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Assessment of Biodurability of Nanomaterials and their Surface ligands

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No. 86

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Series on the Safety of Manufactured Nanomaterials

No. 86

ASSESSMENT OF BIODURABILITY OF MANUFACTURED NANOMATERIALS AND THEIR SURFACE LIGANTS

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The Environment, Health and Safety Division publishes free-of-charge documents in 11 different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials**. More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organisations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

The OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (the Joint Meeting) held a Special Session on the Potential Implications of Manufactured Nanomaterials for Human Health and Environmental Safety (June 2005). This was the first opportunity for OECD member countries, together with observers and invited experts, to begin to identify human health and environmental safety related aspects of manufactured nanomaterials. The scope of this session was intended to address the chemicals sector.

As a follow-up, the Joint Meeting decided to hold a Workshop on the Safety of Manufactured Nanomaterials in December 2005, in Washington, D.C. The main objective was to determine the "state of the art" for the safety assessment of manufactured nanomaterials with a particular focus on identifying future needs for risk assessment within a regulatory context.

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to avoid adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. It promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of manufactured nanomaterials.

This document was led by South Africa. The purpose of this document is to compile the relevant information on the biodurability of the pristine and functionalised nanomaterials in biological and environmental media *in vitro* and *in vivo*, as well as describing brief methods for measuring the stability and halftimes of nanomaterials.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, pesticides and Biotechnology of the OECD.

1. Executive Summary

Biodurability of nanomaterials (NMs) through dissolution and enzymatic biodegradation or chemical disintegration is an important property that needs to be investigated for their potential to cause harm to humans and the environment. NMs may therefore be differentiated based on their biodurability between those that are amenable and those that are resistant to dissolution, biodegradation and/or disintegration.

In vitro cellular and acellular as well as *in vivo* tests are available to assess the biodurability of NMs. With cellular and acellular *in vitro* tests, the dissolution of NMs is determined using static and flow-through protocols in the presence of different biological and environmental media with different pH values and chemical compositions. Examples of biological media include artificial pulmonary interstitial fluid (Gamble's) balanced electrolyte solution (neutral) and alveolar lysosomal (ALF) (acidic) as well as gastric (acidic) and intestinal (neutral) fluids. Examples of environmental media include synthetic freshwater, sea water, estuarine water, sediments, soils and digested sludge under conditions that mimic actual environmental conditions such as presence of microbes, pH, redox potential and temperature. *In vivo* tests include animal inhalation and intratracheal instillation studies.

The surfaces of NMs may be the principal determinants of their durability under conditions of dissolution and/or biodegradation in biological and environmental fluids. Surfaces of NMs are modified through the use of surfactants, capping agents or attached ligands. it is therefore important to study the (bio)-durability of the surface coatings and ligands of NMs in biological and environmental media as well as their impact on the (bio)-durability of these core NMs.

In this document, the *in vitro* and *in vivo* systems that are used to measure biodurability in biological and environmental systems, are presented for the pristine NMs of the OECD sponsorship programme. In addition, the effect of the physicochemical properties of these NMs and the properties of the biological and environmental media as well as surface coating and ligands on their dissolution and biodegradation are described. NMs with low dissolution rates have included TiO_2 and CeO_2 and due to their primary genotoxicity, it was proposed that their responses after long-term exposure need to be further evaluated due to their accumulation in systemic organs. NMs with high dissolution rates have included Zinc oxide (ZnO), copper oxide (CuO), and quantum dots (QD) that release zinc, copper, or cadmium ions, respectively and induce severe toxicity. Those that are not as yet been investigated for their biodurability either through dissolution or biodegradation included, dendrimers, nanoclays, and aluminium oxide nanoparticles (Al_2O_3NPs). Therefore, those with dissolution rate are not biodurable and hence may cause short term toxicity and health effects, opposed to those with slow dissolution rate which are biodurable and hence may cause both short and long term health effects and show high environmental persistency. Therefore, to increase the predictive potential of these tests, the existing identified *in vitro* and *in vivo* standard techniques should further

be validated in relation to their ability to predict pathogenic potential and environmental persistence of NMs.

Table of contents

1. Executive Summary 12

2. Abbreviations 16

3. Glossary of Terms 20

4. Background 23

5. Scope 25

6. Nanomaterial Structural Alterations in Biological and Environmental Media 26

7. Assessing Biopersistence and/or Biodurability 28

7.1. *In vivo* animal tests 28
7.2. *In vitro* cellular tests 29
7.3. *In vitro* acellular tests 30
7.3.1. Static protocol 30
7.3.2. Continuous Flow Through (CFT) protocol 30
7.4. Methods of detection 31
7.5. Simulated biological and environmental media 31

8. Biodurability of Pristine OECD Nanomaterials *in vitro* and *in vivo* in Biological Media and in Environmental Media 33

9. Studies in Biological Media 34

9.1. Carbon nanotubes 34
9.1.1. SWCNTs 34
9.1.2. MWCNTs 35
9.2. Fullerenes 36
9.3. Cerium oxide nanoparticles 36
9.4. Quantum dots nanoparticles 36
9.5. Silicon dioxide nanoparticles 37
9.6. Silver nanoparticles 38
9.7. Titanium dioxide nanoparticles 38
9.8. Zinc oxide nanoparticles 39
9.9. Iron oxide nanoparticles 40
9.10. Gold nanoparticles 41
9.11. Dendrimers 41
9.12. Nanoclays 41
9.13. Aluminium oxide nanoparticles 42

10. Studies in Environmental Media 43

10.1. Carbon nanotubes 43
10.1.1. SWCNTs 43

10.1.2. MWCNTs 44
10.2. Fullerenes 44
10.3. Cerium oxide nanoparticles 45
10.4. Quantum dots nanoparticles 45
10.5. Silicon dioxide nanoparticles 46
10.6. Silver nanoparticles 46
10.7. Titanium dioxide nanoparticles 47
10.8. Zinc oxide nanoparticles 47
10.9. Iron oxide nanoparticles 48
10.10. Gold nanoparticles 48
10.11. Dendrimers 48
10.12. Nanoclays 48
10.13. Aluminium oxide nanoparticles 48

11. Effects of the Physicochemical Properties of NMs and Properties of Biological and Environmental Media on Dissolution 50

12. The Stability and Biodegradation of the Surface Coatings and Ligands and their Influence on Biodurability of NMs *in vivo* and *in vitro* 53

12.1. Stability of surface coatings and ligands in biological and environmental media 53
12.2. Influence of surface coatings and ligands on (bio)-durability and subsequently (bio)-persistence of NMs *in vitro* and *in vivo* 54
12.2.1. Carbon nanotubes 54
12.2.2. Cerium Oxide nanoparticles 56
12.2.3. Quantum dots nanoparticles 56
12.2.4. Silver nanoparticles 57
12.2.5. Gold nanoparticles 57
12.2.6. Dendrimers 58

13. Toxicological Implications of Dissolution and Biodegradation 59

13.1. Biodurable fibres with toxicity and pathogenicity 59
13.2. Particles with low dissolution rate 60
13.3. Particles with high dissolution rate 60

14. Summary and Recommendations 62

15. Bibliography 64

Figures

Figure 1. An illustration of a possible cleavage plane present in a particle where dissolution is more likely to be initiated 51

Boxes

Box 4.1. Terms and terminology often utilized in (bio)-persistence studies 24

2. Abbreviations

AAS	Atomic absorption spectroscopy
AFM	Atomic force microscopy
Ag^{+}	Ionic silver
Ag^{0}	Elemental silver
AgCl	Silver chloride
$AgNO_3$	Silver nitrate
AGF	Artificial gastric fluid
AgNPs	Silver nanoparticles
Ag_2S	Silver sulfide
Al	Aluminium
ALF	Alveolar lysosomal fluids
Al_2O_3NPs	Aluminium oxide nanoparticles
$Al(OH)_3$	Aluminium hydroxide
AMs	Alveolar macrophages
AuNPs	Gold nanoparticles
BSA	Bovine serum albumin
Ca^{2+}	Calcium ion
C_{60}	Fullerenes
Cd	Cadmium
CeO_2	Cerium oxide
CeO_2NPs	Cerium oxide nanoparticles
CFT	Continuous flow through
CM-CeO_2-NPs	Carboxymethyl dextran CeO_2-NPs
CNTs	Carbon nanotubes
[-COOH]	Carboxylic acids
[-COO-R]	Esters
CO_2	Carbon dioxide
CuO	Copper oxide

DEAE-CeO_2-NPs	Diethylaminoethyl dextran CeO_2NPs
DEX-CeO_2NPs	Dextran CeO_2NPs
DMEM	Dulbecco's Modified Eagle's Medium
DOM	Dissolved organic matter
DTPA	Diethylenetriaminepentaacetic
F/s	Flow rate to surface area ratio
Fe	Iron
Fe_2O_3	Iron oxide
Fe_2O_3NPs	Iron oxide nanoparticles
Fe_2O_3NPs	α-Fe_2O_3 nanoparticles
FE-SEM	Field-emission scanning electron microscopy
FTIR	Fourier Transform Infra Red
Gamble's fluid	Artificial pulmonary interstitial fluid
HCl	Hydrochloric acid
$HClO_4$	Perchloric acid
H_2O_2	Hydrogen peroxide
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HRP	Horseradish peroxidase
HRTEM	High-resolution transmission electron microscopy
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
ICP-MS	Inductively coupled plasma–mass spectroscopy
ICR	Imprinting Control Region
I_2	Iodine
ISE	Ion selective electrodes
k_{dis}	Dissolution rate constant
K_{oc}	Partition coefficient between organic carbon and water
K_{ow}	Octanol-water partition coefficient
LC/MS	Liquid chromatography–mass spectrometry
LPC-SWNTs	Lysophophatidylcholine SWCNT
LSPR	Localized surface plasmon resonance
Mg	Magnesium
MgAl-LDH-CO_3	Magnesium aluminium layered double hydroxides carbonate
MgAl-LDH-Cl	Magnesium aluminium layered double hydroxides chloride
Na^+	Sodium cation

MM VF	Man-made vitreous fibres
MnP	Manganese peroxidase
MPA	3-mercaptopropionic acid
MPO	Myeloperoxidase
MWCNTs	Multi-walled carbon nanotubes
NaCl	Sodium chloride
$NaNO_3$	Sodium nitrate
$[-NH_2]$	Amine
NMs	Nanomaterials
NOM	Natural organic matter
O_2^-	Superoxide anion radicals
OH^-	Hydroxyl ions
$OH^\cdot$	Hydroxyl radical
$[-OCH_3]$	Methoxy
[-OH]	Hydroxyl
O-SWCTs	Oxidized (carboxylated) SWCNTs
PAMAM	Polyamidoamine
PBS	Phosphate buffered saline
PEG	Polyethylene-glycol
PVP	Polyvinylpyrrolidone
QDs	Quantum dots
RES	Reticuloendothelial system
RPMI	Roswell Park Memorial Institute medium
RNES	Rat nasal epithelial cells
ROS	Reactive oxygen species
S	Sulphur
Se	Selenium
SH-PEG	*Thiol* Polyethylene glycol
Si	Silicon
SiC	Silicon carbide
SiO_2NPs	Silicon dioxide nanoparticles
SP-ICP-MS	Single-particle-inductively coupled plasma mass spectroscopy
SPF	Specific specific-pathogen free
SWCNTs	Single-walled carbon nanotubes

$t_{1/2}$	Halftime
Te	Tellurium
TEM	Transmission electron microscopy
TGA	Thermogravimetric analysis
THP-1	Human monocytic leukaemia cells
TiO_2	Titanium dioxide
TiO_2NPs	Titanium dioxide nanoparticles
TOPO	Trioctylphosphine oxide
Tris	Tris(hydroxymethyl)aminomethane
UV	Ultraviolet
UV vis	Ultraviolet–visible spectroscopy
WWTP	Waste water treatment plant
XPS	X-ray photoelectron Spectroscopy
Zn^{2+}	Zinc ions
ZnONPs	Zinc oxide nanoparticles

3. Glossary of Terms

Abiotic degradation	A process in which a substance is converted to simpler products by physico-chemical mechanisms such as hydrolysis and photolysis.
Agglomeration	A reversible process in which dispersed molecules or particles assemble rather than remain as isolated single molecules or particles, where the dispersed particles are held together by weak physical interactions
Aggregation	An irreversible process in which dispersed molecules or particles assemble rather than remain as isolated single molecules or particles, where the dispersed particles are held together by strong physical interactions
Bioaccessibility	The fraction of a substance that dissolves under surrogate physiological conditions and is therefore potentially available for absorption into systemic circulation or interaction with local sites
Bioaccumulation	The process by which the concentration of a chemical in an organism (usually an aquatic organism) exceeds the concentration of the chemical in the surrounding (usually water) as a result of chemical uptake through all possible routes (e.g., dietary, dermal and the respiratory system)
Bioavailability	The proportion of a substance considered to be extracted in the gastrointestinal tract or lungs compared with the total substance that has been ingested or inhaled.
Biodurability	The tendency to resist chemical and biochemical alteration through dissolution and enzymatic biodegradation or chemical disintegration within biological media leading to structural alteration
Biodegradation	Also referred to as biotic degradation, biodegradation is the degradation of a substance resulting from interaction with the biological environment
Bioelution	As a measure of the bioaccessibility of a substance, bioelution refers to *in vitro* extraction methods that are used to assess the extent to which a substance is released into artificial biological fluids
Biopersistence	The ability of a material to persist in the body due to its biodurability and in spite of physiological clearance mechanisms
Biosolubility	The extent to which a solid material dissolves in fluids in living systems

Biotransformation	Alteration of a substance resulting from interaction with biological systems
Degradability	The ability of a substance to be broken down in the environment through microbial and/or physico-chemical processes
Degradation	A process in which a substance is broken down in the environment through microbial and/or physico-chemical processes
Degradation half-time	A time interval that corresponds to a concentration decrease by a factor of 2
Dispersion	Microscopic multi-phase system in which discontinuities of any state (solid, liquid or gas: discontinuous phase) are dispersed in a continuous phase of a different composition or state
Dissociation	The separation of the constituents of any aggregate of molecular entities
Dissolution	The release of ions or molecules from the surface of a solid and the subsequent distribution of the ions or molecules throughout the available liquid volume as a result of entropy
Dissolution rate	The rate at which ions or molecules are released from the surface of a solid into the surrounding liquid medium
Fate	The disposition of a material in various environmental compartments such as soil, water, air as a result of transport, partitioning, transformation and degradation
Hydrolysis	A reaction of a substance with water in which there is a net exchange of a functional group with OH from water
Ligands	Atoms or groups of atoms joined to the central atom
Nanomaterial	A material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale
Nanoparticle	A nano-object with all three external dimensions in the nanoscale
Octanol-water partition coefficient (K_{OW})	A measure of the transfer of a substance from the aquatic environment to an organism, for example, fish, and the potential bioaccumulation of the substance at equilibrium concentration
Organic carbon-water partition coefficient (K_{OC})	The ratio between the concentration of a substance in soil and the concentration of the substance in water normalized to the organic content
Persistence	The ability of a substance to remain unchanged in the environment for a long time
Photolysis	Also referred to as photodegradation, photolysis is the break down or alteration of a substance by light.
Simulated body fluid	A solution with an ion concentration close to that of a physiological fluid

Stability	The ability of (nano)particles to remain in the same chemical composition, in the same shape or size and without settling down from their dispersed state
Solubilisation	The process through which a substance becomes soluble

4. Background

1. With anticipated different industrial and biological applications based on their novel physicochemical properties, proactive research is imperative on nanomaterials (NMs) to ensure their suitability and safe use for humans and the environment. Although numerous studies have concentrated on assessing their toxicity, a challenging but as yet unaddressed issue of NMs is their biopersistence.

