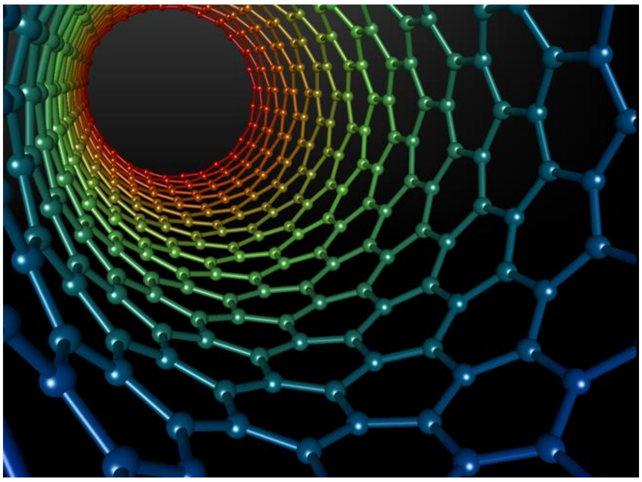
HOUSES OF PARLIAMENT
PARLIAMENTARY OFFICE OF SCIENCE & TECHNOLOGY

POSTNOTE

Number 562 October 2017

Risk Assessment of Nanomaterials



The unique properties of engineered nanomaterials are beneficial to a range of industries. However, uncertainties in assessing their potential health and environmental risks could hinder their safe use. This POSTnote summarises the current regulation of nanomaterials and highlights potential future directions for regulatory testing approaches.

Overview

- Nanomaterial uses and benefits are diverse and increasing, such as in cosmetics, textiles, electronics and medicine.
- Current regulatory frameworks applicable to nanomaterials within the UK are mainly set at EU level.
- There are some indications of potential health and environmental risks, but conclusions are limited by insufficient long-term evidence and difficulties in translating results from the laboratory to the real world.
- Post-Brexit, the UK will need to establish regulatory frameworks for nanomaterials.
- The wide range of forms and uses of nanomaterials present many regulatory challenges, such as ensuring consistency in testing and finding valid ways of grouping nanomaterials so that their risks may be assessed more efficiently.

Background

'Nanomaterials' generally refers to materials containing a significant proportion of particles with at least one dimension between 1-100 nm (a nanometre is one-billionth of a metre), which is about a thousandth of the width of human hair.[1,2] Nanoscale materials can include nanoparticles, nanotubes and nanofilms.[3] However, the regulatory definition is still being debated.[4] This POSTnote focuses on engineered nanomaterials, but they may also be produced naturally, e.g. in volcanic ash, or incidentally by human activity, e.g. by the combustion of fossil fuels and fragmentation of microplastics.[5,6,7]

Current Applications of Nanomaterials

Applications of nanomaterials are wide ranging (Box 1) and increasing. Over 1,800 known products already on the market contain engineered nanomaterials and this is expected to grow.[8] Exact global annual production quantities are unknown, but are estimated at up to 1,000 tonnes for carbon nanotubes and up to 10,000 tonnes for titanium dioxide nanomaterials.[9] According to industry reports, nanotechnology is estimated to be worth over US$173 billion globally by 2025.[10] The diversity and rapid development of new nanotechnology applications makes assessing their effects difficult. The nano form of a chemical often has very different properties to larger particles of that chemical. For instance, silver nanoparticles have stronger

Box 1. Applications of nanomaterials

- **Silver nanoparticles** have antibacterial properties and are used widely in antibacterial sprays, clothing and deodorants.[11,12,13]
- **Zinc oxide nanomaterials** block UV light and are used in sunscreens, as well as in cosmetics and fertilisers.[14,15,16]
- **Titanium dioxide nanomaterials** are also used in sunscreens due to their UV blocking properties, as well as in catalysts to reduce pollution from vehicles and power stations.[14,17,18]
- **Cerium oxide nanoparticles** are used in diesel fuel to reduce particulate emissions.[19]
- **Gold nanoparticles** are used in medical applications such as medical imaging (e.g. x-ray) (Box 3).[20]
- **Quantum dot nanoparticles** are semiconductors used in a range of applications such as TVs, computing and solar cells.[21]
- **Carbon nanotubes** are very strong nanomaterials and applications include wind turbine blades and sports equipment.[22]
- **Graphene nanomaterials** are highly conductive and so are useful for electronics and batteries.[23]
- **Fullerene nanoparticles** have antioxidant properties that are used in skin care products and cosmetics.[24]
- **Silica nanoparticles** are used in various coatings, such as for increasing scratch resistance, as well as for drug delivery.[25,26]
- **Clay nanomaterials** have been added to plastics; for instance, in food packaging to enhance their ability to act as a barrier to oxygen and thus reduce food spoiling.[27]

