	15	5.3	–	ng/kg
	SW	170	180	120	9.6	500	530	150	fg/L
	Sed	3.2	3.2	2.1	0.17	9.1	9.4	2.8	ng/kg

STP sewage treatment plant, *eff* effluent, *sl* sludge, *LW* landfilled waste, *IW* incinerated waste, *BA* bottom ash, *FA* fly ash, *NUS* natural and urban soil, *STS* sludge-treated soil, *SW* surface water, *Sed* sediment, *EU* European Union 27, *CE* Central Europe, *EE* Eastern Europe, *NE* Northern Europe, *SE* Southern Europe, *SEE* Southeastern Europe, *CH* Switzerland

concentrations (tens of mg/L for sterically stabilized NMs), especially in high ionic strength media such as seawater for char charge stabilized NMs, which then settle into the sediment (Doyle et al. 2014; Alabresm et al. 2017). NM concentration, pH, ionic strength, divalent ion concentrations, and NOM concentrations can all influence aggregation behaviour, while surface modification can stabilize NMs (Handy et al. 2008b; Bian et al. 2011; Baalousha et al. 2016). Sedimentation is generally slowed by the presence of natural organic matter (NOM) such as humic substances which form eco-coronas on an NM surface alongside or instead of engineered polymeric coatings (Diegoli et al. 2008; Badawy et al. 2010). Both environmental and engineered coatings affect the colloidal stability, with higher steric stability linked to longer residence times for NMs in a water column (Huynh and Chen 2011; Wang et al. 2016).

Although there is much work on changes in behavior and toxicity due to transformation processes, studies under environmentally relevant conditions are less common. However, improvements in analytical characterization of NMs and NM-enabled products, as well as comprehensive and environmentally relevant

Table 4 Transformation processes for textile-embedded Ag NMs and their causes and effects

Transformation	Cause	Effects
Oxidation	Washing, bleaching	Increased toxicity and decreased effectiveness via dissolution, product leaching as AgCl
	Detergents	Complexation and stabilization
Reduction	Washing	Reduction of Ag ions to new zero-valent particles
Precipitation	Air exposure	Secondary particle formation
	Exposure to digestive fluids	Sulfidation to insoluble Ag/Cl/S complexes
	Washing	Formation of AgCl solids
UV irradiation	Sun exposure	Altered reactivity
	Wastewater treatment	No efficacy in Ag NM removal
Incineration	Disposal	Reduced agglomeration of NMs, production of Ag-laden waste ash
		Degradation of Ag polymer coating and reduction in stability

From Mitrano et al. (2015)

testing protocols, have improved the data obtained from mesocosm studies substantially. Mesocosms are an important study design that enable a more realistic analysis of NM fate and behaviour in the environment than laboratory studies (Lead et al. 2018; Geitner et al. 2020). Mesocosm and laboratory studies sometimes agree but at other times cannot be rationalized. For instance, mesocosm studies on exposure to Ag NMs have suggested that the effects of dissolved and NM formulations of Ag are similar (Colman et al. 2014; Bone et al. 2015), while laboratory studies demonstrate a nano-specific effect dependent on physico-chemical properties, organisms studied, and media (Leclerc and Wilkinson 2014). However, chronic low dose studies with Ag NMs show agreement between mesocosm and laboratory studies (Baker et al. 2016; Merrifield et al. 2017). Further data suggests that sorption of NOM to NMs reduces hazard to organisms by stabilizing NMs in the environment and reducing dissolution, biouptake, and other processes (Mudunkotuwa and Grassian 2015). Previously it was unknown whether a separate and novel risk existed between pristine NMs and NM-enabled products and those that have been weathered by a transformation process (Nowack et al. 2012). However, evidence now suggests that ions released from NMs, NMs in suspension, and agglomerated NMs each exhibit unique environmental behaviours (Lead et al. 2018). Examples of the major transformation processes for NMs are listed in Table 5 (Nowack et al. 2012; Lead et al. 2018).