2. In human particle toxicology, biopersistence is the ability of a material to persist in the body due to its biodurability and in spite of physiological clearance mechanisms. Biodurability is defined as the tendency to resist chemical and biochemical alteration through dissolution and enzymatic biodegradation or chemical disintegration within biological media leading to structural alteration, which in turn may lead to bioaccumulation of NMs following their translocation and distribution. Materials (particles and fibres) may be differentiated based on their biodurability between those that are amenable and those that are resistant to dissolution, biodegradation and/or disintegration. The biopersistence of particles within tissues is believed to be an important property determining their potential to cause disease. For example, the biopersistence of some fibres with their resistance to dissolution and/or enzymatic biodegradation is considered to be one of the most important determinants of fibre pathogenicity (Donaldson et al., 2006).

3. The resistance of NMs to dissolution and/or biodegradation is proposed to be the determining factor on their accumulation and ensuing injury (Borm et al., 2006a). Subsequently, the importance of biodurability has recently been shown to be true for NMs such as pristine and functionalised carbon nanotubes (Liu et al., 2010, Mercer et al., 2010) and for quantum dots (Wiecinski et al., 2009). Furthermore, dissolution affects the bioavailability of dissolved species to local targets sites or the systemic circulation. The bioavailability or bioaccessibility can be measured using various bioelution methods that assess the extent to which a substance is released into artificial biological fluids.

4. Dissolution, degradation and biodegradation also determine the persistence of NMs in the environment. Persistence and degradability is defined as the potential for the substance or the appropriate constituents of a mixture to degrade in the environment, either through biodegradation or other processes, such as oxidation or hydrolysis (UN, 2011). Higher environmental persistence for a substance implies a higher chance of accumulation in the environment to be available to exert toxicity.

5. It is therefore imperative that, in addition to their size, surface area, surface activity, shape etc, the biodurability of NMs is determined, through the study of their dissolution rates and/or degradation halftimes ($t_{1/2}$) *in vivo* and *in vitro*, taking into consideration that the dissolution rates being more important for metal NMs and degradation $t_{1/2}$for carbonaceous NMs. In addition, it is important to study the (bio)-durability of the surface coatings and ligands of NMs in biological and environmental media as well as their impact on the (bio)-durability of these core NMs. Hence, a reliable prediction of (bio)-persistence and/or (bio)-durability of NMs could be useful in their

hazard classification and in their risk assessment. For clarification, the various related terms that are utilized in the study of (bio)-persistence of NMs are presented in the Glossary of terms and in Box below.

Box 4.1. Terms and terminology often utilized in (bio)-persistence studies

In environmental surroundings, ***degradation*** refers to a process in which a substance is broken through microbial and/or physicochemical processes where *degradation* is related to ***persistence***, the ability of a substance to remain unchanged in the environment for a long period of time; Degradation is often measured in terms of a ***degradation half-time***, the time interval corresponding to a reduction in concentration by a factor of 2; ***Biodegradation*** or ***biotic degradation***, refer to the degradation of a substance resulting from interaction with the organisms only where *degradation* is measured using various *in vitro degradability* tests.

In biological surroundings, ***persistence*** or ***biopersistence*** refers to the ability of a material to persist in the body due to its ***biodurability*** and resistance to physiological clearance. ***Biodurability*** is the tendency to resist chemical and biochemical alteration through **dissolution** and enzymatic biodegradation or chemical disintegration. ***Dissolution*** is defined as the release of ions or molecules from the surface of a solid and the subsequent distribution of the ions or molecules throughout the available liquid volume as a result of entropy ***Biopersistence*** is determined using ***in vivo*** methods while ***biodurability (dissolution and biodegradation)*** is measured using ***in vitro*** acellular and cellular tests.

In both environmental and biological surroundings ***biotransformation*** refers to alteration of a substance resulting from interaction with environmental and biological systems.

5. Scope

6. The scope of this document is to:

- Briefly describe the *in vivo* and *in vitro* cellular and acellular systems implemented for assessing the biodurability of NMs.
- Briefly describe methods for assessing abiotic and biotic degradation of NMs
- Briefly describe the biological and environmental media used for assessing the biodurability of NMs.
- Briefly describe factors that affect the biodurability/biopersistence as well as the fate and persistence of NMs.
- Compile relevant information on the *in vivo* and *in vitro* cellular and acellular biodurability of the pristine NMs included in the OECD Sponsorship Programme for the Testing of Manufactured NMs.
- Collect available information on the biodurability of covalently and non-covalently attached ligands as well as their effect on the *in vivo* and *in vitro* biodurability of the pristine NMs included in the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials.
- Discuss the toxicological implications of (bio)-durability within the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials for human- and eco-toxicology of these NMs.

7. The overall aim is therefore to compile the available information on the determination of the biodurability of different NMs included in the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials as indicator for their toxicity. This may further satisfy the need for rapid hazard assessment of NMs and thus augment the predictive power of these assay systems for their toxicity. This will in turn, contribute to the development of a biologically acceptable foundation for the safety of NMs which could then ultimately be used for their categorisation and risk assessment.

6. Nanomaterial Structural Alterations in Biological and Environmental Media

8. The ability of particles and fibres to reside long-term in tissues is generally referred to as biopersistence. The residence time of particles and fibres depends on the physiological and mechanical clearance rate (clearance) but also on their biodurability due to their resistance to mechanical and chemical disintegration and/or biological enzymatic biodegradation and also to their resistance to chemical dissolution in different biological and environmental media (Fubini et al., 1998, Hesterberg et al., 1996b). The chemical composition and crystalline nature are some of the properties that affect particle biopersistence. On their turn, differences in structure provide for differences in the ability of fibres to resist chemical attack in the lungs. Some types of fibres undergo dissolution and either break up into smaller fragments or dissolve entirely while other types, such as amphibole asbestos, resist dissolution. In the lung, these differences are reflected in a tendency for long fibres of non-biopersistent material to be cleared, as they dissolve or break up into shorter fibres that can be removed (Hesterberg et al., 1998a, Searl et al., 1999). On the other hand, the long biopersistent fibres such as asbestos and silicon carbide (SiC) will be harmful (Miller et al., 1999). Based on extensive earlier studies with these fibres, biopersistence is therefore now seen as the most important factor dictating their pathogenicity.

9. Mineral particles and fibres that are biopersistent are those that resist structural changes through leaching or solubilisation of structural elements within a biological environment such as the lung-lining fluid or the internal environment of macrophages. However, those that are less resistant to such biotransformation may be amenable to breakage to be short enough for successful clearance (Davis, 2007, Donaldson and Tran, 2004). Biotransformation of particles and fibres including NMs in biological and environmental media may take place through dissolution by release of ions and molecules (Behra et al., 2013, Rogers et al., 2012), through transverse breakage (Bellmann et al., 1987, Searl, 1994), and/or through biodegradation by enzymatic reactions (Nowack et al., 2012, Zhang et al., 2014, Zhao et al., 2011).

10. Dissolution of larger particles and fibres as well as NMs is defined as a dynamic process in which constituent molecules or ions of the dissolving solid migrate from the surface to the bulk solution through a diffusion layer (Borm et al., 2006a). The rate of dissolution depends on size and surface properties of the particles and fibres and also on the composition of the biological environment within which they reside. For example, Zinc oxide nanoparticles (ZnONPs) classify as “soluble” at low pH of the gastric environment and “biopersistent” at neutral pH of the lung environment." (Avramescu et al. 2017). Biodegradation of NMs on the other hand, may take place enzymatically in biological and environmental surroundings (Kotchey et al., 2011, Zhang et al., 2014). These interactions will equally apply to the core as well as to the surface coatings.

11. The physicochemical changes, introduced to particles and fibres and also to NMs upon their exposure to biological and environmental surroundings will have significant effects on their subsequent biokinetics and metabolic or environmental fate (Abraham et

al., 2013, Johnson, 1994, Klaine et al., 2008, Kreyling and Scheuch, 2000) which in turn, will determine their internal dose and thus determine type and extent of long-term observed responses (Harrison et al., 1999)

12. Subsequently, particles and fibres may be differentiated by their biodurability with their low dissolution rate and also low degradability compared to those with low biodurability with high dissolution rate and high degradability causing to former to accumulate and produce tissue injury. For ecotoxicology, similar considerations on biodurability of NMs were raised, where once again, it was accepted that the longer the residence-time in the environment, the greater the possibility will be for their accumulation and subsequent higher bioavailability and toxicity (Klaine et al., 2008, Powers et al., 2006, Tiede et al., 2009). The importance of the assessment of their possible interactions, transformations and routes of NMs loss and breakdown in the environment was therefore acknowledged (Abraham et al., 2013).

7. Assessing Biopersistence and/or Biodurability

13. Over the last three decades, *in vivo* animal experiments, *in vitro* cellular and *in vitro* acellular systems have been used to estimate the biopersistence and/or the biodurability of larger particles and fibres. Earlier *in vitro* biodurability tests were originally aimed to analyze the dissolution rate of asbestos as well as man-made vitreous fibres (MMVF) in synthetic lung-fluids (Christensen et al., 1994, Sebastian et al., 2002). More recently, the importance of such biodurability tests have also been recognized for NMs to assess the potential of their residence time in specific compartments of the respiratory, gastro-intestinal or intracellular location (Cho et al., 2011, Liu et al., 2010, Osmond-McLeod et al., 2011, Wiecinski et al., 2009). These have indicated that dissolution protocols described for larger particles and fibres could also be adapted to the study of the dissolution of NMs, provided their physicochemical properties and other variables are appropriately described, to better understanding their biological response. However, it has to be emphasized that none of the dissolution protocols for larger particles and fibres has been so far appropriately validated and they are not generally used in the regulatory area.

14. Traditionally, biopersistence has been assessed from *in vivo* animal experiments that address both durability and clearance processes of mineral particles and fibres. *In vitro* cellular assays although may not totally mimic *in vivo* conditions, could yet offer a less expensive, more rapid and more controlled alternative to classic long-term toxicity testing in animals (Searl and Buchanan, 2000). *In vitro* acellular dissolution studies are conducted with the understanding that these tests determine only the durability of particles and fibres in a cell-free system. However, they could also provide useful information when performed as companion experiments with *in vivo* studies if conditions of exposure and test agent can be made similar (Potter and Mattson, 1991, Thelohan and De Meringo, 1994). Presently, accurate extrapolation of *in vitro* information to *in vivo* situations is limited by lack of standards of the types of biological fluid, exposure routes for testing, as well as lack of guidance or guidelines for adequate *in vitro* testing or (quantitative) criteria to discriminate between low and high dissolution rate nanomaterials. Additionally, there is also need to design ways of factoring into *in vitro* tests the possibility of correlating dissolution rates to all the variable *in vivo* endpoints such as acute *versus* chronic toxicity and local *versus* systemic toxicity.

7.1. *In vivo* animal tests

15. The measurement of *in vivo* biopersistence in the lung is considered one of the most important parameters for estimating the potential hazard of a type of fibre. For this assessment, two alternatives *in vivo* methods are identified namely, inhalation and intratracheal instillation. The former is however preferred over the latter because it mimics more closely human exposure. For biopersistence studies, a short-term 1-wk (6 h/day for 5 days) inhalation exposure followed by 26-wk follow-up of lung burden of fibres, a short term intratracheal study or a sub-chronic 90 days inhalation have been

proposed. In these short term studies, rats are exposed to fibres (well characterised and respirable size) via intratracheal instillation once a day for 4 consecutive days. Following the instillation period, subgroups of the animals are sacrificed and certain time periods and the lung burden is determined (Bernstein and Riego Sintes, 1999). Upon confirmation of the biopersistence of a fibre with these short-term studies, the need for further testing of the pathogenic potential of the fibre with long-term chronic inhalation studies have been recommended (Bellmann and Muhle, 1994, Bellmann et al., 1994, Bernstein et al., 2005, Driscoll et al., 2000, NIOSH, 2010, see protocol in Bernstein and Riego Sintes, 1999).

16. Such short- or long-term inhalation biopersistence studies (Bernstein et al., 2005, Hesterberg and Hart, 2000, Hesterberg et al., 1998b, Hesterberg et al., 1993, Hesterberg et al., 1996a, Kamstrup et al., 1998, Mast et al., 1995, McConnell et al., 1994) and intratracheal instillation (Oberdörster, 2000, Oyabu et al., 2006) experiments were conducted with pathogenic asbestos types, crocidolite and amosite fibres as well as with non-pathogenic MMVF (stone wool fibres with approximate lengths of 1 μm (Kamstrup et al., 1998). Exposure *via* intratracheal instillation was also used to assess the biopersistence of potassium o*ctatitanate* whiskers (with sizes ranging between 0.35 and 4.4 μm in length) in rats (Oyabu et al., 2006). Whichever method was used, the determination of biopersistence and/or biodurability involved the assessment of changes in the structure, size distribution, decrease in mass, number and diameter, dissolution of the metal constituents and morphology as well as the calculation of a retention halftime ($t_{1/2}$) (Bellmann et al., 1994, Creutzenberg et al., 1997, Eastes et al., 2000b, Hesterberg et al., 1998a, Holmes and Morgan, 1967, Langer et al., 1972, Morgan et al., 1982, Muhle et al., 1994, Searl et al., 1999).

17. Similar animal inhalation and intratracheal instillation studies were also used to assess the biopersistence and/or biodurability of NMs *in vivo* by assessig their levels in organs after long post exposure periods (Lee et al., 2013, Oyabu et al., 2014, Oyabu et al., 2007). Radio-labelled, fluorescently or magnetically tagged monitoring was also implemented to assess NM biopersistence (Kreyling et al., 1999, Kreyling et al., 2002, Möller, 2001).

7.2. *In vitro* cellular tests

18. Inhaled larger particles and fibres are shown to be phagocytosed by many cell types, but the majority is shown to be found within alveolar macrophages (AMs) with a small fraction within the epithelial cells lining the respiratory tract and the fibroblasts and macrophages within the interstitium as well as in the mesothelial cells. These cells have therefore been used to assess the biodurability of particles and fibres. For example, for MMVF, crocidolite and chrysotile asbestos fibres it was investigated the efficacy of the intracellular phagosomal conditions within these cells to change the chemical structure and/or change in their diameter or the release, congruently or incongruently (Casey, 2008, Casey et al., 1993), of their elemental constituents including silicone (Si), iron (Fe), magnesium (Mg), and aluminium (Al) (Cole et al., 1991, Guldberg et al., 1998, Jaurand et al., 1977, Jaurand et al., 1984, Jaurand, 1994, Luoto et al., 1994, Luoto et al., 1995, Nguea et al., 2008).

19. Differences in the biodurability of the tested particles and fibres could be observed among these various cell types. For example, a more rapid dissolution of MMVF fibres with the AM cultures could be seen compared to rat nasal epithelial cells (RNES) (Johnson, 1994). When investigated, differences in the pH within phagosomes of

these cells could be seen, where the interior of the phagosome in AM was found to be acidic, with a pH 4 to 6 (Nyberg et al., 1989), while it was neutral in RNES phagosomes (Johnson, 1994). Neutral pH could also be seen within the mesothelial phagosomes (Jaurand et al., 1984) and also in the cytoplasm of epithelial cells (Van Erp et al., 1991). The main concern with cellular systems though is that the dissolution is static within small volumes, in contrast to the very high dissolution potential available in the lung. Another major concern with the *in vitro* cellular systems compared to *in vivo* systems is that in the latter, in addition to dissolution, the normal physiological processes present in the lung also affect the biopersistence of particles and fibres.

7.3. *In vitro* acellular tests

20. The biodurability of particles and fibres may be assessed by use of a milieu that mimics extracellular and intracellular tissue fluids as well as environmental media. In such environments, particles and fibres may either be disintegrated due to dissolution or weakened by partial leaching of components so that they break mechanically.

21. Using these physiological simulant solutions, a number of methods have been applied to follow the dissolution of particles and fibres and those developed through the years have been summarized in a review article (De Meringo et al., 1994). These have included static or continuous flow through (CFT) systems (Christensen et al., 1994, Eastes et al., 2000a, Hume and Rimstidt, 1992, Jurinski and Rimstidt, 2001, Maxim et al., 2006, Potter, 2000, Werner et al., 1995).