anti-bacterial properties than larger silver particles and a range of applications from sterilising medical equipment to preventing odours in clothing.[13] In 2014-15, Defra and Sciencewise conducted a study into public attitudes towards nanomaterials,[28] which showed that participants were generally more in favour of applications when they perceive the exposure risk to be low; for instance, the use of nano-materials in paint rather than in sunscreen. However, the perception of risk by consumers may not reflect actual risk.

Regulation of Nanomaterials

A range of EU regulatory frameworks may apply to the production and use of nanomaterials (Box 2).[29] The predominant regulation is the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).[30]

Under REACH, all substances that are manufactured or imported into the EU at volumes over one tonne per year must be registered by the manufacturers and importers. For each substance, REACH requires a dossier of information supplied by industry on the toxicology, eco-toxicology and the physical and chemical properties of the substance in all forms, including in nano form. The European Chemicals Agency (ECHA) has developed REACH guidance documents providing specific recommendations for the characterisation and hazard assessment of nanomaterials but these are not mandatory.[31] Modifications of REACH to specifically address nanomaterials are currently under review by the European Commission and are being discussed with member states.[32]

Under the Organisation for Economic Co-operation and Development (OECD) agreement of the Mutual Acceptance of Data in the Assessment of Chemicals (MAD), results from tests that follow OECD guidelines must be accepted by all member states,[33] including:

- Physical and chemical properties
- Environmental fate (degradation and accumulation)
- Environmental and mammalian toxicology.

However, these guidelines were not specifically developed for nano-scale chemicals. The OECD have developed guidance for testing nanomaterial safety and are still revising MAD for use with nanomaterials.[34,35]

Possible Risks of Nanomaterials

Assessment of the risk posed by engineered nanomaterials is based on both the hazard that they present and the level of exposure.[36] The diversity of nanomaterials makes it difficult to generalise their risks.[37] The toxicity of nanomaterials may also differ between humans, animals, plants, and the environment.

Potential Human Health Effects

The potential for a nanomaterial to have toxic effects can be related to its physical and chemical properties, such as size, shape, surface area, charge and reactivity, and solubility.[38,39] For instance, certain long multi-walled carbon nanotubes may have a long straight needle-like shape and there are concerns that some of these forms may behave similarly to asbestos fibres inside the body.[40] The properties of nanomaterials may increase the likelihood of chemicals passing through natural barriers in the body,[41] but there is no conclusive evidence for the acute toxicity of nanomaterials by virtue of their size alone.[55] If a chemical is toxic in its larger form, it is likely that it will also be toxic in its nano form, while the reverse is not necessarily true. The distribution of materials in the body and how easily they are cleared by the body's defence system may differ between nanomaterials and larger particles.[56] This is particularly important in more vulnerable populations, such as young children, the elderly and those with pre-existing health conditions.[57,58,59] The human body may be exposed to nanomaterials via a variety of routes, including through the:

- **Lungs:** Inhalation is considered the most likely way for nanomaterials to be introduced into the human body. For example, the handling of dry powders by workers during manufacturing or via the use of sprays by consumers.[60,61,62] Nanomaterials may penetrate deeper into the lungs than larger particles; the deeper they penetrate, the longer it takes for the lungs to clear them.[63] Prolonged exposure increases the risks of any adverse health effects.