Obtaining accurate determinations of NM concentrations and extent of transformation in the environment and organisms has been a significant challenge due to the limitations of available analytical techniques (Loosli et al. 2020). However, progress has been made by coupling highly sensitive separation methods to inductively coupled plasma mass spectrometry (ICP-MS) such as asymmetrical flow-field flow fractionation (AF4), or using ICP-MS modes of analysis such as single-cell (SC) and single-particle (SP) workflows, and/or time-of-flight mass (TOF) spectrometry

Table 5 Examples of environmental processes that can lead to NM transformation and influence exposures to organisms (Nowack et al. 2012; Lead et al., 2018)

Process	Type	Example	Reference
Photolysis	Physical/ chemical	Weathering of quantum dots and increase in toxicity	Wiecinski et al. (2013)
Oxidation and reduction	Chemical	Silver oxidation prior to dissolution	Grillet et al. (2013)
Dissolution and precipitation	Physical/ chemical	Silver NMs dissolve into silver ions followed by reprecipitation and ripening	Merrifield et al. (2017)
Adsorption of NMs onto larger particles	Physical/ chemical	Interaction of NMs with external surfaces of organisms followed by uptake	Handy et al. (2008a, b)
Adsorption of NOM and ions onto NMs	Physical or chemical	Ecocorona formation and (commonly) reduction in toxicity	Mudunkotuwa and Grassian (2015)
Combustion	Chemical	Altered CeO_2 NM speciation during sewage sludge incineration	Gogos et al. (2019)
Biodegradation	Biological	Degradation of organic polymer coatings	Kirschling et al. (2011)

(Merrifield et al. 2017; Praetorius et al. 2017; Merrifield et al. 2018; Loosli et al. 2020). SC and SP methods are especially effective in quantifying NMs in biological material, while TOF approaches are able to separate engineered NMs from natural background NMs in environmental media (Gondikas et al. 2018). Further metrological improvements will help to validate MFA and FB modelling approaches which need to be compared with benchmarks for environmental NM concentrations to reduce the uncertainty of the data they generate (Nowack et al. 2012). The uncertainty of the output of MFA and FB models remains high because the probable environmental concentrations and volumes of NMs have uncertainties of several orders of magnitude in some cases, are likely to fluctuate significantly from year to year, and cannot yet be reliably validated on a large scale using current analytical techniques (Jankovic and Plata 2019). The reliability of these models can be improved by using relevant environmental conditions in laboratory experiments and mesocosm studies (Bone et al. 2015; Hansen et al. 2017). Overall, MFA models are useful for estimating and predicting NM releases, and FB models allow researchers to determine the sinks of NMs based on data generated using MFA models. Combining both modelling approaches is promising as a comprehensive tool for fate and transport studies.

The longer a NM is stable in suspension, the greater chance there is for reactions to occur on the NM surface. For instance, sulfidation can occur with metal NMs such as Ag, in environments high in sulfides or low in oxygen (such as anaerobic digesters at wastewater treatment plants – Kim et al. 2010; Kaegi et al. 2011; Lombi et al. 2013). This reaction can influence particle size, charge, and solubility by depositing sulfur atoms onto the NM surface. Depending on NM composition and properties such as size, sulfidation impacts solubility and resulting toxicity to aquatic organisms (Kaegi et al. 2011). Natural colloids, such as suspended solids, can also change the surface of an NM and influence stability and toxicity (Manciulea et al. 2009; Mudunkotuwa and Grassian 2015; Baalousha et al. 2015; Römer et al. 2016). Agglomeration of dissolved metals into NMs under environmental conditions and sorption of toxic substances have also been observed (Scarano and Morelli 2003; Ferreira et al. 2014).

Terrestrial systems are generally less studied than aquatic systems, though the same principles of colloidal behaviour and challenges in metrology apply to NMs in both media (Burleson et al. 2004; Gimbert et al. 2005; Klaine et al. 2018). Colloid generation, fate, nutrient sequestration, and contaminant transport are influenced by physicochemical properties of the molecules as well as the media, for instance, soil texture, pH, ionic strength, and cation exchange capacity (Quirk and Schofield 1955; Noack et al. 2000; Cornelis et al. 2011; Zhang et al. 2012; Cornelis et al. 2014). As in water, dissolution of ZnO NMs occurs in a pH-dependent manner, and interactions with NOM in the soil reduce toxicity of NMs (Tong et al. 2007; Kasel et al. 2013; Heggelund et al. 2014). To date, inputs of NMs into terrestrial systems have been biosolids applications, which release TiO_2, ZnO, and Ag NMs (Shah et al. 2014). The process of colloid transport through pore spaces in a terrestrial system is shown in Fig. 5 (Cornelis et al. 2014).