7.3.1. Static protocol

22. In the static protocol, the dissolution is assessed by simply exposing known masses of particles/fibres to water or other experimental fluids in a beaker. Dissolution rates are then assessed from changes in sample mass, particles/fibres diameter or by monitoring the chemical changes in the experimental fluid (Touray and Baillif, 1994). It has been shown that the main limitation of the static assays is that with a restricted volume of fluid, it is possible for the supernatant to become supersaturated with one of the solute species, inhibiting further dissolution (Campopiano et al. 2014).

7.3.2. Continuous Flow Through (CFT) protocol

23. To overcome the potential problems of supersaturation encountered with the static protocol, it is recommended to use a CFT protocol (Eastes and Hadley, 1994). In this *in vitro* dissolution a peristaltic pump is used to impulse the passage of the simulated biological or environmental fluids from a large reservoir at a temperature of ± 37 °C through test cells containing weighed samples of test material over an extended period. The pH of test fluids (neutral or acidic) is monitored before and after interaction with each sample and controlled by bubbling carbon dioxide through the fluid reservoir. The dissolution rate of each sample is then assessed from the concentrations of released ions in test fluid that has passed through each cell or by measuring total mass loss or the decrease in diameter of the test material (Bauer et al., 1994, Christensen et al., 1994, Mattson, 1994, Potter and Mattson, 1991, Scholze and Conradt, 1987, Searl and Buchanan, 2000, Sebastien et al., 1994, Thelohan and De Meringo, 1994). Using the CFT system, with the measurement of decrease in diameters of individual fibres, the dissolution rate of fibres (k_{dis}), in units of ng/cm^2/hr, could be determined (Christensen et al., 1994, De Meringo et al., 1994, Koenig et al., 1993, Potter, 2000).

24. It is also recommended that during these experiments, the flow rate of the simulated fluid is adjusted as it is shown that dissolution rates increase with increasing ratio of flow rate to surface area (F/a ratio) of the samples (Searl and Buchanan, 2000). Moreover, the total duration of individual experiments should also be long enough to determine whether there is a substantial change in dissolution mechanism through time, this may range between 90 days to much shorter periods of 4 weeks (De Meringo et al., 1994). Finally, the number of time points where the eluates are analysed should be sufficient enough to enable the calculation of dissolution rates. Using such *in vitro* assays, the dissolution rates of various synthetic silicate minerals were determined using simulated lung and lysosomal fluids (Hume and Rimstidt, 1992, Jurinski and Rimstidt, 2001, Werner et al., 1995). For example, using this system with a flow rate of 120 mL/day an F/a ratio of 2.6 x 10^{-6} was calculated (Brázda et al. 2008). However, it is important that the flow rate need to be optimized for each specific NP.

7.4. Methods of detection

25. Following the implementation of *in vitro* and *in vivo* methodologies, the dissolution and dissolution rates of particles and fibres are assessed through the measurement of the levels of the elements (Si, Mg, Al, Fe, etc.) released from the particles and fibres into the eluate using a number of techniques (Elmer, 1984). These have included atomic absorption spectroscopy (AAS) or the most widely used method(s): inductively coupled plasma atomic emission spectroscopy (ICP-AES) or inductively coupled plasma–mass spectroscopy (ICP-MS). Techniques have also been implemented to separate the released components using filtration, ultracentrifugation, dialysis or centrifugal ultrafiltration (Ma et al., 2011). Such separation techniques may not be required when assessing dissolution *in situ* where direct methodologies may be implemented. These include atomic force microscopy (AFM), ion selective electrodes (ISE) (Benn and Westerhoff, 2008), localized surface plasmon resonance (LSPR), or ultraviolet-visible (UV-VIS) absorbance spectroscopic methods (Zook et al., 2011), or single-particle-inductively coupled plasma mass spectroscopy (SP-ICP-MS), depending on the size of the nanomaterial. Particles smaller than 10 nm cannot be detected using the latter methodology (Mitrano et al., 2012).

26. The enzymatic biodegradation of carbonaceous NMs on the other hand can be assessed using transmission electron microscopy (TEM) and field-emission scanning electron microscopy (FE-SEM) (Elgrabli et al., 2008, Liu et al., 2010, Russier et al., 2011).

7.5. Simulated biological and environmental media

27. For dissolution and biodurability studies, simulated biological media are used to mimic the behaviour of the particles and fibres when exposed to these types of fluids or media. Examples include artificial pulmonary interstitial fluid (Gamble's) balanced electrolyte solution (neutral) and alveolar lysosomal fluids (ALF) (acidic) as well as gastric (acidic) and intestinal fluids (neutral) which may play a significant role in the dissolution as well as in the biodegradation of NMs (Bernstein et al., 2005, Hu et al., 2013, Marques et al., 2011, Mattson, 1994, Nyberg et al., 1989, Stefaniak et al., 2005, Wiecinski et al., 2009).

28. The pH of the alveolar fluid was determined to be neutral (Kanapilly, 1977). It is therefore believed that by measuring the *in vitro* dissolution rate at neutral pH (7.2-7.8) in

Gamble's solution (complex salt solution designed to mimic the salt balance of extracellular fluid) will represent the dissolution in the extra-cellular lung fluid (Mattson, 1994, Scholze and Conradt, 1987, Zoitos et al., 1997). On the other hand, by measuring the *in vitro* dissolution rate at acidic pH (4.5-5), will represent the pH environment within the phagolysosomes of the pulmonary alveolar macrophages (Christensen et al., 1994, Kanapilly, 1977, Kreyling et al., 1991, Nyberg et al., 1989, Nyberg et al., 1992, Touray and Baillif, 1994).

29. Environmental degradability tests for organic chemicals are usually conducted to assess the effects of biotic and abiotic processes under conditions that mimic actual environmental conditions such as presence of microbes, pH, redox potential and temperature (OECD, 2005). Biotic degradability processes are studied through various aerobic and anaerobic conditions requiring the use of simulated environmental media such as synthetic freshwater, sea water, estuarine water, sediments, soils and digested sludge (OECD, 1992a; 1992b; 2002a; 2002b; 2005; 2006; Smith et al 2002; Weber et al. 1989) and fullerene (C_{60}) nanoparticles (Hartmann et al, 2011). The applicability of these tests using different environmental media was already confirmed in the assessment of the biodegradability of organic NMs such as carbon nanotubes (Kummerer et al., 2011). The assessment of the biodegradability could also be achieved through ^{14}C-labeling of these NMs such as fullerenes and multi-walled carbon nanotubes (MWCNTs) (Avanasi et al. 2014; Zhang et al., 2013).

30. Environmental degradability tests for organic chemicals with abiotic processes are usually conducted to assess the effects of processes, in addition to dissolution, hydrolysis (OECD, 1981), oxidation (OECD, 1992), and photodegradation (photolysis) (OECD 2002c; OECD, 2007). The applicability of some of the dissolution tests to inorganic NMs in different environmental media was confirmed for silver nanoparticles (AgNPs) (Chinnapongse et al., 2011), zinc oxide nanoparticles (ZnONPs) (Franklin et al., 2007), and quantum dots (QDs) (Navarro et al 2011). Similarly, an OECD expert meeting on applicability of ecotoxicology and environmental fate concluded that "the majority of the OECD Test Guidelines (TG) for chemicals were generally applicable for the testing of NMs", with the exception of TG 105 (for water solubility) and TG 106 (for adsorption-desorption) (Kühnel and Nickel, 2014). With respect to biodegradation, it was noted at this meeting that common biodegradation methods are not feasible for inorganic NMs. But also for those with organic coating as the concentration of organic material may be too low to detect and quantify the turnover. In consequence, determination of abiotic degradation processes such as hydrolysis, oxidation, sulfidization and differences in redox conditions become particularly important for fate assessment of NM in the environment (OECD, 2014). Furthermore, the expert group of the same meeting highlighted special considerations when conducting these tests on NMs, especially regarding sample preparation, dispersion, analysis, dosimetry and characterisation.

8. Biodurability of Pristine OECD Nanomaterials *in vitro* and *in vivo* in Biological Media and in Environmental Media

31. The release of pristine nanoparticles into biological surroundings may introduce numerous changes to the particles within these surroundings due to their dissolution and/or biodegradation. Using the *in vivo* and *in vitro* cellular and acellular systems as well as the biological media described, the biodurability of NMs was investigated.

32. Similarly, once released into the environment, NMs may be transformed by physical and biological processes altering their toxicity and fate through photochemical transformation, oxidation and reduction, dissolution, precipitation, adsorption/desorption and corona formation, combustion, biotransformation, and abrasion, among other biogeochemically driven processes (Nowack et al., 2012). Furthermore, as most waste materials undergo various treatment processes before being released to the environment, the behaviour of NMs as they undergo waste treatment processes will determine their fate and transport in the environment. Consequently, the understanding of environmental transformations and fate of NMs, including biodurability and persistence, will enable safe use of NMs as well as in the environmental pollution control and remediation (Metz et al., 2009). Using these environmental conditions, the biodurability of NMs was also investigated.

33. However, studies of environmental transformation, degradation and persistence of NMs under environmentally relevant conditions have been hampered by lack of analytical techniques for measuring NMs in natural systems, especially due to very low detection limits required, challenges in distinguishing manufactured NMs from background NMs, and also due to interfering environmental matrices (Bourgeault et al., 2015, Fabrega et al., 2011, Von der Kammer et al., 2012). Nevertheless, a number of studies have been conducted on behaviour and fate of nanoparticles during waste treatment and management processes as well as in the environment (Kaegi et al. 2011, Li et al. 2010b, Ma et al. 2013, Chowdhury et al. 2012, Judy et al. 2011, Gómez-Rivera et al. 2012, Zhang et al. 2013).

34. In the following sections the *in vitro* and *in vivo* systems, used to measure biodurability in biological and environmental systems, are presented for the pristine NMs of the OECD sponsorship programme. In addition, the effect of the physicochemical properties of these NMs and the properties of the biological and environmental media on their dissolution and biodegradation are described.

9. Studies in Biological Media

9.1. Carbon nanotubes

35. Carbon nanotubes (CNTs), including single-walled carbon nanotubes (SWCNTs) and MWCNTs, can be found in a variety of shapes and sizes, with different lengths, diameters etc. Since these NMs are fibre-like, they are believed to follow the fibre paradigm (Donaldson et al., 2006). Carbon nanotubes belong to the family of material known as graphenic carbon, which is known to be quite stable in environmental and biological media (Liu et al., 2010). Considering this and the high persistence and hydrophobicity of CNTs (Allen et al., 2009), they are generally associated with bioaccumulative substances (Helland et al., 2008). Methodologies described in the literature to assess the dissolution of larger particles and fibres may not be readily applicable to CNTs, since they are not able to release metal ions (as with inorganic nanoparticles), which can be detected. However, these NMs are shown to be oxidized, enzymatically biodegraded in biological media depending on their functional groups (Liu et al., 2010) or remain unchanged in the environment such as fullerenes and MWCNTs (Avanasi et al. 2014; Kummerer et al., 2011; Zhang et al., 2013).

36. Earlier studies have shown that some organic fibres appear to be amenable to degradation through enzymatic mechanisms. For example, studies with *p*-aramid fibrils recovered from the lungs of exposed rats suggested their biodegradability (Bellmann et al., 2000, Kelly et al., 1993, Warheit et al., 2001, Warheit et al., 2000, Warheit et al., 1992) confirming those observed with *in vitro* acellular as well as *in vitro* cellular systems involving alveolar macrophages and macrophage lung epithelial cell co-cultures (Warheit et al., 2001).

9.1.1. SWCNTs

37. *In vivo* biopersistence studies were also conducted with SWCNTs where pristine, non-functionalised SWCNTs (10 – 30 nm bundles with lenghts of 2 -3 μM), were shown to be present in male CD-ICR mice 3 months after intravenous exposure (Yang et al., 2008).

38. The *in vitro* cellular degradation studies of SWCNTs have shown that the fibres are engulfed by phagocytic cells and in response, leads to the generation of reactive oxygen species (ROS). The latter may then be able to break C-C and C-H bonds by activating innate peroxidases such as myeloperoxidase and eosinophil peroxidase. It was hypothesised that the same principle may apply in the degradation of SWCNTs initiated by enzymes in the presence of hydrogen peroxide (H_2O_2) (Russier et al., 2011; Kotchey et al., 2013). However, the degradation of pristine SWCNTs could not be detected when exposed to a degradation enzyme horseradish peroxidase (HRP) in an oxidizing medium, such as H_2O_2 (Allen et al., 2009). On the other hand, their incubation with ferric iron species such as $FeCl_3$ and hemin could enhance the degradation (Andón et al., 2013).

39. In a similar process observed with organic fibres, it has been shown that SWCNTs may also undergo oxidative degradation due to enzymatic activity. This degradation may produce defects on the CNTs hence reducing their length from approximately 500 μm to 200 μm over an 8 week period (Allen et al., 2008). However, it was also shown that enzymatic biotransformation of SWCNTs ranging from 0.5 to 30 μm in length could result in $t_{1/2}$ of 80 years, by incubating them with HRP and H_2O_2 (Flores-Cervantes et al., 2014). This was in contrast to SWCNTs (0.8–1.2 nm diameter and 0.1–1 μm length) which were rapidly degraded under these conditions (Russier et al., 2011). The amenability to degradation was explained by the presence of concentric layers in SWCNTs (Kotchey et al., 2012, Zhao et al., 2011).

40. On the other hand, using *in vitro* acellular systems containing no enzymes, the biodurability of some SWCNTs was also assessed in neutral Gamble's solution. In a study using commercially available SWCNTs (3.6 μm in length and a 5 nm width), no significant loss of mass by week 24 could be observed (Osmond-McLeod et al., 2011). Moreover, SWCNTs (with a diameter of 1 - 2 nm, 1.9 μm in length) were unaffected in an oxidizing simulated biological fluid for up to 90 days (Liu et al., 2010).

9.1.2. MWCNTs

41. *In vivo* animal biopersistence studies in tissues of animals were conducted using MWCNTs after a long exposure period. For example, intratracheal instillation of MWCNTs (20 – 50 nm in diameter and 0.5 μm -2 μm in length), have led to the observation that they appear to be biopersistent as they have deposited and persisted within the lung of male Sprague-Dawley rats for up to 6 months (Elgrabli et al., 2008). The oral administration of MWCNTs to mice showed that the fibres were partially degraded in the stomach, and the remaining debris translocated to the intestines and finally excreted with the faeces. These MWCNTs were however shown to cause severe damage such as necrosis in intestinal tissue (Masyutin et al., 2015).

42. *In vitro* cellular systems, using a human monocyte cell line Human monocytic leukaemia cells (THP-1), have shown that the biological pathway for MWCNT (20 – 50 nm in diameter, with lengths varying between 0.5 to 2 μm) degradation in macrophages involved superoxide anion radicals ($O_2^{\cdot}$) production and hydroxyl radical hydroxyl ($OH^{\cdot}$) attack on the graphitic nanostructure which led to the scarring of these CNTs. Scarring was observed as holes in the carbon walls, which increased over time, followed by a mean thickness reduction of the wall (Elgrabli et al., 2015).

43. *In vitro* acellular systems were also used to assess the biodurability of MWCNTs. For example, it was shown that MWCNTs (long tubes: 40 – 50 nm in diameter and 13 μm in length, tangled: 15 nm in diameter with 5 -20 μm in lengths) were biodurable in Gamble's solution with no significant loss of mass by week 24, with the exception of a long-shaped MWCNTs (8 – 10 nm in diameter with 200 – 300 μm) which was recovered at only ~70% of its original weight from week 3 onward (Osmond-McLeod et al., 2011). On the other hand, at lower pH values, an incomplete degradation of pristine MWCNTs could be observed when fibres were exposed for a period of 24 hours to an acidic media (0.1 M Hydrochloric acid (HCl)) and gastric fluid extracted from murine stomach (Masyutin et al., 2015).