Box 2. EU Regulations

Key legislation for regulating nanomaterials in the EU includes:

- **Registration, Evaluation, Authorisation and Restriction of Chemicals** ((EC) 1907/2006) (REACH).[30] REACH is the overarching legislation applying to the manufacturing and importing of chemical substances in the EU. Nanomaterials fall under REACH's definition of a chemical substance, but it was developed prior to their widespread use.
- **Classification, Labelling and Packaging** ((EC) 1272/2008) (CLP).[42] Nanomaterials that meet the hazard criteria of CLP must be classified and labelled.
- **Biocidal Products Regulation** ((EU) 528/2012) (BPR).[43] Biocidal products are products that contain active substances used to protect against harmful organisms, e.g. disinfectants. BPR requires that specific risk assessment tests are conducted on biocidal products containing nanomaterials and that product labelling indicates that it contains nanomaterials.
- **Cosmetic Products** ((EC) 1223/2009) regulation requires pre-market notification for cosmetic products containing nanomaterials and that they are listed in the ingredients of the product (e.g. (nano) Titanium dioxide in sunscreen).[44]
- **Novel Foods** ((EU) 2015/2283)[45] regulation from 2018 will require that engineered nanomaterials are subject to risk assessment and authorisation requirements before being placed on the market.[46] These are linked to requirements to indicate the use of engineered nanomaterials in the list of ingredients.
- **Food Contact Plastics** ((EU) 10/2011)[47] regulation requires that nanomaterials used in plastic materials that come into contact with food undergo explicit authorisation and risk assessment.
- **Medical devices** containing nanomaterials are regulated under: Directive 90/385/EEC (implantable devices);[48] Directive 93/42/EEC (medical devices);[49] Directive 98/79/EC (diagnostic devices).[50] Two new EU Regulations will replace these over the next 3-5 years.[51]
- **Workplace safety** is regulated through the EU Framework Directive 89/391 (which encourages measures to improve worker health and safety) and the EU Framework Directive 98/24 (addresses risks associated with chemical substances).[52,53] Under these directives, the UK implements its own regulations. The main governing regulation relevant to nanomaterials is the Control of Substances Hazardous to Health (COSHH) Regulations, which requires monitoring of exposures.[54]

- **Gastrointestinal tract:** Nanomaterials may be ingested and enter the digestive system, e.g. from the air if mucus is cleared from the lungs and swallowed.[64]
- **Skin:** The skin may be exposed to nanomaterials in cosmetics and toiletries, but is unlikely to be a major route into the body if the skin is healthy and intact.[64,65]
- **Nose**: A small number of laboratory studies have suggested that the smallest nanomaterials inhaled nasally may be transported to the brain. Although the amounts transported are likely to be low (much less than 1% of inhaled nanomaterials), the body is unable to expel nanomaterials from the brain.[66,67]

Once inside the human body, nanomaterials may affect cells; for instance, by interacting with the cell surface or by entering the cell itself. Nanomaterials may become coated in proteins and form a 'corona' around their surface, which further influences their interaction with the body.[68] The composition of this corona can change over time and may affect how nanomaterials are cleared from the body.[69,70] A range of nanomaterials, including silver nanoparticles, have been shown to produce oxidative stress (excessive levels of reactive forms of oxygen), which can cause inflammation and damage a cell's genetic material.[71,72] However, the doses used in testing are much higher than current levels of exposure. There are also concerns that nanomaterials could act as a 'Trojan horse' and carry other, toxic, chemicals that are attached to its surface into cells.[73]

Persistence of Nanomaterials

A small percentage of inhaled nanomaterials may spread more widely around the body as there is only a very thin membrane separating inhaled air from the blood capillaries.[74] Some nanomaterials have been observed to persist in the body. For instance, gold nanoparticles were found in the human body three months after initial exposure.[56] This raises concerns that nanomaterials may circulate and accumulate in certain tissues in the body, but also has important potential benefits for nanomedicine (see Box 3).[75,74] In general, nanomaterials transported by the blood circulatory system are most likely to accumulate in the liver.[76,77] There is currently very little data on the health effects of long-term exposure to nanomaterials as most studies to date focus on short-term exposure effects.[78,79]

Potential Environmental Effects

It is difficult to know exactly how and where nanomaterials may be released into the environment because of the wide range of applications and potential pathways for release.[80] Nanomaterials may be released into the environment at any stage in their life-cycle.[81,82] Release can be intentional, such as for the remediation of contaminated land (Box 4), or unintentional, such as through the disposal or wear and tear of products containing nanomaterials.[83,84] Certain processes and activities during nanomaterial production, such as mixing and weighing dry powders, can often be associated with their release.[61,85] Nanomaterials contained in sunscreen (and cosmetics) are applied directly to skin, which are then washed off and may end up in aquatic ecosystems via wastewater systems or directly during swimming.[86,87]