Hazard of NMs to Organisms

Environmental transformations, particle size, chemical composition and synthesis method, particle charge, and even shape can impact toxicity of NMs to organisms (Jia et al. 2005; Hawthorne et al. 2012). Benthic crustaceans and mussels uptake NMs and exhibit oxidative DNA damage from exposure (Lovern and Klaper 2006; Zhu et al. 2006; Gagné et al. 2008; Moore et al. 2009). Similarly, earthworms have been shown to exhibit toxic reactions to ZnO NMs in soil (Heggelund et al. 2014). Most ecotoxicological data generated for NMs are for *Daphnia*, algae, bacteria, various species of fish, and some invertebrates such as worms, with investigations into effects on reptiles, birds, and mammals lacking (Lead et al. 2018). A number of toxic effects from NMs have been observed across multiple species. Membrane disruption, changes in ion uptake, cytoskeletal motility, protein function, and generational impacts from NM exposure have been observed in laboratory studies of animals (Park et al. 2003; Soenen et al. 2011; Wu et al. 2013; Yue et al. 2015, 2016; Schultz et al. 2016). Toxicity mechanisms differ between aquatic and terrestrial species; for example, in fish particulate (including NM) uptake occurs through the gills, gastrointestinal tract or skin followed by induction of active transport mechanisms (Geppert et al. 2016). Target organs for NMs are usually similar to bulk or dissolved substances, though the spleen is involved in particulate processing and is particularly affected by NMs in fish (Handy et al. 2011).

The same NM type can have different biological uptake and toxicity behaviour under different conditions. With *Danio rerio* (zebrafish) for example, the rate of Ag

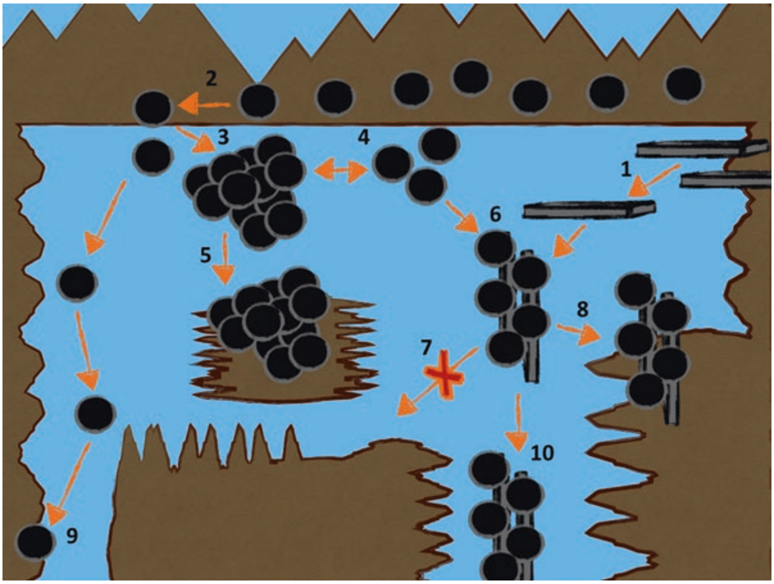

Fig. 5 The fate and transport processes in soil, based on a diagram from Cornelis et al. (2014). **1**: natural colloid formation; **2**: release of NMs from biosolids; **3**: homoaggregation; **4**: fragmentation; **5**: sedimentation; **6**: heteroaggregation; **7**: size exclusion; **8**: straining; **9**: deposition; **10**: convective transport