44. In the presence of HRP, the degradation of two different MWCNTs (0.5 – 2 μm in length with diameter of 20 – 30 nm, and 1.5 μm in length and 9.5 nm in diameter respectively), could also be shown over a longer time period of several months (Russier et al., 2011).

9.2. Fullerenes

45. Fullerenes, also known as buckyballs or C60 nanoparticles, are carbon-based NMs similar to CNTs, and they come in different shapes and sizes. Fullerenes with diameters ranging from 60 – 270 nm) were shown to be internalized by human monocytes at several sites within the cell including secondary lysosomes, along the outer cell membrane, adjacent to the nuclear membrane and most notably, inside the cell nucleus (Porter et al., 2006).

46. In an *in vitro* cellular internalization study a THP-1 macrophage cell line was treated with fullerene nanowhiskers (6 μm in length with an average diameter of 660 nm). Almost 70% of the particles were internalized after 48 hours and subsequently were decomposed within 28 days into C60 with no further degradation (Nudejima et al., 2010).

9.3. Cerium oxide nanoparticles

47. Cerium oxide nanoparticles (CeO_2NPs) have been studied both *in vitro* and *in vivo*. *In vivo* biopersistence studies, using male Wistar rats, were conducted and shown that following inhalation the CeO_2NPs (nominally <5000 nm, 40 nm and 5 – 10 nm in size) were found to be biopersistent and remain in the lungs for long periods (Geraets et al., 2012) and using male Sprague Dawley rats after oral administration showed that CeO_2NPs (30 nm) were also persisted for up to 7 and 14 days (Park et al., 2009). After intravenous administration CeO_2NPs (7.6 nm of size) it was shown that they were not eliminated to any significant extent and were mostly present as intracellular CeO_2NPs as agglomerates in mononuclear phagocytes as well as in organs including the liver, spleen, and bone marrow with granulomatous changes in the liver (Tseng et al. 2012). It was therefore proposed that the observed long-term effects of CeO_2NPs entering cells warrant further investigation, considering the irreversibility of its accumulation (Yokel et al., 2012).

48. In an *in vitro* cellular study, it was shown the CeO_2NPs (8 nm) could be internalised into macrophage and epithelial cells and the ceria nanoparticles was found to be not amenable to dissolution (Xia et al., 2008).

9.4. Quantum dots nanoparticles

49. QDs are engineered nanoparticles with semiconductor properties which mostly consist of cadmium (Cd) with the addition of other elements such as selenium (Se), tellurium (Te) or sulphur (S). Although the coating of CdSe quantum dots is shown to render them nontoxic, their long-term stability and biodurability have not been thoroughly evaluated and therefore, the need to further explore the long-term stability of the coatings used, both *in vivo* and also when exposed to environmental conditions, was highlighted (Bouldin et al., 2008).

50. In an *in vivo* study on the degradation of CdTe/ZnS quantum dots (19.3 ± 2.2 nm) in male Imprinting Control Region (ICR) mice, it was shown that these particles could indeed undergo degradation. The released Cd^{2+}, accumulated in the liver, kidneys and spleen, was still present after 28 days (Liu et al., 2013a). Similar observations were made in another *in vivo* study, with ^{65}Zn-labelled CdSe/CdS/ZnS QDs (with sizes ranging between 5.5 and 7 nm), where it could be shown that they were taken up by the liver and spleen after intravenous injections in wild type FVB/N mice. Also, a substantial

degradation and loss of fluorescence from the QDs could also be observed after 4 weeks in liver and spleen (Bargheer et al., 2015).

51. In an *in vitro* cellular study, where mouse embryonic stem cell line R1 and fibroblast cells were labelled with a Qtracker® 655 Cell Labelling Kit consisting of quantum dots, loss of fluorescence could be observed after 24 hours indicating their degradation (Pi et al., 2010). In an *in vitro* acellular dialysis study using 19.3 nm CdTe/ZnS QDs exposed to a neutral fluid (pH 7), the luminescence of the QDs was seen to remain stable for the first 20 days but it gradually decreased over the following 20 days, and after 80 days the luminescence would drop to 43.8% indicating their degradation (Liu et al., 2013a).

9.5. Silicon dioxide nanoparticles

52. *In vivo* biodistribution of 50, 100 and 200 nm-sized silicon dioxide nanoparticles (SiO_2NPs) studies after intravenous injection of BALB/c mice was shown to be size-dependent, where most of the nanoparticles accumulated in liver, spleen and kidney (Cho et al., 2009). Similarly, intravenously adminstered 70 nm SiO_2NPs were observed to cross into placenta, foetal liver and foetal brain in BALB/c mice as opposed to 300 nm and 1,000 nm particles which were not biodistributed into these organs (Yamashita et al., 2011). Following a single intravenous dose of 23 nm SiO_2NPs to male BALB/c mice, the SiO_2NPs were rapidly distributed to tissues of the reticuloendothelial system (RES), including the spleen, liver, kidney, lung, and cervical lymph nodes, and persisted in the tissues throughout the 8-week study period. The SiO_2NPs were eliminated through the renal and biliary routes, with the 69.4% and 30.6% of the total amount of SiO_2NPs excreted over the first 24 h through urine and feces, respectively (Malfatti et al., 2012).

53. The *in vitro* acellular dissolution of SiO_2NPs in water was shown to involve chemical hydrolysis and condensation reactions, respectively, catalyzed by hydroxyl ions (OH^-). This process was shown to be affected by a number of factors that include, but are not limited to, crystallinity, porosity, particle size and degree of hydroxylation (Napierska et al., 2012).

54. There have been other *in vitro* acellular studies on the dissolution of SiO_2NPs in other media, where the dissolution was reported to be dependent on their size and surface area. For example, the maximum solubilities of 7.28 nm, 8.98 nm, 13.46 nm and 14.26 nm SiO_2NPs in Tris(hydroxymethyl)aminomethane (Tris) buffer solution and in aqueous sodium chloride (NaCl) solution ranged from the maximum 2.30 mmol/L to 2.70 mmol/L, which were shown to be dependent on size (Roelofs and Vogelsberger, 2004), whereas the dissolution rates for 7.7 nm SiO_2NPs in Tris buffer solution (Vogelsberger et al., 2008) and the dissolution rates for SiO_2NPs with particle sizes ranging from 25 nm to 177 nm in aqueous solutions (Diedrich et al., 2012) were shown to be dependent on surface area.

55. Using dissolution rate constants, diameters and molar volumes from some of these studies the lifetimes of SiO_2NPs were estimated using the shrinking sphere model, as indicated in the following equation:

$$\tau = \frac{d}{2V_m k}$$

Where τ is the dissolution lifetime (s), d is the diameter of the spherical particle (m), V_m is the molar volume (m^3/mol), and k is the rate constant (mol/m^2.s) (mol/ m^2.s^1) (Jurinski,

1998). The lifetime of 6.7 nm SiO_2NPs was estimated to be 12 years and those of 3.6 nm SiO_2NPs to be about 2 years (Utembe et al., 2015).

9.6. Silver nanoparticles

56. *In vivo* experiments have been conducted to assess the biopersistence/biodurability of AgNPs. A 28-day study with repeated oral doses of 60 nm AgNPs with male and female, specific-pathogen free (SPF) Sprague-Dawley rats found that the accumulation is dose-dependent, with a two-fold higher accumulation in female rats compared to male rats across all dose groups (Kim et al., 2008). In a similar study where Sprague-Dawley rats were again treated orally with < 20 nm AgNPs in a 28-day exposure, the highest silver concentrations were detected in the tissues of the gastrointestinal tract and also in the liver and spleen. Silver was also detected in the testis, brain, kidneys and lungs where both silver ions and AgNPs were detected. Interestingly, AgNPs was also detected in the organs of the mice that were treated with silver nitrate ($AgNO_3$) indicating that silver ions were capable of forming silver salt particles *in vivo* (van der Zande et al., 2012). In a more recent study, where Sprague-Dawley rats were again exposed orally to AgNPs (10 and 25 nm) for 28 days, it was found that regardless of the AgNP size, the silver content in most tissues decreased gradually over a 4 month period, with the exception of the brain and testes (Lee et al., 2013).

57. An *in vitro* acellular dissolution study has shown that high concentration of silver nanoparticles (with sizes of 10, 20, 50 and 80 nm) may affect their dissolution as ionic silver (Ag^+) can be adsorbed to AgNPs, and subsequently, high particle concentrations would provide more binding surfaces for Ag^+ (Kennedy et al., 2010). For this reason, even simple colloids were shown to contain three forms of silver: Ag^0 solids, free Ag^+ (or its compounds) and surface-adsorbed Ag^+ (Liu and Hurt, 2010). Therefore, the dissolution of AgNPs implies an oxidation reaction at the NP surface, from the elemental Ag^0 to Ag^+, and possibly a subsequent binding of Ag^+ to a ligand, according to the general scheme:

$$Ag^0 + oxidant \rightarrow Ag^+ + (oxidant)^-$$

also

$$Ag^+ + L^{x-} \rightarrow AgL^{(x-1)-}$$

where the oxidant is oxygen or ROS, or any other strong oxidant, and L is a ligand forming a complex with Ag^+ (Navarro et al., 2008b).

58. *In vitro* acellular dissolution of 10 nm Ag NPs was also conducted in Gamble's fluid at neutral pH or in ALF the particles were more stable in Gamble's fluid compared to ALF fluid (Stebounova et al., 2011). However, higher dissolution could be observed in simulated human stomach fluid for AgNPs with a nominal size of 40 nm (Rogers et al., 2012). On the other hand, it was confirmed that even at low pH, dissolved oxygen is required for the dissolution of AgNPs, which indicates that dissolution of AgNPs is dependent on oxygen and the presence of ligands (Liu and Hurt, 2010, Xiu et al., 2011).

9.7. Titanium dioxide nanoparticles

59. *In vivo* experiments with thirteen-week repeated oral administration of titanium dioxide nanoparticles (TiO_2NPs) (37.8 ± 0.4 nm, 80% anatase, 20% rutile) to Sprague-

Dawley rats resulted in no significant increase in tissue distribution of TiO_2NPs in the liver, spleen, kidney, and brain, even in the group receiving the highest dose of 1041.5 mg/kg body weight (Cho et al., 2013). A single oral dose of 12 nm TiO_2NPs (95% anatase) administered by gavage to mice indicated that the NMs are biodurable for up to 24 hours when sequestered in gut epithelial tissue. Moreover, this intracellular residence time did not induce any diameter decrease of TiO_2NPs, and hence did not induce any dissolution (Brun et al., 2014). However, intravenous administration of TiO_2NPs (20–30 nm, 70% anatase and 30% rutile) to male Wistar rats resulted in detectable levels in the liver, spleen, lung, and kidney, but not in blood cells, plasma, brain or lymph nodes (mediastenal, mesenteric, and popliotenal) (Fabian et al., 2008).

60. The excretion of TiO_2NPs following intravenous administration of 20 nm rutile TiO_2NPs to ICR mice was observed to be higher through urine than through faeces, indicating that renal excretion is the main pathway of TiO_2NP elimination (Xie et al., 2011). On the other hand, there was a much higher elimination of orally administered TiO_2NPs (37.8 ± 0.4 nm, 80% anatase, 20% rutile) through faeces than through urine in Sprague-Dawley rats (Cho et al., 2013). In either case, TiO_2NPs appear not to be well eliminated from the body, which may result in bioaccumulation. Consequently, the $t_{1/2}$ of orally and intravenously administered TiO_2NPs (80–150 nm, anatase and rutile) in Wistar rats were estimated to range from 28–248 days (Geraets et al., 2014).

61. TiO_2 exists in three different crystalline structures (rutile, anatase and brookite) that are known to affect their dissolution in *in vitro* acellular systems. For example, the solubility of nano rutile (<100nm) was found to be lower than that of nano-anatase (<25nm) at low pH (1.5), while NIST nano-TiO2 reference material (SRM 1898), a mixture of both crystal forms (76 % nano-anatase and 24 % nano-rutile), demonstrated dissolution behaviour between that of nano-anatase and nano-rutile (Avramescu et al 2017). This finding is consistent with Schmidt and Vogelsberger (2009) who observed that "pure nano-anatase was more soluble than mixed nano-anatase and nano-rutile". Experiments with micron-sized rutile TiO_2 (0.6 µm - 91 µm) has also confirmed that dissolution in synthetic body fluids of pH ranging from 1.6 to 7.4 was dependent on their surface composition, phases, structure, particle size, impurities, solution pH, and solution complexation ability (Hedberg et al. 2012). Similarly, the maximum dissolution of anatase and rutile TiO_2NPs of sizes ranging from 4.7 nm to 28.3 nm, in aqueous sodium chloride (NaCl) solutions at temperatures of 25°C and 37 °C was shown to be dependent on the pH, morphology of the titanium dioxide, the phase present, and on the size of the particles (Schmidt and Vogelsberger 2006).

62. In contrast to micron-sized and bulk TiO_2, the TiO_2NPs displayed a behaviour referred to as the 'kinetic effect', where the solubility would show a maximum at the beginning of the dissolution process, whereas over time, the solubility levels would show a decrease (Schmidt and Vogelsberger, 2006, Vogelsberger et al., 2008).

9.8. Zinc oxide nanoparticles

63. *In vivo* oral and intraperitoneal administration of 93.35 nm ZnONPs to male ICR mice resulted in absorption and distribution of the NMs to the liver, spleen, and kidney within 30 min after dosing. However, intraperitoneally administered ZnONPs remained in serum for 72 hrs whereas orally administered ZnONPs were eliminated through faeces after 6 hours (Li et al 2012). Inhalational exposure to 15 nm ZnONPs resulted in a high dissolution of ZnONPs in lung tissues and bronchoalveolar lavage fluid, with subsequent translocation of zinc ions (Zn^{2+}) to the blood circulation (Adamcakova-Dodd et al. 2014).

Following a single oral dose adminstration of positively and negatively charged 20 nm and 70 nm ZnONPs, the pharmacokinetics (absorption distribution and elimination) has been shown to be charge- rather than size-dependent (Paek et al., 2013).

64. Rapid dissolution studies of ZnONPs (25, 40 and 70 nm) were conducted *in vitro* cellular systems using Dulbecco's Modified Eagle's Medium (DMEM) and Roswell Park Memorial Institute medium (RPMI) cell culture media. There was a higher extent of dissolution in the former media than in the latter or in pure or moderately hard water and in some cases the precipitation of zinc carbonate could affect this dissolution (Reed et al. 2012).

65. *In vitro* acellular systems were also implemented to assess the dissolution of 40 nm ZnONPs where it was found that in an acidic environment about 98% of the ZnONPs had dissolved in artificial gastric fluid (AGF, pH 1.7) within 24 hours whereas ZnONPs in distilled deionised water showed minimal dissolution (Seok et al., 2013). The dissolution of ZnONP (10.7 ± 0.7 nm) was also studied in artificial ALF and in Gamble's solution where around 90% of the mass of the NPs was dissolved within 24 hours in ALF at pH 4.5, whereas the NPs did not dissolve in artificial pulmonary interstitial fluid (Cho et al., 2011). In a similar study, less than 1% of ZnONPs dissolved in Gamble's fluid after 2 wks in comparison to the 100% of the ZnONPs that dissolved within the first 24 hr of mixing in ALF solution (Adamcakova-Dodd et al. 2014). Furthermore, ZnONPs (50 nm in diameter and 200 nm in length) were shown to dissolve fast in uterine solution. In this case the release rate of Zn^{2+} was shown to depend on pH and (decreased with increasing pH of the simulated uterine solution) and also on the presence of human serum albumin (Yang and Xie, 2006). These results could therefore show that ZnONPs are not likely to be biopersistent in the acidic environment of the phagolysosomes (Cho et al., 2011).