Box 3. Nanomedicine

Engineered nanomaterials have the potential to provide new advances in medicine.[88,89,90,91] Nanomedicine is predominantly still in the research and development stage, but key potential benefits include:

- Development of new drugs.
- More efficient delivery of existing drugs.
- Targeted drug delivery to tumours.
- Controlled release of drugs.
- Construction of prosthetics and tissue engineering.
- More efficient diagnosis of disease.
- Ability to deliver multiple drugs at once (e.g. for tuberculosis treatment), reducing treatment time and cost.

For example, in the case of diagnosis, gold nanoparticles can be visualised and targeted to specific cell types by modifying their surface chemistry.[20] They are useful for medical imaging, such as X-ray based imaging techniques and Magnetic Resonance Imaging (MRI). In the treatment of disease, nano forms of chemotherapy drugs have been used in lab studies to target specific tumour cells without causing toxicity in healthy cells, which would reduce the side effects of chemotherapy in cancer patients.[88,92] Inhaled nanomedicines have the potential for treating lung disease and infection.[93] The translocation of nanomaterials from the lungs into the blood circulatory system could be used to treat disease elsewhere in the body, such as diabetes, as an alternative to administering drugs via injection.[88,56,74,75]

Freshwater Ecosystems

Engineered nanomaterials may end up in lakes, rivers, oceans, aquatic sediments and soils. When nanomaterials enter water, they tend to aggregate together to form larger particles and settle in the sediment layer.[94,95] So far, most studies into the effects of nanomaterials on aquatic life have focused on freshwater species, such as water fleas, pond snails and fish. Results from these studies suggest that nanomaterials can reduce growth, reproduction, locomotion, breathing and feeding, but these studies used higher concentrations of nanomaterials than current predicted exposure levels.[96,97,98] Furthermore, the wider effects, such as on ecosystem services (PN 542), are unknown.

Marine Ecosystems

Fewer studies have been carried out in the marine environment, but studies so far indicate that results observed in freshwater systems also apply to marine environments.[99,100] For example, nanomaterials have been observed to accumulate in species at the bottom of the food chain, such as macroalgae. which could result in the transfer and accumulation of nanomaterials up the food chain, but there is no clear evidence demonstrating this.[101,102]

Soils

Nanomaterials can enter soils and terrestrial ecosystems via pathways such as the application of sewage sludge, fertilisers and pesticides to plants and soils.[103] Food crops can absorb and accumulate nanomaterials, which can either benefit or harm them.[104,105] The likely concentrations of engineered nanomaterials in soils are estimated to be much smaller than those required to produce toxic effects.[106] However, regular application of persistent nanomaterials to soils could result in concentrations building up over time. In theory, extended exposure to low concentration levels could also lead to long-term effects.

Box 4. Nanoremediation
Nanoremediation is the intentional release of nanomaterials to remediate contaminated soil or groundwater.[83,107,108] It can treat contaminants faster than other remediation methods and can extend the range of treatable contaminants; for instance, to include persistent contaminants such as polychlorinated biphenyls (PCBs).[109,110] The EU funded project NanoRem investigated the toxicity of several nanomaterials commonly used for remediation and found no significant toxic effects on soil and water organisms under standard laboratory test conditions.[111,112] However, other studies have produced mixed results regarding the toxicity of zero-valent iron nanoparticles (a nanomaterial used for nanoremediation) and *in situ* studies are limited.[108,109] The extent of environmental exposure is likely to be low as these nanoparticles tend to have a limited lifespan (on the scale of months) and only travel a few metres from where they are released.[109] A voluntary moratorium on the use of nanoremediation in the UK has been in place since 2005.[28] Defra keeps evidence on the toxicity and fate of nanomaterials under review and will evaluate it in making any future decisions on the moratorium.