NM uptake is reduced by the presence of NOM which reduces toxicity (Xiao et al. 2020). Similar behaviour has been observed in other fish as well (Piccapietra et al. 2012; Li et al. 2015; Yue et al. 2017). The sub-lethal effects of NMs in animals may allow for bioaccumulation at higher trophic levels, though the toxicity of chronic ingestion of NM-contaminated food has not yet been established (Judy et al. 2011). In addition, the consumption of food containing NMs alters fish gastrointestinal microbiota, which may be critical in key metabolic processes (Merrifield et al. 2013). Studies on the effects of NMs on zebrafish (*Danio rerio*) have provided basic toxicological data on "no observed effect concentration" (NOEC), "lowest observed effect concentration (LOEC), "median effect concentration" (EC50), and "median lethal concentration" (LC50) for various NMs, and some effort has been placed on developing comprehensive databases of ecotoxicology data for NMs (Juganson et al. 2015). Additionally, zebrafish embryos experience developmental abnormalities from exposure to Au, SiO_2, CdSe/ZnS NMs (King-Heiden et al. 2009; Duan et al. 2013; Kim et al. 2013). Freshwater fish such as rainbow trout (*Oncorhynchus mykiss*) and largemouth bass (*Micropterus salmonoides*) have also been found to be sensitive to Ag and fullerene NM exposures (Oberdörster 2004; Yue et al. 2016).

Several aquatic invertebrates, including snails, crustaceans, and worms have been subjected to ecotoxicology studies based on NM exposures. Oliveira et al., showed that Ag NMs were slightly toxic to the snail *Biomphalaria glabrata* (2019). Castro et al., found that the association of graphene oxide NMs with NOM decreased the EC50 of the NMs for the crustaceans *Artemia salina* and *Daphnia magna*, suggesting increased toxicity; the same study found that nematodes decreased toxicity to algae, indicating a complex, species dependent interaction with NMs (2018). Lovern and Klaper showed that *Daphnia magna* were also sensitive to TiO_2 and fullerene NMs and found the LC50 to rise significantly when each type of NM was sonicated versus filtered (2006). The estuarine sediment-dwelling lugworm (*Arenicola marina*) also showed gastrointestinal damage with exposure to TiO_2 at a concentration of 1000 μg g^{-1} (Galloway et al. 2010). Gagné showed that freshwater mussels, *Elliption complanata*, suffer immunological damage from CdTe quantum dot NMs (2008). The sea urchin *Paracentrotus lividus* was also shown to have severe developmental defects following nanoplastic exposure (Della Torre et al. 2014). The broad range of affected invertebrates indicates the importance of understanding how NMs behave in the environment.

Microorganisms are also susceptible to the effects of NM exposure. Bacteria such as *Escherichia coli* and *Bacillus subtilis* are affected by fullerenes and quantum dot NMs, as well as antimicrobial NMs such as Ag (Mashino et al. 1999; Kloepfer et al. 2005). Other microorganisms such as algae demonstrate sorption which represents a risk for exposure to fish feeding on them (Leclerc and Wilkinson 2014; Li et al. 2015). Castro et al., found that graphene oxide NMs were also slightly toxic to *Pseudokirchneriella subcapitata* (2018). Several other studies have been performed on algae, which are listed, along with the major fish and invertebrate ecotoxicological data, in Table 6.

The mechanisms of NM localization into specific cellular organelles are not fully understood, though model systems exist for aquatic and terrestrial organisms such as fish, insects, amphibians, and plants (Nations et al. 2011; Priester et al. 2012; Millaku et al. 2013; Bacchetta et al. 2014; Zhao et al. 2015; Minghetti et al. 2017). A key effect of NM exposure is alteration of nitrogen, phosphorus, and carbon cycling (Colman et al. 2013; Schug et al. 2014). For microorganisms, NMs become embedded in extracellular matrices of biofilms and interfere with ion and nutrient uptake (Zhang et al. 2013; Park et al. 2003). NMs that enter cells interact with proteins and organelles such as lysosomes (Linse et al. 2007; Harush-Frenkel et al. 2008; Shemetov et al. 2012; Stern et al. 2012) and mitrochondria (Fröhlich 2013). Smaller NMs such as quantum dots under 9 nm or Au under 39 nm can associate with histones to alter gene expression (Panté and Kann 2002; Nabiev et al. 2007). Larger NMs between 70 and 100 nm can also be incorporated into nuclei during cell division (Lénárt et al. 2003; Chen and von Mikecz 2005).