66. The rapid dissolution of ZnONPs will, on the other hand, result in rapid increase of localised concentrations of Zn^{2+} ions which may damage lysosomes and other organelles in the cytoplasm, leading to cell death. This mechanism has been referred to as the "lysosome-enhanced Trojan horse effect" since this protective cellular machinery is designed to protect the cell from foreign object through their degradation, however for NMs, this very mechanism would be responsible for their toxicity (Sabella et al., 2014). The "lysosome-enhanced Trojan horse effect" has been postulated as the mechanism of toxicity for progressive severe lung injury by 10.7 nm ZnONPs (Cho et al., 2011) as wells as cell toxicity of 19 nm ZnONPs (Brunner et al., 2006). For 70 nm ZnONPs with non-ionic, anionic and cationic dispersants the toxicity and rapid release of Zn^{2+} ions is said to be affected by size and the charge on the nanoparticles (Prach et al., 2013).

9.9. Iron oxide nanoparticles

67. In an *in vitro* cellular study using male Wistar Kyoto rat AMs, dissolution rates of different micro-sized iron oxide (Fe_2O_3) particles ($^{59}Fe_2O_3$-labelled) of 0.5 and 1.5 µm in size, were determined intra- and extracellularly. It was found that only a small amount of the Fe was released extracellulary and remained constant for the rest of the incubation period. In contrast, the intracellular dissolved fractions increased with time where more than 70% of the dissolved iron remained within AM (likely associated to iron-binding protein), whereas only 30% was released out of the cell into the extracellular medium (Beck-Speier et al., 2009).

68. The *in vitro* acellular dissolution of different larger sized iron oxide crystalline phases (hematite, maghemite, magnetite) particles was studied in acidic solutions of

sulphuric, nitric and oxalic acid. Magnetite was found to give the highest dissolution when exposed to oxalic acid, additionally an increase in the temperature from 15 to 35 ^{o}C resulted in a higher dissolution rate (Salmimies et al., 2011). The dissolution rates of these three crystalline phases were faster in HCl compared to perchloric acid ($HClO_4$) (Sidhu et al., 1981)

9.10. Gold nanoparticles

69. Not much work has been conducted on the dissolution of gold nanoparticles (AuNPs) *in vivo* or *in vitro*. *In vivo* studies have however investigated their biodistribution and biopersistence where the clearance of small (13 nm) and large (105 nm) AuNPs were studied after a 5-day inhalation period in Sprague–Dawley rats. The biodistribution of the AuNPs from the lungs to blood and to other organs such as liver, spleen, brain, and testes was found to be significantly higher for the smaller AuNPs and their elimination halftime from the lungs was significantly shorter (t1/2 = 44.5 days) compared to the larger AuNPs (t1/2 = 179.5 days) (Han et al., 2015). The size-dependent organ distribution of 10, 50, 100 and 250 nm AuNPs in Wistar-derived rats was also reported by others where the largest translocation to organs was shown for the smallest AuNPs (10 nm) distributing to blood, liver, spleen, kidney, testis, thymus, heart, lung and brain (De Jong et al., 2008). Finally, inhalation of 20 nm AuNPs for 5 days showed their accumulation in the olfactory bulb of rats (Yu et al 2007).

9.11. Dendrimers

70. Interest in dendrimer-based nanomedicines has recently been growing, as it is possible to precisely manipulate their molecular weight, chemical composition, and surface functionality, tuning their properties according to the desired biomedical application. Dendrimers can be based on polyamines, polyamides, polyesters, carbohydrates and a few other types of polymers. However, one important concern about dendrimer-based therapeutics is their non-degradability under physiological conditions that can result in cytotoxicity induced by the accumulation of nondegradable synthetic materials inside cells or in tissues (Duncan and Izzo, 2005, Jain et al., 2010).

71. The use of biodegradable materials that, under biological and environmental conditions, degrade in time into smaller fragments that can be excreted or eliminated through metabolic pathways is expected to overcome the risk of complications associated with the long-term presence of high-molecular-weight compounds. Therefore, biodegradable dendrimers represent an attractive class of NMs, since they present advantages over conventional non-degradable dendrimers regarding the release of the loaded molecules and the prevention of bioaccumulation of synthetic materials and subsequent cytotoxicity. Subsequently, the polyester dendrimers are found to be biodegradable for their rapid and safe elimination of non-toxic dendrimer fragments in urine (Twibanire and Grindley, 2014). The biodegradable dendrimers have recently been reviewed (Leiro et al., 2015).

9.12. Nanoclays

72. Nanoclays are nanoparticles of layered mineral silicates. They are classified as montmorillonite, bentonite, kaolinite, hectorite, and halloysite, depending on chemical composition and nanoparticle morphology (Uddin, 2008). The uptake of nanoclays by human epithelial cell line A549 was studied where it was shown that they accumulate in a

specific manner within the cellular cytoplasm around the nucleus (perinuclear region) but not inside the nucleus (Verma et al., 2012).

73. A number of studies have assessed the toxicity of nanoclays *in vitro* and *in vivo* (Chung et al., 2011, Lordan et al., 2011, Verma et al., 2012, Warheit et al., 2010) and some other studies have also assessed their dissolution where it could be shown that magnesium aluminium layered double hydroxides chloride (MgAl-LDH-Cl) anionic clay dissolved faster in both simulated lysosomal (pH 4.5) and body fluid (pH 7.4) conditions than magnesium aluminium layered double hydroxides carbonate (MgAl-LDH-CO_3). The less soluble MgAl-LDH-CO_3 anionic clay exhibited higher toxicity than MgAl-LDH-Cl anionic clay (Baek et al., 2011). A large number of dissolution studies in biological and environmental fluids have been reported in the literature on their larger counterparts where it was indicated that the dissolution of nanoclays were very much dependent on temperature, pH, surface chemistry, and biological ligands (Hayashi and Yamada, 1990, Huertas et al., 1999, Ramos et al., 2011, Rozalén et al., 2009, Zysset and Schindler, 1996).

9.13. Aluminium oxide nanoparticles

74. An *in vivo* study with rod-like aluminium oxide nanoparticles (Al_2O_3NPs) (administered orally to male ICR mice) have shown no uptake or accumulation in organs and therefore was concluded to be of no toxicity (Yang et al., 2012). However, similar *in vivo* studies have suggested that the Al_2O_3NPs are taken up by the organs. After 28 days of oral administration in female Wistar rats with 30 – 40 nm Al_2O_3NPs, it was found that the particles were taken up by the brain, thymus, lungs and kidneys, but not by the liver, spleen and testis (Balasubramanyam et al., 2009, Park et al., 2011).

75. The intracellular uptake of three different commercially available Al_2O_3NPs with sizes of 14, 111 and 750 nm, was studied with cellular *in vitro* assay using human lung epithelial A549 and human skin keratinocytes HaCaT cells, where they were shown to accumulate and agglomerate inside the cytoplasm of these cells but they did not accumulate in the the nucleus (Böhme et al., 2014) or the lysosomes (Di Virgilio et al., 2010).

76. Although no studies have as yet been reported to assess the acellular *in vitro* dissolution and biodurability Al_2O_3NPs in biological media, their dissolution in water was shown to be pH dependent (Roelofs and Vogelsberger, 2006) as well as dependent on size, surface tension and mass of the particles exposed to dissolution defined as kinetic size effect (Vogelsberger et al., 2008).

10. Studies in Environmental Media

77. There are not many reports of studies specifically designed to assess biodurability of NMs in environmentally relevant fluids or systems. Consequently, the terms “biodurability” and “bioperistence” are not commonly used in the environmental context and information on related processes in the environment may only be found by searching for the terms "persistence”, “(bio-)degradation” or “transformation”. This notwithstanding, most of the studies reviewed in this section refer to assessment of (bio)degradation, bioaccumulation or transport in the environment. However, it is recognized that (bio) degradation, bioaccumulation and transport are not normally included in the studies of biodurability/biopersistence. Therefore, these studies are only used as indicative examples of the areas where the research on biodurability of NMs should be focused. Furthermore, as the behaviour of NMs in waste treatment processes determines their transport and fate, this section has also included studies on the behaviour of NMs as they undergo waste treatment processes such as in waste water treatment plants (WWTP). It is evident in the discussions for each type of NM discussed below, that studies of persistence and fate of NMs in the environment are hampered by limited information, especially regarding possible complexation with natural or synthetic ligands, transport, and distribution in the different environmental compartments as well as in biota and the influence of morphology, agglomeration, and formation of secondary particles on their transport and fate (Handy et al., 2008; Levard et al., 2012). Determination of NMs fate and behaviour in the environment is limited by the fact that commonly derived partitioning coefficients for water, soils and sediment are not applicable for NMs as they assume thermodynamic processes reaching a state of equilibrium. However, as particulate materials, NMs undergo rather kinetic processes to distribute between environmental compartments (ECHA, 2017). In addition, water solubility which is generally determined to describe the fate of a substance in water, is only of low significance for NMs as sparingly soluble substances. Instead, parameters like dissolution rate and dispersion stability under relevant media conditions need to be examined to reliable assess the environmental fate of NMs (ECHA, 2017).

10.1. Carbon nanotubes

10.1.1. SWCNTs

78. Although SWCNTs could be degraded by strong enzymes and oxidising environments, SWCNTs of undefined size could not be degraded by the fungus *T. versicolor* and natural microbial cultures found in sediments and aerated WWTP (Parks et al., 2015). Therefore, SWCNTs are expected to be persistent in the environment if released untreated. However, exposure of SWCNTs to the benthic organisms *Americamysis. Bahia, Ampelisca. Abdita and Leptocheirus plumulosus* for a period of 7 days did not indicate bioaccumulation, with the ingested SWCNTs remaining within the gut lumen and not passing through the gut epithelium (Parks et al., 2013).

79. It has also been proposed that the biodegradation of SWCNTs may take place in plants through natural, enzymatic catalysis by plant peroxidases (Allen et al., 2008). Similarly, SWCNTs may be ingested by invertebrate and vertebrate organisms and may subsequently be excreted, resulting in minimal bioaccumulation (Petersen et al., 2008b).

10.1.2. MWCNTs

80. MWCNTs were shown to be readily absorbed by some species and not well absorbed by others. For example, it could be shown that although MWCNTs could accumulate in *Daphnia magna* but would remain in the gut and not absorbed into cellular tissues (Petersen et al., 2009). Similarly, MWCNTs were not readily absorbed into the tissues of earthworm *Eisenia fetida* (Petersen et al., 2008a) while they were absorbed and bioaccumulated in zebrafish (*Danio rerio*) (Maes et al., 2014), and in algae *Desmodesmus subspicatus* (Rhiem et al., 2015).

81. Moreover, MWCNTs were able to penetrate into plant tissues (Khodakovskaya et al., 2009, Khodakovskaya et al., 2011, Wild and Jones, 2009). It was also shown that plant roots could interact with the MWCNTs present in soils and MWCNTs present in air could attach to leaves and other aerial parts of plants and be translocated to different tissues of the plant (Navarro et al., 2008a).

82. In the environment, carboxylated MWCNTs (36.5 ± 12.7 nm, 100 - 2000 nm in length) were shown to be degraded by bacteria (*Burkholderia kururiensis, Delftia acidovorans, and Stenotrophomonas maltophilia*) under environmentally relevant conditions, in a process that appears to require an external carbon source involving co-metabolism and the cooperation of several microorganisms (Zhang et al., 2013).

10.2. Fullerenes

83. The environmental persistence of pristine fullerenes is expected to be largely determined by their low solubilities in water (Beck and Mándi, 1997). Consequently, pristine fullerenes are resistant to degradation in soil for at least at 1 to 2 years, where they can be internalized by plants and other organisms (Tervonen et al., 2010).

84. In ambient air, fullerenes react with ozone (Chibante and Heymann, 1993) to undergo fast degradation. This was also observed in the presence of ultraviolet laser radiation. The reactions with ozone and photolysis are expected to reduce the persistence of fullerene in air (Juha et al., 1993).

85. In the soil, fullerenes are likely to persist for extended periods of over 2 years, where they can be internalised by plants to a small extent (Avanasi et al., 2014). Fullerenes could also bioaccumulate in in *E. Fetida* (Li et al., 2010a). On the other hand, the two species of white rot basidiomycete fungi (*Phlebia tremellosa* and *Trametes versicolor*) appear to have ability to metabolize and degrade oxygenated C_{60} to carbon dioxide (CO_2) (Schreiner et al., 2009).

86. While suspended in water, rapid uptake and relatively slow depuration has been shown to result in bioaccumulation of fullerenes in *D. Magna* (Tervonen et al., 2010). On the other hand, fullerenes appear to have low probability of bioaccumulation in *Lumbriculus variegates* (Wang et al., 2014). Solution pH and dissolved oxygen concentration appear to play a role in the aggregation of fullerenes, with high pH and dissolved oxygen promoting dispersion (Wiesner et al., 2008).

10.3. Cerium oxide nanoparticles

87. *In vitro* acellular dissolution studies in aquatic environments could show that the dissolution of CeO_2NPs was size-dependent, with the disssolution of 77.5 nm CeO_2NPs occuring at almost half the dissolution rate of 32.5 nm CeO_2NPs. Furthermore, the dissolution was shown to depend on the concentration of phosphorous and on the pH, where virtually no dissolution occurred above pH 7.45 (Dahle et al, 2015). The dependence on pH of the dissolution of CeO_2NPs at this neutral pH was shown to change the oxidation state on the surface of CeO_2NPs where the Ce(IV) could show a very low solubility at this pH (Hayes et al., 2002, Yu et al., 2006). Similarly, the solubility of Ce(III) could be shown to be below 0.5% (Rogers et al., 2010; Schwabe et al., 2013).

88. In a WWTP, 96.6% of total Ce of 50-nm CeO_2NP was removed through aggregation and settling of CeO_2NPs that were promoted by CeO_2NPs interactions with organic and/or inorganic constituents in the wastewater, as well as by biosorption (Gómez-Rivera et al., 2012). Therefore, this study shows that dissolution does not affect the fate of CeO_2NPs in WWTP, with 96.6% of CeO_2NPs accumulating in waste sludge.

89. In the terrestrial environment, dissolution of CeO_2NPs (diameter < 5 µm) was shown to be very low with no dissolved Ce detected in soils spiked with CeO_2NPs. Furthermore, adsorption of the CeO_2NPs was also very low, indicating their low retention in soils that may result in contamination of water bodies through run off (Cornelis et al., 2011).

90. In organisms, particle-size dependent bioaccumulation and trophic transfer have been observed for 330 and 155 nm CeO_2NPs in zucchini (*Cucurbita pepo L.*), crickets (*Acheta domesticus*) and wolf spiders (family Lycosidae) (Hawthorne 2014). On the other hand, surface charge dependent bioaccumulation of 4 nm CeO_2NPs in *Caenorhabditis elegans* has been reported (Collin et al., 2014).

10.4. Quantum dots nanoparticles

91. In the environment, CdTe/CdS QDs (5.7 nm, 4.3 nm and 4.2 nm) were shown to be internalised by *Chlamydomonas reinhardtii* where they caused different effects compared to the effects elicited by Cd^{2+} ions (Domingos et al., 2011). Bioaccumulation has also been demonstrated for 15–20 nm QDs in the amphipod *Leptocheirus plumulosus* where there was greater bioaccumulation through food than through water, indicating a greater potential for trophic transfer (Jackson et al., 2012). Furthermore, the uptake and bioaccumulation of 15 and 25 nm QDs in *Drosophila melanogaster* have been shown to be dependent on the surface coating (Galeone et al., 2012).

92. QDs undergo degradation in the environment. In this regard, toxic inorganic constituents could be released from QDs (6 × 12 nm) due to weathering of the NPs under acidic or alkaline conditions following the degradation of surface coatings (Mahendra et al., 2008). Such weathering occurring under acidic (pH $\leq$ 4) or alkaline (pH $\geq$ 10) conditions was also shown to significantly increase bactericidal activity due to the rapid release of Cd^{2+} and Se^{2-} ions. QDs (core diameter 2.6 ± 0.1 nm) were also shown to be readily degraded under simulated oxidative environmental conditions, resulting in the release of Cd^{2+} (Metz et al., 2009). Also, studies using hydroquinone-driven Fenton's reaction used by lignolytic fungi have demonstrated that QDs were readily degraded under simulated oxidative environmental conditions, where the ZnS shell was eroded and cadmium was released from the QD core (Metz et al., 2009).