Transformation of Nanomaterials
So far, the majority of toxicity studies have focused on the original forms of engineered nanomaterials.[113] A variety of exposure conditions, such as pH or salinity, can transform the physical and chemical properties of nanomaterials and therefore their potential toxicity.[95] Transformed versions of nanomaterials are increasingly being studied, but it is challenging to accurately assess how a nanomaterial's form and behaviour might change throughout its life-cycle. It is not yet known whether the toxicity of nanomaterials will be enhanced or reduced following their transformation, which is likely to depend on the conditions of exposure.[114]

Exposure Data
Studies have demonstrated that is possible to detect engineered nanomaterials in natural systems, but it is challenging because of their diversity.[115] For example, it is difficult to distinguish low concentrations of engineered nanomaterials from background levels of similar naturally occurring nanomaterials in the environment. There may also be seasonal variability in nanomaterial exposure; for instance, because of the greater use of sunscreen in the summer coupled with lower water levels.[87] Models can be used to predict average exposure levels across an environment, but their validation depends on exposure data that is often not readily available because of factors such as those discussed above, and because companies do not typically release production data.[116,117]

Future Options for Regulatory Testing
The UK will need to establish its own regulatory system post-Brexit. As companies will still need to comply with EU regulations to continue exporting products containing nanomaterials to the EU, there is general consensus among stakeholders that the UK should align with these. Future challenges for regulatory testing are set out below.

Inconsistencies in Toxicity Testing
There is a lack of consistency in the generation and storage of nanomaterial toxicity data and the characterisation of their properties.[118] Different approaches are taken to the toxicity testing of nanomaterials in the laboratory and the full methodology is often not reported, making it difficult to compare between studies or to reproduce results.[63,119] A further challenge for toxicity testing is developing laboratory tests that produce results that are representative of nanomaterial toxicity in living organisms, especially for long-term low-level exposure.[120]

Grouping Nanomaterials
Current testing of nanomaterials is conducted on a case-by-case basis. However, given the large and expanding diversity in nanomaterial types, forms and uses, applying full risk assessment testing is likely to be unfeasible.[121,122] Grouping nanomaterials based on their physical and chemical properties enables a 'read-across' approach to risk assessment.[123] This allows data gaps on potential hazards to be filled using information about another nanomaterial in the same group and that has been tested. Challenges include the generation of sufficient data about the properties of nanomaterials to reliably group them.[123]

Predictive Models
In addition to *in vitro* and *in vivo* studies, the toxicity of nanomaterials could also be tested using computer models (*in silico)*.[124] Quantitative Structure-Activity Relationship (QSAR) models are already used to predict the toxicity of standard chemical substances and are based on physical and chemical properties that can be measured or calculated.[125] Nano-QSAR models are currently under development and represent a time- and cost-efficient approach, while reducing the need for animal testing.[126] The relationships established could be used to guide the development of "Safer-by-Design" nanomaterials (Box 5).[127] The success of these models is limited due to insufficient high quality standardised data to validate them.[124]

Nanomaterial Registries
REACH doesn't cover chemical substances produced at volumes under one tonne per year, so some EU member states, including France, Belgium and Denmark, have established mandatory nanomaterial registries.[128] ECHA is creating an Observatory for Nanomaterials as an alternative to an EU- wide registry.[129] The Observatory will be implemented in stages (from 2017) and will collect, analyse and review nanomaterials available on the EU market.

Box 5. Designing Safer Nanomaterials
The aim of Safer by Design nanomaterials is to reduce risks at an early stage of the innovation process by using current scientific knowledge to guide nanomaterial design.[130,131] Application of this concept is still in its infancy and its development requires close collaboration between industry and scientists. Producing Safer by Design nanomaterials has been a research focus in the EU Horizon 2020 project NanoReg2, which will run until 2019,[132] and in the recently completed FP7 project NanoMILE.[133]

Case Study: Zinc Oxide Nanoparticles
It has been suggested that zinc oxide nanoparticles, which are used in sunscreens, may cause DNA damage in human cells at high concentrations.[16,134] Researchers from Harvard University have shown that by encapsulating a zinc oxide nanoparticle in an inert silica-based coating, the risk of DNA damage is significantly lowered without affecting its beneficial UV filtering properties.[135] It is not clear if the coated nanoparticle would comply with EU regulations.

Endnotes

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to Rosa Milodowski for researching this briefing, to NERC for funding her parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Dr Jonathan Wentworth.