Environmental risks of NMs and Mitigation Strategies

An NM life cycle can be broken down into production, usage, disposal, and discharges (Holden et al. 2016). Production of NMs may lead to effluent discharge to the air, water, or soil in addition to indirect environmental effects based on energy consumption and synthesis processes employed (Holden et al. 2016). Usage of NMs

Table 6 Selected organisms studied organisms from NMs

Organism	Nanomaterial	NOEC (ug mL^{-1})	EC/LC50 (ug mL^{-1})	GESAMP rating[a]	Reference
Danio rerio	MXene	50	257.5	Practically non-toxic	Nasrallah et al. (2018a)
	ZnO	<10	13.29	Slightly toxic	Al-Kandari et al. (2019)
	Reduced GO/ TiO_2	<400	748.6	Practically non-toxic	Al-Kandari et al. (2019)
	Magnetic mesoporous SiO_2	1600	>1600	Non-toxic	Nasrallah et al. (2018b)
	Multi-walled CNTs	40	>60	Slightly toxic	Asharani et al. (2008)
	GO	–	>100	Practically non-toxic	Castro et al. (2018)
Daphnia magna	GO	–	>0.58	Highly toxic	Castro et al. (2018)
	Sonicated fullerenes	0.2	7.9	Moderately toxic	Lovern and Klaper (2006)
	Sonicated TiO_2	–	>500	Practically non-toxic	Lovern and Klaper (2006)
	ZrO_2	–	>400	Practically non-toxic	Zaleska-Radziwill and Doskocz (2016)
Pseudokirchneriella subcapitata	GO	–	>66.6	Slightly toxic	Castro et al. (2018)
	ZnO	0.017	0.042–0.068	Very highly toxic	Aruoja et al. (2009) and Franklin et al. (2007)
	TiO2	0.984	5.83	Moderately toxic	Aruoja et al. (2009)
	CuO	0.421	0.71	Highly toxic	Aruoja et al. (2009)
Tetraselmis suecica	ZnO	0.1	3.91	Moderately toxic	Li et al. (2017)
Dunaliella tertiolecta	SiO_2	125	187.77	Practically non-toxic	Manzo et al. (2015)
	TiO_2	7.5	24.1	Slightly toxic	Manzo et al. (2015)
Karenia brevis	TiO_2	–	10.69	Slightly toxic	Li et al. (2015)
Skeletonema costatum	TiO_2	–	7.37	Moderately toxic	Li et al. (2015)

(continued)

Table 6 (continued)

Organism	Nanomaterial	NOEC (ug mL^{-1})	EC/LC50 (ug mL^{-1})	GESAMP rating[a]	Reference
Chlamydomonas reinhardtii	CuO	<100	150.45	Practically non-toxic	Melegari et al. (2013)

NOEC no observed effect concentration, *EC50* median effect concentration, *LC50* median lethal concentration, *GO* graphene oxide.
[a]From GESAMP (2002)

creates another set of pathways into the environment. For example, products such as sun cream that contain TiO_2 in a dispersed form are commonly used at the beach, which washes off directly into the water, while TiO_2 suspended in paint is intended to dry, immobilizing NMs away from environmental discharge (Nowack et al. 2012). Disposal of NMs or NM-enabled products primarily leads to transport through plumbing infrastructure, wastewater treatment plants, and landfills (Holden et al. 2016). Discharges of NMs can occur incidentally through spills or leaks, or through deployment such as in environmental remediation. Especially for remediation applications, understanding the environmental risk of NMs is key prior to regulatory approval (Lead et al. 2018).

To minimize some of the environmental impacts of large-scale NM production, research into green synthesis methods for NMs has been performed (Pati et al. 2014; Jankovic and Plata 2019). For the purposes of comparing the environmental impacts of NM production, a life cycle assessment framework can be employed to weigh the upstream and downstream impacts embodied in a complete product, such as cumulative energy demand of the reactants (embodied energy), carbon emissions, metal depletion, land use, and ecotoxicity (Pati et al. 2014). Additional by-products generated from NM manufacture such as inactive NMs, molecular coatings, and produced wastewater can be discharged directly into the environment in potentially high concentrations (Holden et al. 2016). Incorporation of NMs into products can also create wastes that are then discharged into landfills or wastewater treatment plants (Holden et al. 2016; Lead et al. 2018).