10.5. Silicon dioxide nanoparticles

93. SiO2NPs (10–20 nm), in the amorphous form, have been shown to undergo little dissolution in a WWTP and therefore it is said to also undergo little dissolution in the environment (Mu et al., 2011). SiO2NPs (200–800 nm) were also shown to be stable in tap water and had low removal efficiencies even on flocculation with alum, requiring filtration (Zhang et al., 2008). These observations were consistent with another study where the sedimentation rates for SiO2NPs were in the order of 0.0001 m/day (Quik et al., 2014). The high stability and slow sedimetation rate is expected to result in poor removal of SiO2NPs from WWTPs with the subsequent release of SiO2NPs to the environment. Indeed, uncoated 56 nm SiO2NPs were shown to not undergo sedimentation, while their sedimentation were shown to be improved by surface functionalisation with non-ionic surfactant Tween 20 (Polysorbate 20) (Jarvie et al., 2009).

10.6. Silver nanoparticles

94. In the aquatic environment, AgNPs (20 nm) have been shown to bioaccumulate in *D. magna* (Zhao and Wang, 2010). Similarly, in terrestrial environments earthworms (*E. fetida*) have been shown to accumulate Ag after exposure to 30–50 nm AgNPs (Shoults-Wilson et al., 2011), while rhygrass (*Lolium multiflorum*) accumulated Ag after exposure to gum arabic coated 6 and 25 nm AgNPs (Yin et al., 2011).

95. The behaviour of AgNPs in WWTPs is important as studies have shown that AgNPs are released during washing, and will therefore go through WWTPs before being released into the environment (Benn and Westerhoff, 2008, Geranio et al., 2009). Thermodynamic and kinetic analysis of dissolution of 1.9 nm AgNP indicates that AgNPs will not be persistent in the presence of dissolved oxygen (Liu and Hurt, 2010). In WWTP, it was observed that AgNPs (average size 28 nm) were adsorbed to wastewater biosolids in both sludge and in the effluent. At a low concentration of 0.5 mg/L over 90% of the AgNPs were nearly transformed to silver sulfide (Ag_2S) within 2 hours, whereas at a higher concentration of 5 mg/L only about 60% of the AgNPs were transformed into Ag_2S in the same period (Kaegi et al., 2011). Other studies have also confirmed the presence of 5-20 nm Ag_2S in sewage sludge (Kim et al., 2010), indicating that although AgNPs undergo rapid dissolution, the Ag^+ ions were rapidly transformed to insoluble forms such as Ag_2S and silver chloride (AgCl).

96. Eighteen months after either direct application of 10 nm AgNPs to a freshwater mesocosm or to the terrestrial environment, most (70 wt %) of the added Ag resided in the soils and sediments, with most of the silver remaining in the compartment in which it was applied. In the terrestrial environment, the AgNPs once again were transformed to Ag_2S (~52%), whereas in sediments AgNPs were present as Ag_2S (55%) and Ag-sulfhydryl compounds (27%) (Lowry et al., 2012).

97. Dissolution is the main dissipation process for AgNPs in the environment. The dissolution of AgNPs is complex since environmental systems contain chloride, carbonate and phosphate ions which form precipitates and complexes with silver ions (Li and Lenhart, 2012, Li et al., 2010b). The dissolution of the AgNPs is dependent on many factors such as pH (Rogers et al., 2012), aggregation state (Stebounova et al., 2011), ionic strength (Jin et al., 2010, Li and Lenhart, 2012, Li et al., 2010b, Rogers et al., 2012), sunlight (Gorham et al., 2012, Liu and Hurt, 2010), and the presence of complexing ions/molecule (ligands) in the solution (Gondikas et al., 2012), as well as capping agents

(Ho et al., 2010, Khan et al., 2012, Lee et al., 2012, Li and Lenhart, 2012, Rogers et al., 2012, Schultz et al., 2012, Lee et al., 2013, Mwilu et al., 2013).

10.7. Titanium dioxide nanoparticles

98. Because of the widespread use TiO_2NPs in sunscreens, the fate and behaviour of TiO_2NPs (< 0.45 µm) from sunscreens in wastewater treatment system was assessed, where a reduction in the concentration of TiO_2NPs from 30 µg/L in the influent to 3.2 µg/L to the effluent, was observed (Johnson et al., 2011)

99. Studies have also shown accumulation of TiO_2NPs in environmental organisms. For example, the accumulation was observed for dietary TiO_2NPs (21 nm on average, 25% rutile and 75% anatase) in the gill, gut, liver, brain and spleen of rainbow trout (*Oncorhynchus mykiss*) (Ramsden et al., 2009) as well as intravenously administered 32.4 nm rutile and anatase TiO_2NPs in the kidneys of *O. Mykiss* (Scown et al., 2009). Bioaccumulation could also be shown for 21 nm TiO_2NPs (20% rutile and 80% anatase) in *D. Magna* exposed through water (Zhu et al., 2010a), 10.4 ± 3.3 nm anatase TiO_2NPs in zebra mussels (*Dreissena polymorpha*) exposed through water and diet (Bourgeault et al. 2015), and 432 ± nm rutile TiO_2NPs in goldfish (*Carassius auratus*) exposed through water (Ates et al., 2013). Moreover, the potential for trophic transfer of 21 nm TiO_2NPs (of unknown crystallinity) from *D. magna* to *D. rerio* could also be shown, but with no biomagnificaion (Zhu et al., 2010b).

10.8. Zinc oxide nanoparticles

100. ZnONPs (30−40 nm) from commercial products were shown upon dissolution to Zn^{2+} ions to rapidly convert to Zn sulfides and phosphates during anaerobic digestion of wastewater and post-treatment processing of sewage sludge (Lombi et al., 2012; Ma et al., 2013).

101. The rapid dissolution of ZnONPs has been expected to play a significant role in the low persistence of ZnONPs in the environment. For example, ZnONPs (average size < 35 nm) were found to undergo rapid dissolution in soil where the ZnONPs could not be detected after incubation for 1 hour (Wang et al., 2013). Rapid dissolution has also been observed to occur in living organisms where the Zn^{2+} ions have been linked with many adverse effects in many species including marine diatoms *Skeletonema costatum* and *Thalassiosia pseudonana*, the crustaceans *Tigriopus japonicus* and *Elasmopus rapax*, and the medaka fish *Oryzias melastigma* (Miao et al., 2010, Wong et al., 2010).

102. Application of ZnONPs (<100 nm) to sand at the root zone of wheat (*Triticum aestivum L.*) have also resulted in the detection of zinc phosphate, indicating that Zn uptake into the plants occurs through uptake of dissolved Zn^{2+} rather than by uptake of ZnO particles (Dimkpa et al., 2013). The bioacumulation of Zn^{2+} resulting from dissolution of ZnONPs has also been demonstrated in juvenile carp (*Cyprinus carpio*) (Hao et al., 2013). Uptake, bioaccumulation and trophic transfer of ZnONPs have been shown to be affected by functionalisation, with rapid uptake, bioaccumulation and trophic transfer from crustaceans (*D. magna*) to zebrafish (*D. rerio*) for 30 nm ZnONPs and 30 nm ZnO-octyl-NPs, and very little uptake and trophic transfer for 30 nm ZnO-OH-NPs (Skjolding et al., 2014).

10.9. Iron oxide nanoparticles

103. The environmental fate of iron oxide nanoparticles (Fe3O4NPs) is important because of their applications in environmental remediation, especially for detoxification and removal of many environmental contaminants, such as pesticides and chlorinated organic solvents (Zhang, 2003), and metals (Shipley et al., 2011). The solubility, stability, and aggregation behavior of Fe3O4NPs have been shown to change depending on pH and the concentration of organic matter. In this regard, at pH 2 approximately 35% of the total iron was present in the dissolved phase, rapidly diminishing to 10% at pH 3 and to almost zero at higher pHs (Baalousha et al., 2008). Therefore, Fe3O4NPs are expected to be persistent in the neutral pHs of natural aquatic environments, and may therefore result in bioaccumulation as was demonstrated by the bioaccumulation of 20-40 nm Fe3O4NPs in Ceriodaphnia dubia (Hu et al., 2012). Bioaccumulation has also been shown in terrestrial environments, where pumpkins (Cucurbita maxima) grown in an aqueous medium containing 20 nm Fe3O4NPs accumulated the nanoparticles throughout the plant tissues, especially near the roots and in leaves (Zhu et al., 2008).

10.10. Gold nanoparticles

104. Not much work is reported on the environmental persistence/degradation of AuNPs. However, under laboratory conditions it was shown that spherical gold nanoparticles had high stability against low-power UV-irradiation (254 nm), while gold nanorods/nanoprisms could be photodissolved under low-power-UV irradiation at room temperature in the presence of semiconductor-like Ag clusters (Attia et al, 2015). Moreover, it could be shown that gold nanoparticles could be atomically dissolved with aromatic thiols (ArSH) at room temperature but also gold nanoparticles could also be regenerated upon treatment with H2O2 indicating that the dissolution and regeneration of Gold nanoparticles is a reversible process and is simply controlled by the presence of aromatic thiols or H2O2 (Wang et al 2012).

10.11. Dendrimers

105. As discussed earlier, the degradability of dendrimers depends on the constituent polymer (polyamines, polyamides, polyesters or carbohydrates). There is much research on the development of dendrimer systems that can undergo hydrolysis (Kohman and Zimmerman, 2009), photolysis (Nazemi et al., 2013) or enzymatinc degradation (Amir and Sabat, 2004, Seebach et al 1996). However, there appears to be no studies on the degradation of dendrimers in the environment.

10.12. Nanoclays

106. There appears to be no literature on the environmental behaviour and fate of nanoclays.

10.13. Aluminium oxide nanoparticles

107. Dissolution is expected to play a minor role in the environmental persistence of Al_2O_3NPs as little dissolution has been observed for 60 nm (Jiang et al., 2009) and 50 nm Al_2O_3NPs (Sadiq et al., 2011) in water, as well as for <50 nm Al_2O_3NPs in a WWTP (Mu et al. 2011). These studies were however not consistent with those obtained with

Al_2O_3NPs (mean diameter 82.6 ± 22 and 246.9 ± 39 nm) showing significant dissolution within 72 h in lake water (Pakrashi et al., 2013). In natural aquatic systems, the colloidal behaviour of 60 nm Al_2O_3NPs was observed to be significantly influenced by the solution pH and natural organic matter (NOM), where humic acids stabilised the nanoparticles in neutral to alkaline conditions and not in acidic conditions (Ghosh et al., 2008). In an aquatic ecosystem, bioaccumulation and trophic transfer of Al_2O_3NPs (40-100nm) was demonstrated in the primary producer (*Chlorella ellipsoides*) i.e. plant species or autotrophs and the primary consumer, (*Ceriodaphnia dubia*) the species that fed directly on the plant (Pakrashi et al., 2014).

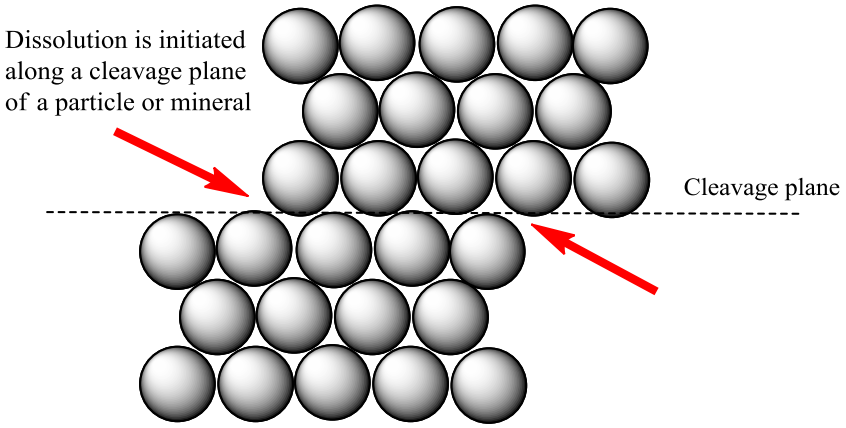
11. Effects of the Physicochemical Properties of NMs and Properties of Biological and Environmental Media on Dissolution

108. Over the last several decades there have been numerous publications on the relation of various physicochemical characteristics of larger particles and fibres to their dissolution rate in physiological solutions. These have included among others the chemical composition, diameter, surface properties (structural defects, porosity, surface area, crystallinity and crystal structure) and most importantly their surface coatings (surface bonds, their spatial arrangements, the presence of impurities or adsorbed atoms) (Behra et al., 2013, Maxim et al., 2006, Potter, 2000, Potter and Olang, 2013, Searl, 1994). For example, it was proposed that dissolution may be initiated at cleavage planes with varying degrees of defects on the surfaces due to surface vacancies and impurities. For example, dissolution was considered to be more likely initiated along a cleavage plane (where a mineral breaks in a preferred direction to produce more surface area). The dissolution may also be initiated where number of defects is present on the surface. These defects may be present as surface vacancies or impurities (see Figure 1 below). Subsequently, it is said that the higher the number of such surface defects, the greater the potential for instability. This is the case with chrysotile asbestos fibres, which are more susceptible to dissolution than amphibole asbestos (Searl, 1994). It is shown that surface dissolution may cause alterations in internal structure sufficient to cause mechanical breakage (Bellmann et al., 1987, Searl, 1994).

109. Similar to larger particles and fibres, the dissolution of NMs is also affected by their physicochemical properties. These may include size, shape (morphology), surface area, surface molecules or ligands and the aggregation and agglomeration state of the particles. It is generally assumed that dissolution may increase as particle size decreases (Borm et al., 2006a, Vogelsberger et al., 2008) for the fact that smaller nanoparticles have larger surface areas which make it more reactive and more prone to dissolution (Behra et al., 2013, Haase et al., 2012, Jin et al., 2010, Mwilu et al., 2013). For example, size was found to be the primary physicochemical property affecting dissolution of AgNPs (Ma et al., 2011, Zhang et al., 2011c) and also of SiO_2NPs (Diedrich et al., 2012).

Figure 1. An illustration of a possible cleavage plane present in a particle where dissolution is more likely to be initiated

Source: Searl, 1994.



110. Shape and surface morphology (e.g. mesoporosity, hollow/compact) were also found to affect dissolution (Borm et al., 2006a). Accordingly, it may be predicted that dissolution of triangular-shaped AgNPs will be faster than silver nanospheres or nanorods because of their allegedly higher concentration of exposed (Jani et al. 1989) facets (Pal et al., 2007) where non-spherical AgNPs were observed to dissolve preferentially at locations with a small radius of curvature (Zhang et al., 2005). Moreover, it was also shown that crystallinity of nanoparticles may also affect their dissolution. For example, the dissolution of anatase TiO_2 was found to be lower compared to rutile (Snäll and Liljefors, 2000). In addition, evidence was also provided that the dissolution rate of polycrystalline AgNPs will be faster than single-crystalline AgNPs due to the presence of high-energy defects at grain boundaries that may provide active sites for oxidation and dissolution (Elechiguerra et al., 2005, Wiley et al., 2004, Yang et al., 2007).

111. In addition to intrinsic properties of NPs, the extrinsic characteristics of biological and environmental media such as the composition, pH, ionic strength, water hardness and presence of organic components - polysaccharides, proteins - may also affect the rate of dissolution of NMs by either increasing or decreasing their dissolution. For example, the dissolution of AgNPs was found to be inversely proportional to the pH of the solution (Liu and Hurt, 2010) while acidic simulated solution has caused the increased dissolution AgNPs (Rogers et al., 2012). On the other hand, when the dissolution of AgNPs was conducted in Gamble's fluid at neutral pH or in the acidic ALF, the particles were more stable in Gamble's fluid compared to ALF fluid (Stebounova et al., 2011). This was also found for the dissolution of SiO_2NPs (Roelofs and Vogelsberger, 2004) as well as for ZnONPs (Miao et al., 2010) where the dissolution was increased significantly at lower pH.