1 Size of the Nanoscale
2 The Royal Society and The Royal Academy of Engineering, 2004, Nanoscience and Nanotechnologies: Opportunities and Uncertainties,
3 Working at the Nanoscale
4 Boverhof *et al*, 2015, *Regulatory Toxicology and Pharmacology*, 73.1, 137-150
5 Strambeanu *et al*, 2015, *Natural Sources of Nanoparticles*
6 D'Anna, 2009, *Proceedings of the Combustion Institute*, 32.1, 593-613
7 Galloway *et al*, 2017, *Nature Ecology & Evolution*, 1: 0116
8 Consumer Products Inventory
9 Piccinno *et al*, 2012, *Journal of Nanoparticle Research*, 14.9, 1109
10 Global Nanotechnology Market Analysis & Trends – Industry Forecast to 2025
11 Chen & Schlesener, 2008, *Toxicology letters*, 176.1, 1-12
12 Kim *et al*, 2015, *Journal of Nanomaterials*, 2015:8
13 Wigger, 2017, *Case study: Clothing textiles with incorporated silver nanoparticles*
14 Smijs & Pavel, 2011, *Nanotechnology, Science and Applications*, 4:95
15 Liu & Lal, 2015, *Science of the Total Environment*, 514, 131-139
16 European Commission Scientific Committee on Consumer Safety (SCCS), 2012, Opinion on Zinc Oxide (nano form)
17 European Commission Scientific Committee on Consumer Safety (SCCS), 2013, Opinion on Titanium Dioxide (nano form)
18 Chemical Safety Factsheets: Titanium Dioxide
19 Selvan *et al*, 2009, *Journal of Engineering and Applied Sciences*, 4.7:1819-6608
20 Mieszawska *et al*, 2013, *Molecular Pharmaceutics*, 10.3, 831-847
21 Zhou & Coleman, 2016, *Current Opinion in Solid State and Materials Science*, 20.6, 352-360
22 De Volder *et al*, 2013, *Science*, 339.6119, 535-539
23 Perreault *et al*, 2015, *Chemical Society Reviews*, 44.16, 5861-5896
24 Mousavi *et al*, 2017, Nanomedicine: Nanotechnology, Biology and Medicine, 13.3, 1071-1087
25 Nanotechnology Enables Breakthrough Coatings with Improved Resistance to Chipping, Scratching & Water Spotting
26 Slowing *et al*, 2008, *Advanced Drug Delivery Reviews*, 60.11, 1278-1288
27 Lagaron & Lopez-Rubio, 2011, *Trends in Food Science & Technology*, 22.11, 611-617
28 Public Dialogue to Understand Public Perceptions of Nanotechnologies
29 British Standards Institute (BSI), 2013, Nanomaterials and Nanotechnology-based Products – Guide to Regulation and Standards
30 EU, 2006, Regulation (EC) No 1907/2006*, Off. J. Eur. Union*, L396, 1-849
31 ECHA, Guidance on Information Requirements and Chemical Safety
32 Commission Rejects Idea of EU Nano Register
33 Organisation for Economic Co-operation and Development (OECD), Mutual Acceptance of Data (MAD)
34 OECD, 2009, *OECD Guidance Manual for the Testing of Manufactured Nanomaterials: OECD's Sponsorship Program*
35 OECD Countries Address the Safety of Manufactured Nanomaterials
36 Maynard, 2006, *Nano Today*, 1.2, 22-23
37 Maynard, 2007, *Annals of Occupational Hygiene*, 51.1, 1-12
38 Nel *et al*, 2006, *Science*, 311.5761, 622-627
39 Nel *et al*, 2012, *Accounts of Chemical Research*, 46.3, 607-621
40 Poland *et al*, 2008, *Nature Nanotechnology*, 3, 423-428
41 Zhu *et al*, 2012, *Accounts of Chemical Research*, 46.3, 622-631
42 EU, 2008, Regulation (EC) No 1272/2008, *Off. J. Eur. Union*, L353, 31
43 EU, 2012, Regulation (EU) No. 528/2012, *Off. J. Eur. Union*, L167, 1