NM surface modifications can improve stability. For example, zero-valent NMs have a highly reactive metal core with an oxidation state of zero, and are highly predisposed to agglomeration. Surface modification provides a balance between increased protection from environmental transformations and reduced reactivity (Klaine et al. 2018). Whether an NM is intended for personal care, environmental use, or other use with potential for accidental spillage or release, these modifications may not last and potential transformations should still be assessed prior to large-scale usage (Lead et al. 2018). Since there can be undesired effects when using synthetic reactants; chemicals generally regarded as safe, such as citrate, polyvinylpyrrolidone, or NOM are competitive alternatives to surfactants and other coatings used to improve environmental stability, since they tend to have higher bioavailability and uptake, lower toxicity, and are more readily biodegradable

(Angel et al. 2013; Pati et al. 2014). While other aspects of a NM production method influence environmental footprint, such as mineral and energy requirements and carbon emissions, these impacts are indirect and are more of a focus for sustainability than ecotoxicology – though still relevant considerations.

Over time, NMs will be cycled through the environment. Prior to this, they may pose a nano-speciifc risk to environmental organisms. Subsequently, they increase total load in the environment, which becomes important for potentially toxic elements and compounds. Currently, studies are limited to a small number of species such as *Daphnia magna*, specific algae and bacteria, and certain fish. In addition, environmental exposure to humans presents a continuing risk (Jankovic and Plata 2019; Holden et al. 2016). The potentially widespread dispersion of NMs into the environment is an issue because they pose a novel risk compared to larger particulates and dissolved counterparts (Lead et al. 2018). The analytical challenges in assessing NM behaviour in real-world situations limits our understanding, although there has been a massive development in knowledge including on the influence of NM properties and transformations on fate, behaviour, and biological effects (Klaine et al. 2018; Nowack et al. 2012; Holden et al. 2016). One drawback to studies performed so far is the lack of long-term exposure data for NMs, which will likely be addressed by integrating newly developed techniques with standardized experimental designs specific to NMs (Lead et al. 2018). Understanding how NMs are weathered in various environments points to the need to assess not only pristine NMs, but NM-enabled products and environmentally transformed NMs as well (Nowack et al. 2012).

Conclusions

The development of environmentally benign processes that include thorough analysis of waste production and active product yield, which work in conjunction with modelling frameworks developed to predict environmental concentrations of NMs, has improved understanding of the environmental risks of NMs (Wang and Nowack 2018; Jankovic and Plata 2019). The focused study on environmental transformations has elucidated the physico-chemical properties of NMs which influence environmental risk, and has hastened the development of engineered surface modifications that limit NM environmental footprints as well as the likelihood of environmental transformation (Balasubramanian and Burghard 2005; Angel et al. 2013; Pati et al. 2014; Yin et al. 2015). Developments in analytical techniques help to validate these models and reduce the uncertainty in estimating NM exposures. In addition, ecotoxicological experiments are increasingly being performed under environmentally relevant operational conditions, providing a clearer idea of the compartmentalization of NMs into environmental and biological systems (Geitner et al. 2020). This effort also provides insight into the threshold concentrations that cause a range of divergent effects including apoptotic responses to enhanced growth. Unique processes in aquatic and terrestrial environments have also been shown to influence the hazard of NMs in their respective systems and highlight some of the challenges in ecotoxicology for each medium. Evidence of uptake mechanisms for NMs has been obtained, with dynamic effects on microorganisms, plants, and animals alike. A key finding has been the localization sites of NMs into specific cellular organelles based on size, composition, and charge, which enables further minimization of the risk of NMs through knowledge-based product engineering.

Chapter Summary

This chapter has provided an overview of the potential human health and environmental impact of NMs. Presently, the research, development, and production of new NMs is moving faster than the generation of data ascertaining to their hazard risk. The future resolution of this issue is imperative in order to identify NM properties that infer health and environmental risks. The plethora of issues and potential toxicological endpoints broadly covered in this chapter are discussed in further detail throughout the chapters of this book.

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