112. The aggregation state of NMs may also affect their dissolution. A decrease in dissolution was observed with increasing aggregation (Rogers et al., 2012, Stebounova et al., 2011), which in turn, can be induced by the high ionic strength of environmental waters and biological systems (Behra et al., 2013, Jin et al., 2010, Mwilu et al., 2013, Rogers et al., 2012). On the other hand, ion complexes can increase dissolution in certain cases, e.g. in seawater increased dissolution was observed due to formation of silver chloride complexes (Quik et al., 2014). Similarly, the presence of cysteine and methionines may also increase the dissolution of AgNPs (Gondikas et al., 2012, Xiu et al., 2011). High ionic strength, as mentioned above, increases aggregation due to screening of electrostatic double layer repulsion that is present between similar particles (Jin et al., 2010). For example, it was found that uncoated and citrate- and $NaBH_4$-coated AgNPs aggregated at higher ionic strengths (100 mM sodium nitrate ($NaNO_3$)) and/or acidic pH (3.0), while the presence of calcium ions (Ca^{2+}) (10 mM) resulted in aggregation of the AgNPs without any influence of pH (El Badawy et al., 2010, Jin et al., 2010).

113. Sunlight may also affect the aggregation state and consequently the dissolution of AgNPs. Indeed, aggregation in the presence of sunlight was observed with polyvinylpyrrolidone (PVP) coated AgNPs (Gorham et al., 2012). The effect of the sunlight was size-dependent, as the aggregation and the subsequent dissolution increased as the particle size decreased. The opposite effect of dissolution could also be observed where upon exposure to sunlight, ionic Ag and Au could be converted to metallic nanoparticles (Yin et al., 2012). On the other hand, the dissolution of CdSe quantum dots is shown to be dependent not only on the presence of ligands but also on the temperature of the dissolution medium (Siy and Bartl, 2010).

114. In environmental media, the dissolution of nanoparticles is also found to be affected by the dissolved oxygen where it was found that the higher the concentration of oxygen the higher was the oxidation of nanoparticles, where AgNPs at zero oxidation state could be converted to Ag^+ ions (Rogers et al., 2012).

12. The Stability and Biodegradation of the Surface Coatings and Ligands and their Influence on Biodurability of NMs *in vivo* and *in vitro*

115. The surfaces of NMs may be the principal determinants of their durability under conditions of dissolution and/or biodegradation in biological and environmental fluids. Surfaces of NMs are modified through the use of surfactants, capping agents or attached ligands. Common agents used include citrate (Ho et al., 2010, Khan et al., 2012, Lee et al., 2012, Rogers et al., 2012, Li and Lenhart, 2012, Lee et al., 2013, Mwilu et al., 2013), PVP (Levard et al., 2011, Mwilu et al., 2013), peptide coatings (Haase et al., 2012), polyethylene glycol (PEG) (Liu et al., 2013b) and tween (Li et al., 2011b). These ligands may be of small molecules or polymers, all of which may carry different functional groups including carboxylic acids [-COOH], methoxy [-OCH_3] amine [-NH_2], hydroxyl [-OH], and esters [-COO-R] (Grubbs, 2007).

116. These surface modifications of NMs influence their stability, agglomeration, biocompatibility, hydrophilicity, dispersibility, cytotoxicity, cellular penetration, and circulation time in blood stream and also their biodistribution and clearance (Templeton et al., 2000, Shon and Choo, 2003, He et al., 2008, Zhang et al., 2009, Liu et al., 2013b). The stability of covalently and non-covalently attached molecules with different functional groups could be investigated using a number of methodologies including proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy (Jokerst et al., 2011), Fourier transform infra-red (FTIR) (Mulvihill et al., 2010, Mudunkotuwa et al., 2014), TEM, high-resolution transmission electron microscopy (HRTEM), ICP-MS, UV-vis spectroscopy, X-ray photoelectron spectroscopy (XPS) and thermogravimetric analysis (TGA) (Jokerst et al., 2011), which may provide information for the identification of the surface bound molecules as well for analysis of functional groups.

117. Bound multiple ligands may also be qualified and quantified by using Liquid chromatography–mass spectrometry (LC/MS). However, it should be noted that the ligands can only be analysed once it is cleaved from the particle surface. For example, thioctic acid and its derivatives were used to chemically modify surfaces of AuNPs. The ligands were cleaved when the AuNPs were oxidised in the presence of Iodine (I_2) and analysed (qualitative and quantitative) using a LC/MS/UV system (Zhang and Yan, 2010).

12.1. Stability of surface coatings and ligands in biological and environmental media

118. It is imperative to study the stability or biodurability of these ligands as this will affect the fate, lifetime and toxicity of NMs. It is additionally known that surface ligands with low affinity towards the particle surface, can easily be displaced by other higher affinity ligands. For example, with α-Fe_2O_3 nanoparticles (Fe_2O_3NPs) coated with aspartic acid, it was shown that the coating would remain on the surface if there were no competing molecules in the media. As the complexity of the media increased, different components were found to adsorb onto the surface and displace the coating

(Mudunkotuwa and Grassian, 2015). However, when using a high molecular weight SH-PEG, the functional groups were not displaced by the bovine serum albumin (BSA) molecule, and the ligands co-adsorbed after rearrangement of the existing functional groups (Tsai et al., 2011). A similar process was observed for carbon nanotubes when tested *in vivo* where the synthetic surfactant (Pluronic F108) molecules were displaced by blood proteins within seconds (Cherukuri et al., 2006).

119. Surface coatings and ligands can also be eroded or removed through reactions with other chemicals in their surroundings. For example, the protective aluminium hydroxide ($Al(OH)_3$) layer that is designed to prevent the formation of ROS such as $OH^{\cdot}$ and O_2^{-} in nano TiO_2-based sunscreen formulations was removed when in contact with swimming pool water (Virkutyte et al, 2012; Virkutyte and Al-Abed, 2012) and sea water (Virkutyte and Al-Abed, 2012). However, the $Al(OH)_3$ coating was shown to remain intact on the surface of the TiO_2NPs in deionized water (Auffan et al, 2009; Nickel et al, 2012), while organic molecules such as polydimethylsiloxane (Auffan et al, 2009; Labille et al, 2010) and dimethicone/glycerol (Nickel et al, 2012) were desorbed. Furthermore, the stability of dimethicone/glycerol molecules was shown to be greatly affected by the level of energy input in form of stirring and sonification, where the release of the organic coating increased with increasing energy input (Nickel et al, 2012).

120. Within both vertebrates and invertebrates, ligands on NMs are shown to be non biodurable due to their degradation. For example, it has been proposed that the desorbed ligands are metabolised subsequently to desorption. For example, covalently PEGylated SWCNTs were shown to be slowly defunctionalised in liver, while they were very stable against biotransformation in spleen for more than 8 weeks. It was therefore concluded that the biodegradation of these ligands were organ-dependent and therefore may require individual evaluation for each accumulation organ (Yang et al., 2009). Also, the lipid coating of lysophophatidylcholine SWCNT (LPC-SWNTs) was shown to undergo digestion in *D. magna* (Roberts et al., 2007).

12.2. Influence of surface coatings and ligands on (bio)-durability and subsequently (bio)-persistence of NMs *in vitro* and *in vivo*

121. The studies in the literature regarding the effect of surface coatings and ligands on the biodurability on NMs are limited to only few of the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials.

12.2.1. Carbon nanotubes

122. The influence of surface coatings and the presence of different types of ligands on the durability of number of CNTs due to dissolution or degradation in biological and environmental media *in vivo* as well as in cellular and acellular *in vitro* systems were investigated. Degradation is expected to play a minor role with non-functionalised SWCNTs since they are essentially insoluble in any solvent (Bahr et al., 2001) while their functionalisation with hydrophilic oligomeric or polymeric molecules is expected to increase their solubilisation (Huang et al., 2003, Shiral Fernando et al., 2004).

123. *In vivo* experiments have shown that functionalisation of SWCNT could affect their clearance. For example, it was shown that the degree of PEGylation of SWCNTs (approximately 100 nm in lenght) increased their clearance and that those SWCNTs functionalised with diethylenetriaminepentaacetic (DTPA) group could not be retained in the liver or spleen, and were rapidly cleared from the blood through renal excretion

(Singh et al., 2006, Allen et al., 2009, Kagan et al., 2010, Farrera et al., 2014, Kagan et al., 2014). This was attributed to an enzymatic biodegradation of functionalised SWCNTs as when myeloperoxidase-deficient mice were exposed to these CNTs, impaired clearance and enhanced pulmonary/fibrotic response could be observed (Shvedova et al., 2012) while the biodegradation of these functionalised nanotubes was shown to induce no inflammatory response when aspirated into the lungs of C57BL/6 mice (Kagan et al., 2010).

124. *In vitro* acellular systems using phagolysosomal fluid showed that upon functionalisation of the SWCNTs (1–2 nm diameter) with a carboxyl ligand, their solubility increased and so their degradation (length reduction from 1.9 to 0.4 μm) after 90 days whereas unmodified or pristine SWCNTs would not degrade under these conditions (Liu et al., 2010). Other *in vitro* acellular systems confirmed that indeed functionalisation could also affect their enzymatic degradation (Russier et al., 2011). For example, (517 ± 372 nm) SWCNTs fuctionalised with a carboxyl ligand increased their propensity to biodegradation by HRP and low concentrations of H_2O_2 (~40 μM) at 4 °C over a period of 12 weeks. It was therefore stated that this may give an indication on how the functionalised SWCNTs would react *in vivo* when exposed to the HRP enzyme, and ultimately on how functionalisation influences their biodurability and biopersistence (Allen et al., 2008). On the other hand, pristine SWNTs (diameter of 1.3 nm, length 1.8 nm) could not be degraded by HRP incubation, but they could be degraded by either hemin or $FeCl_3$ (Allen et al., 2009).

125. Other enzymes such as myeloperoxidase (MPO) were also shown to be capable of degrading SWCNTs functionalised with carboxyl ligands. For example, PEG functionalised SWCNTs (1 – 7 nm long) were enzymatically degraded by MPO under *in vitro* conditions using recombinant MPO or *ex vivo* using freshly isolated primary human neutrophils after 7 days of incubation. The degradation was observed through a decrease in the length of the nanotubes. It was found that the degradation efficiency of the enzyme decreased as the molecular weight of the PEG chain increased (Bhattacharya et al., 2014). The degradation of SWCNTs with MPO was found to be more effective than with HRP (Vlasova et al., 2011).

126. Enzymatic biodegradation of pristine and functionalised SWCNTs by the peroxidase and laccase of the saprotrophic white-rot fungi *T. versicolor* and *Phlebia tremellosa* was also investigated. It was shown that functionalisation of SWCNT is essential to upregulate enzymes that may be capable of decomposing CNTs in the environment (Berry et al., 2014). In addition, when the transformation of SWNTs and oxidized (carboxylated) SWCNTs (O-SWCNTs) using three ligninolytic enzymes lignin peroxidase, manganese peroxidase (MnP), and laccase was investigated, it was found that MnP was capable of degrading SWCNTs only but not O-SWCNTs suggesting that oxygen-containing surface functionalities do not necessarily facilitate the biodegradation of carbonaceous NMs, as is commonly assumed (Zhang et al., 2014)

127. An *in vivo* biodegradation study showed also that amino functionalised MWCNTs could be partially degraded within the microglia of the brain cortex in 2 to 14 days, following stereotactic administration (Nunes et al., 2012). On the other hand, *in vivo* studies with tangled oxidized MWCNTs (t-ox-MWCNTs) implanted into rat subcutaneous tissues showed that the majority of the large tangled oxidized CNTs were present in the intercellular space, maintained a layered structure, and did not undergo degradation while small tangled oxidized CNTs were found inside macrophages, where they were gradually degraded in lysosomes (Sato et al., 2013).

128. *In vitro* acellular enzymatic biodegradation rate of MWCNTs (diameter 14 nm and length 1 μm) in the presence of HRP and H_2O_2 showed an increase in biodegradation by the introduction of nitrogen-containing functional groups, where nitrogen-doped MWCNTs were shown to be completely degraded enzymatically within 80 days (Zhao et al., 2011). Recently, it was explained that specific functional molecules can enhance the catalytic activity of specific enzymes, which subsequently may enhance their degradation (Sureshbabu et al., 2015).

129. In natural aquatic environments MWCNTs were shown to be aggregated at sodium cations (Na^+) concentration of above 4.0 mM or and pH of 4.0 (Zhang et al., 2011a). However, the MWCNTs could be stabilised by the presence of dissolved organic matter (DOM) even with a high sodium concentration (40 mM), a concentration beyond those relevant to fresh water systems. Functionalisation by hydroxylated and carboxylated groups could also be observed to reduce the sedimentation of 10–30 nm MWCNTs (20-25 in diameter and 10 to 30 μm in length). Therefore, the presence of DOM in natural water and functionalisation are expected to increase the persistence of MWNTs in water and consequently increase the probability of exposure (Kennedy et al., 2008).

12.2.2. Cerium Oxide nanoparticles

130. The role of funtional groups on the persistence and bioaccumulation of CeO_2NPs and ZnONPs in environmental media was also investigated. For example, it was shown that those that have been derivatised with ionisable or hydrophilic groups are expected to be much more soluble in water and consequently, less persistent (Wudl, 2002) while in aquatic environments, their stabilisation by humic and fulvic acids was shown to increase their persistence (Zhang et al., 2011b). The funtionalisation of 13.9 nm CeO_2NPs with carboxymethyl dextran (CM-CeO_2NPs), 17.8 nm CeO_2 with dextran (DEX-CeO_2NPs), and 15.3 nm CeO_2 with diethylaminoethyl dextran CeO_2-NPs (DEAE-CeO_2-NPs), could increase their bioaccumulation in *Caenorhabditis elegans* (Collin et al., 2014).

12.2.3. Quantum dots nanoparticles

131. It was assumed that when QDs are capped with a ZnS shell their stability in biological systems is improved. The stability of 19 nm CdTe/ZnS QDs *in vivo* was therefore investigated after 28 days of intravenous injection to male ICR mice and degradation of the coating and release of core cadmium was confirmed (Liu et al., 2013a). Similarly, it was found that after oral exposure of female Nu/Nu and CD-1 mice, a number of Cd QDs coated with 3-mercaptopropionic acid (MPA) and pendant thiol groups were not able to protect QDs from chemically induced degradation and surface modification while coatings with a combination of polythiol ligands and silica shell could protect against chemically induced degradation and surface modification both in strong acidic solutions *in vitro* and in animals *in vivo* (Loginova et al., 2012).

132. The effect of coating and functionalisation on the susceptibility to degradation was also investigated for 19 nm CdTe/ZnS QDs using an *in vitro* acellular system where it was shown that they were not stable in *in vitro* acellular tests conducted at neutral pH after 20 days of dialysis in a phosphate buffered saline (PBS) solution (Liu et al., 2013a).

133. Such biodegradation was also observed in acidic conditions for trioctylphosphine oxide (TOPO) capped QDs and gum Arabic coated TOPO capped QDs in the digestive tract of *D. magna* after absorption, followed by rapid excretion within a few hours (Kwon et al., 2012).

134. Similar instability of QDs was also reported in environmental media. QDs of 3.2 nm coated with hydrophilic thiols were demonstrated to be photochemically unstable involving photocatalytic oxidation of the thiol ligands and photo-oxidation of the nanocrystals (Aldana et al., 2001). These covalently bound thiol groups were shown to desorb from the surface of 1.4 nm and 1.8 nm QDs at low particle concentrations (Döllefeld et al., 2002).