44 EU, 2009, Regulation (EC) No 1223/2009, *Off. J. Eur. Union,* L342, 59-209
45 EU, 2015, Regulation (EU) 2015/2283, *Off. J. Eur. Union*, L327, 1
46 Rauscher et al., 2017, *Chemie Ingenieur Technik*, 89.3, 224-231
47 EU, 2011, Commission Regulation (EU) No 10/2011, *Off. J. Eur. Union*, L12, 1
48 EU 1990, Council Directive 90/385/EEC, *Off. J. Eur. Union*, L189, 17
49 EU, 1993, Council Directive 93/42/EEC, *Off. J. Eur. Union*, L169, 1
50 EU, 1998, Directive 98/79/EC, *Off. J. Eur. Union*, L331, 1
51 New EU Rules to Ensure Safety of Medical Devices
52 EU, 1989, Council Directive 89/391/EEC. Off. J. Eur. Union, L183, 0001 – 0008
53 EU, 1998, Council Directive 98/24/EC, *Off. J. Eur. Union*, L131, 23
54 The Control of Substances Hazardous to Health Regulations 2002
55 Donaldson & Poland, 2013, *Current Opinion in Biotechnology*, 24.2, 724-734
56 Miller *et al*, 2017, *ACS Nano*, 11.5, 4542-4552
57 Tang *et al*, 2015, *World Journal of Pediatrics*, 11.3, 197-206
58 Almeida-Silva *et al*, 2014, *Journal of Toxicology and Environmental Health, Part A*, 77.14-16, 867-878
59 Li *et al*, 2014, *International Journal of Molecular Sciences*, 15.3: 3671-3697
60 Bakand & Hayes, 2016, *International Journal of Molecular Sciences*, 17.6, 929
61 Ding *et al*, 2017, *Journal of Hazardous Materials*, 322, 17-28
62 Calderon *et al*, 2017, *Atmospheric Environment*, 155, 85-96
63 Theodorou *et al*, 2014, *International Journal of Molecular Sciences*, 15.12, 23936-23974
64 Tetley, 2007, *Biochemical Society Transactions*, 35.3, 527-531
65 Larese *et al*, 2009, *Toxicology*, 255.1, 33-37
66 Oberdorster *et al*, 2005, *Environmental Health Perspectives*, 113: 823-839
67 Misty *et al*, 2015, *Molecular Pharmaceutics*, 12.8, 2755-2766
68 Nel *et al*, 2009, *Nature Materials*, 8.7, 543-557
69 Monopoli *et al*, 2012, *Nature Nanotechnology*, 7.12, 779
70 Hamad-Schifferli, 2013, *Nanomedicine*, 8.1: 1-3
71 AshaRani *et al*, 2009, *ACS Nano*, 3.2, 279-290
72 Fu *et al*, 2014, *Journal of Food and Drug Analysis*, 22.1, 64-75
73 Valsami-Jones & Lynch, 2015, *Science*, 350.6259, 388-389
74 Choi *et al*, 2010, *Nature Biotechnology*, 28.12, 1300-1303
75 Oberdorster *et al*, 2002, *Journal of Toxicology and Environmental Health Part A*, 65.20, 1531-1543
76 Buckley *et al*, 2017, *Particle and Fibre Toxicology*, 14.1, 5
77 Kreyling *et al*, 2017, *Nanotoxicology*, 11.4, 434-442
78 Kumar *et al*, 2014, *Journal of Nanomaterials*, 2014: 5
79 European Commission, 2017, Assessing the Environmental Safety of Manufactured Nanomaterials
80 Gottschalk & Nowack, 2011, *Journal of Environmental Monitoring*, 13.5, 1145-1155
81 Keller *et al*, 2013, *Journal of Nanoparticle Research*, 15.6, 1692
82 Kohler *et al*, 2008, *Journal of Cleaner Production*, 16.8, 927-937
83 Patil *et al*, 2016, *Environmental Technology and Innovation*, 5, 10-21
84 Shandilya *et al*, 2015, *Environmental Science & Technology*, 49.4, 2163-2170
85 Dahm *et al*, 2012, *Annals of Occupational Hygiene*, 56.5, 542-556
86 Nowack *et al*, 2012, *Environmental Toxicology and Chemistry*, 31.1, 50-59
87 Gondikas *et al*, 2014, *Environmental Science & Technology*, 48.10, 5415-5422