12.2.4. Silver nanoparticles

135. *In vitro* acellular dissolution studies in different electrolyte solutions have shown that certain ligands present on the surfaces of AgNPs may provide more stability to these nanoparticles with a decrease in their dissolution and aggregation. For example, differences in the dissolution behaviour of citrate-and PVP-capped AgNPs could be observed (Huynh and Chen, 2011) where the AgNPs coated with PVP had a greater stability compared to citrate coated AgNPs, with a decrease in dissolution and aggregation in the later (Gondikas et al., 2012, Kent and Vikesland, 2012). Similar observations were made earlier where the PVP-capped particles have shown 50% dissolution compared to citrate-capped AgNPs with 14% dissolution (Kittler et al., 2010). On the other hand, for some surface modifications, the amount of material released did not seem to vary as was the case with uncoated, citrate-capped, and Tween coated AgNPs (Li et al., 2011b). However, although some coatings are shown to have no direct effect on dissolution, they are shown to have effect on the kinetics of the dissolution (Ma et al., 2011). Similarly, the presence of strong complexing ions/molecule (ligands) in different biological and environmental media has shown to increase the dissolution of AgNPs, by forming new complexes that were thermodynamically more favoured. For example, thiol ligands such as cysteine and methionines (Bell and Kramer, 1999, Behra et al., 2013), and proteins (Martinolich et al., 2012) could increase dissolution.

136. In environmental media, the presence of natural capping agents such as humic and fulvic acids are shown to affect the transformation of Ag^+ to AgNPs (Adegboyega et al., 2012). On the other hand, the dissolution of 39 nm PVP-capped AgNPs was shown to result in Ag_2S and thus affecting surface properties of the AgNPs in terms of surface charge and the dissolution rate (Levard et al., 2011). A later study has also shown that the levels of PVP-capped AgNPs (50 nm) in a lake mesocosm would decline rapidly in the first 12 hours, followed by a slower decline with a halftime of about 20 days (Furtado et al., 2014). The presence of ligands on surfaces of AgNPs was also shown to affect their behaviour in natural waters. For example, citrate-stabilized AgNPs were stable in natural freshwaters (Chinnapongse et al., 2011) while uncoated 90.5 nm AgNPs would rapidly sediment from the water column and their functionalisation with PVP would reduce their sedimentation (Quik et al., 2014).

12.2.5. Gold nanoparticles

137. In the aquatic environment, it was shown that humic acid enhanced the stability of sodium acrylate-stabilized and citrate-stabilized AuNPs of sizes ranging from 15 to 22 nm at extreme pH values through substitution and/or coating of the original stabilizing ligands. However, there was rapid aggregation at high ionic strengths (0.1 M) (Diegoli et al., 2008).

12.2.6. Dendrimers

138. Dendrimers are multivalent ligands with the presence of a high number of reactive terminal groups. They can be water-soluble when their end-groups are hydrophilic such as hydroxyl, amino, and carboxyl groups. The biodegradability of dendrimers is an important attribute that will prevent their bioaccumulation. For example, the most widely studied dendrimers, Polyamidoamine (PAMAM), with primary amines on the surface and tertiary amines in the interior, are hydrolytically degradable only under harsh conditions because of their amide backbones and hydrolysis proceeds slowly at physiological temperatures (Tang et al 1996). More promising in terms of hydrolytic degradability are dendrimers based on polyester backbones (Grinstaff et al. 2002; Seebach et al. 1996; Ihre et al 2002) where in one example, polyester dendrimers have been carefully designed such that the ester hydrolysis products are nontoxic, natural metabolites (Grinstaff et al 2002) whereas in another instance high molecular weight polyester dendrimers and dendronized polymers have been shown to degrade to putative excretable and nontoxic lower molecular weight species (Gillies et al 2005; Lee et al 2004).

139. The biodegradation of dendrimers *in vivo* and *in vitro* was also found to be affected by the presence of different surface ligands. Within *vivo* experiments, it was found that smaller PEGylated dendrimers were degraded in the lungs to low molecular weight products that were subsequently absorbed and excreted via the urine. In contrast, larger dendrimers were retained in the lungs for longer periods for up to 7 days (Ryan et al., 2013).

140. *In vitro* experiments have indicated that dendrimers and dendrons containing thiol-reactive disulfides within their branches should possess the ability to be cleaved under the reducing conditions encountered inside of cells (Zhang et al 2003; Rendle et al 2004). In addition, dendrimers that are composed of bonds that are enzyme substrates are biodegraded (Seebach et al 1996; Córdova et al 2001; Haba et al 2005). On the other hand, dendrimers with polyester backbones are reported to be readily enzymatically degradable through hydrolysis in the presence of hydrolytic enzymes such as poly(3-hydroxybutyrate) depolymerase isolated from *Alcaligenes faecalis*, **a** Gram-negative, aerobic, rod-shaped bacteria (Seebach et al., 1996) while the degradation of Side-Chains of N-2- (Hydroxypropyl)Methacrylamide Copolymers was achieved by Lysosomal Thiol Proteinases (Duncan et al 1983).

141. Chitosan-dendrimer hybrids were also found to be biodegraded in standard activated sludge between 2.8 to 33% within 27 days (Sashiwa et al., 2003).

13. Toxicological Implications of Dissolution and Biodegradation

142. Mineral particles and fibres are constantly being inhaled and ingested by humans while most of them are not pathogenic and only a few are pathogenic and cause different diseases. Characteristics such as size, density, morphology, crystallinity, chemical characteristics, and biopersistence and biodurability assessed through their dissolution and biodegradation can all play a role in the short-term toxicity and long-term pathogenic effects of minerals (Van Oss et al., 1999, Plumlee et al., 2006).

13.1. Biodurable fibres with toxicity and pathogenicity

143. Biopersistence (i. e. the ability of a material to persist in the body due to their biodurability in spite of physiological clearance mechanisms) specified by the retention halftime, will dictate the likelihood that inhaled mineral fibres will reach the pleura and the impact that they will have there, and is regarded as one of the most important determinants of the pathogenicity of that mineral. It is therefore the biopersistence of a mineral that is regarded as one of the most important determinants of its pathogenicity (Oberdörster et al., 1994, Hesterberg and Hart, 2000, Oberdörster, 2000, Donaldson et al., 2006). The biodurability can be viewed as resistance to dissolution and subsequent fragmentation, transverse breakage, or were fragmented into smaller parts in the case of glass fibres which can more easily be cleared from lungs (Hesterberg et al., 1998a; 1998b; Warheit et al., 2001). However, when fibres break longitudinally, as in the case of chrysotile or amosite asbestos, resulting in more fibres of the same length with a smaller diameter, the biodurability increases (Wylie et al. 1997; Berman et al., 1995).

144. The potential health effects of inhaled mineral particles in relation to their dissolution is now well established (Maxim and McConnell, 2001) where evidence has indicated that biodurable minerals exhibit fibrotic or carcinogenic potential in animal studies and therefore the measurement of biodurability has been used successfully to predict biopersistence (Bernstein et al. 2001, Donaldson and Tran, 2004). For example, several animal inhalation studies have indicated that oncogenic potential of elongated mineral particles can be determined by their biopersistence and that in addition to being a linear function of exposure concentration, is also a linear function of the weighted halftime observed in inhalation studies with rats (Mast et al., 2000, Bernstein et al., 2001, Moolgavkar et al., 2001). However, dosimetry models

145. for rodents and humans have indicated that, on a normalised basis, clearance rates for these mineral particles were lower in humans than in rats (Maxim and McConnell, 2001) and therefore, results from chronic inhalation studies with rodents were seen to underestimate risks for humans, accordingly it was proposed that adjustment for kinetic differences in particle clearance and retention in rats is required to predict lung disease risks in humans (Kuempel et al., 2001).

146. The correlation between the results of *in vitro* acellular dissolution measurements and fibre durability in the lung has also been established (Oberdörster, 1996, Maxim et

al., 1999, Searl et al., 1999) which in turn, as was indicated earlier, has correlated well with their pathogenicity (Harrison et al., 1999, Hesterberg and Hart, 2000). For example, a low biopersistence of MMVFs has often been related to a high *in vitro* dissolution rate at near-neutral pH and/or acidic pH resulting in a fast *in vivo* clearance rates (Guldberg et al., 1998, Kamstrup et al., 1998) and dissolution rates may be used to estimate whether disease would ensue following inhalation or intraperitoneal injection in animal studies (Eastes et al., 2000a). A similar mechanism of fibre biopersistence and the hypothetical model was proposed for CNTs (Ma-Hock et al., 2009b, Donaldson et al., 2010).

13.2. Particles with low dissolution rate

147. A number of industrially relevant biodurable micro- and nano-sized particles with low dissolution in biological fluids has been identified including TiO_2 and CeO_2 (Oberdörster, 2002, Roller and Pott, 2006, Dankovic et al., 2007, Gebel, 2012). Despite non convincing evidence for a relevant specific systemic toxicity of these particles (Moreno-Horn and Gebel, 2014), but due to their primary genotoxicity (Schins and Knaapen, 2007), it was proposed that their responses after long-term exposure need to be further evaluated due to their accumulation in systemic organs (Shi et al. 2013).

148. Prolonged exposure and high lung burdens of biodurable particles are shown to lead to impairment of macrophage mediated clearance (Borm et al., 2015). This overload condition is also accompanied by increased particle transfer to the lymph nodes and their accumulation in the lung leading to chronic inflammation, increases in lung weights, epithelial cell proliferation, fibrosis, and possibly lung cancer in rats (Lee et al., 1986, Cullen et al., 2000). For example, CeO_2NPs which were shown to be biopersistent, at low lung burdens, they were shown to be cleared at physiological rates whereas at higher concentrations, they were shown to induce retarded clearance and toxicity with inflammation and subsequent granulomatous reaction already after short-term exposure (Keller et al., 2014). Similar toxicities were also observed upon short-term inhalation of TiO_2NPs (Ma-Hock et al., 2009a, Eydner et al., 2012) where they elicited a persistently high inflammatory reaction in the lungs of the animals compared to the larger-sized particles, including epithelial effects (Type II cell proliferation; occlusion of pores of Kohn) and the beginning of interstitial fibrotic foci and thus confirming a correlation of the persistence and adverse effects (Oberdörster et al., 1994).

13.3. Particles with high dissolution rate

149. Dissolution of metal ions from a number of oxide nanoparticles is a key factor in their toxicity (Borm et al., 2006b, Brunner et al., 2006, Navarro et al., 2008b, Horie and Iwahashi, 2014). The cytotoxic activity of nanoparticles depends upon which metal is released. Previous studies report that ZnO and copper oxide (CuO) nanoparticles release Zn^{2+} and copper ions (Cu^{2+}), respectively, into the culture medium, where they induce severe cellular oxidative stress (Karlsson et al., 2008, Fukui et al., 2012, Moschini et al., 2013). The complex correlations of dissolution and toxicity could therefore be elucidated with ZnONPs and Zn^{2+} ions in different media (Xia et al., 2008, Li et al., 2011a). It was therefore suggested that for accurate *in vivo* testing of nanoparticles, one should also consider the effects of metal ion release on their toxicity (Horie and Iwahashi, 2014). It was therefore hypothesised that upon phagocytosis of nanoparticles, rapid pH-dependent dissolution of ZnONPs inside of phagosomes is the main cause of ZnONP-induced diverse progressive severe lung injuries (Cho et al., 2011).

150. Furthermore, there can be a complex interplay between the nanoparticles and the dissolution ions where a suspension of these nanoparticles may contain different forms of the metal including the metal in the nanoparticulate form, free/complexed metal ions and metal ions adsorbed to the nanoparticles. The existence of all these forms of the metal can significantly affect the biological response to these NPs (Liu and Hurt, 2010). Consequently, it can be concluded that as the concentration of intracellular metal ion increase, various cytotoxic mechanisms are also induced, such as enhanced oxidative stress and enzyme dysfunction (Fukui et al., 2012, Cronholm et al., 2013). Indeed, using a recirculating tangential flow filtration system, it was possible to confirm that the dissolution of ions appears to exacerbate the toxicological effect (Maurer et al., 2014). As expected, following administration of 20 nm and 250 nm anatase TiO_2NPs to Fischer 344 rats through inhalation a correlation could be observed between biological effects in both the alveolar and interstitial space and the biopersistence of particles in the respective compartment (Oberdörster et al., 1994).

14. Summary and Recommendations

151. The biopersistency of larger particles and fibres - biodurable due to little dissolution and degradation with low clearance from the tracheobronchial airway - seems to be a major determinant of their pathogenic potential. The clearest evidence is provided from comparative studies of toxicity and carcinogenicity of mineral and vitreous fibres where an increasing rate of dissolution in lung fluid is well-matched with their increasing ability to produce long term effects such as lung fibrosis and cancer. Low dissolution and degradation of some NMs also result in long persistence in environmental settings.

152. Published data on the biodurability or lack of it through dissolution and biodegradation in biological and environmental surroundings of the NMs on the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials has indicated that:

153. Those that are shown to be not amenable to dissolution and (bio)-degradation and hence be biodurable in biological and environmental media may include:

- Pristine SWCNTs and MWCNTs are not degraded in neutral biological and environmental conditions and hence they may be considered biodurable. They are however amenable to degradation in acidic conditions and also in the presence of peroxidases. In both biological and environmental conditions, the presence of surface coatings with specific functional groups could facilitate their degradation and hence could decrease their biodurability.
- Cerium oxide nanoparticles appear to be biodurable in biological and environmental conditions and the presence of ligands and functional groups increases their biodurability especially in environmental media
- Fullerenes appear to be biodurable in both biological and environmental conditions. The functionalisation of fullerenes increases their biodurability, especially in environmental media.
- Silicon dioxide nanoparticles appear to be biodurable in both biological and environmental conditions.
- Titanium dioxide nanoparticles have low clearance rates, are biodurable in organisms and consequently appear to accumulate in organs. AuNPs appear to accumulate in organs and not prone to dissolution and therefore are biodurable. Their functionalisation could further stabilise these nanoparticles in the environment.
- Fe_3O_4NPs are prone to dissolution in both biological and environmental media only in acidic conditions and appear to be biodurable and hence amenable to bioaccumulation in neutral conditions.

154. Those that are shown to be amenable to dissolution and biodegradation and hence may not be biodurable may include:

- QDs are prone to dissolution in biological and environmental media and therefore are not biodurable. Their functionalisation could not protect them from such biodegradation.
- AgNPs although were amenable to dissolution, appear to be biodurable in some organs including brain and testes. They are also prone to dissolution in environmental conditions but with complex mechanisms due to their transformation to other forms depending on the composition of the environmental media. The functionalisation of silver nanoparticles either increases or decreases their dissolution in biological media and also affects their transformation in environmental media.
- ZnONPs appear to be not biodurable with high dissolution rates in biological fluids. They also appear not to be persistent in the environment but they are prone to transformation in environmental media.

155. Those that are not as yet been investigated for their biodurability either through dissolution or biodegradation may include:

- Dendrimers whose biodegradability depends on the type of the polymer in biological media but no studies have yet been conducted on their degradation in the environment.
- Nanoclays whose intracellular accumulation has been shown in biological media but no studies have yet been conducted on their degradation in the environment.
- Al_2O_3NPs were found to bioaccumulate but although their dissolution is shown in water, their biodurability is not as yet confirmed in biological and environmental media.

156. The fact that NMs with high dissolution rate are not biodurable and hence may cause short term toxicity and health effects, opposed to those with slow dissolution rate which are biodurable and hence may cause both short and long term health effects and show high environmental persistency makes it necessary to assess their biodurability through appropriate studies including dissolution for some metal and metal oxides and the biodegradation for carbonaceous NMs.

157. To increase the predictive potential of these tests, the existing identified *in vitro* and *in vivo* standard techniques should further be validated in relation to their ability to predict pathogenic potential and environmental persistence of NMs. Acknowledging the importance of biodurability, increasing number of nanotoxicology studies have therefore incorporated dissolution and/or biodegradation studies for NMs to further support the interpretation of the long term biological response to NM exposure. A harmonisation of such kind of approaches, within the limits imposed by scientific knowledge, the heterogeneity of NMs and the diverse biological and environmental compartments would be highly recommended.

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