88 Thorley and Tetley, 2013, *Pharmacology and Therapeutics*, 140.2, 176-185
89 Holban *et al*, 2015, Current Pharmaceutical Biotechnology, 16.2, 112-120
90 Zhang & Webster, 2009, Nano Today, 4.1, 66-80
91 Sosnik *et al*, 2010, *Advanced Drug Delivery Reviews*, 62.4: 547-559
92 Peer *et al*, 2007, *Nature Nanotechnology*, 2.12, 751-760
93 Kuzmov & Minko, 2015, *Journal of Controlled Release*, 219, 500-518
94 Cross *et al*, 2014, *Environmental Chemistry*, 12.6: 627-642
95 Lowry *et al*, 2012, *Environmental Science and Technology*, 46, 6893-6899
96 Zhao & Wang, 2011, *Environmental Toxicology and Chemistry*, 30.4, 885-892
97 Asghari *et al*, 2012, *Journal of Nanobiotechnology*, 10.1, 14
98 Croteau *et al*, 2011, *Environmental Science and Technology*, 45.15, 6600-6607
99 Baker *et al*, 2014, *Environmental Pollution*, 186, 257-271
100 Canesi & Corsi, 2016, *Science of the Total Environment*, 565, 933-940
101 Turner *et al*, 2012, *Ecotoxicology*, 21.1, 148-154
102 Matranga & Corsi, 2012, *Marine Environmental Research*, 76, 32-40
103 Gardea-Torresdey *et al*, 2014, *Environmental Science and Technology*, 48.5, 2526-2540
104 Servin *et al*, 2015, *Journal of Nanoparticle Research*, 17.2, 92
105 Rico *et al*, 2011, *Journal of Agricultural and Food Chemistry*, 59.8, 3485-3498
106 Batley *et al*, 2012, *Accounts of Chemical Research*, 46.3, 854-862
107 Fu *et al*, 2014, *Journal of Hazardous Materials*, 267, 194-205
108 Crane & Scott, 2012, *Journal of Hazardous Materials*, 211, 112-125
109 Bardos *et al*, 2015, *Remediation Journal*, 25.2, 83-94
110 Gomes *et al*, 2016, *Nanoremediation coupled to electrokinetics for PCB removal from soil*
111 NanoREM Bulletin 4: A Guide to Nanoparticles for the Remediation of Contaminated Sites
112 No Significant Toxicological Effects for Nanoparticles
113 Holden *et al*, 2016, *Environmental Science and Technology*, 50.12, 6124-6145
114 Mitrano *et al*, 2015, Environmental International, 77, 132-147
115 Jiménez & van Tongeren, 2017, *Modelling the Toxicity of Nanoparticles*
116 Gottschalk *et al*, 2013, *Environmental Pollution*, 181, 287-300
117 Hendren *et al*, 2011, *Environmental Science and Technology*, 45, 2562-2569
118 Krug, 2014, *Angewandte Chemie International Edition*, 53.46, 12304-12319
119 Kong *et al*, 2011, *Nanomedicine*, 6.5, 929-941
120 Hussain *et al*, 2015, *Toxicological Sciences*, 147.1, 5-16
121 Oomen *et al*, 2014, *Nanotoxicology*, 8.3, 334-348
122 Dekkers *et al*, 2016, *Regulatory Toxicology and Pharmacology*, 80, 46-59
123 Oomen *et al*, 2015, *International Journal of Environmental Research and Public Health*, 12.10, 13415-13434
124 Oksel *et al*, 2015, *Particuology*, 21, 1-19
125 Cherkasov *et al*, 2014, *Journal of Medicinal Chemistry*, 57.12, 4977-5010
126 Winkler *et al*, 2013, *Toxicology*, 313.1, 15-23
127 Lynch *et al*, 2014, *Nano Today*, 9.3, 266-270
128 Regulating the Unknown: National Mandatory Nano Registers on the Rise
129 ECHA, 2016, ECHA Programming Document 2017-2019,
130 Gottardo *et al*, 2017, NANoREG framework for the safety assessment of nanomaterials
131 Morose, 2010, *Journal of Cleaner Production*, 18.3, 285-289
132 NanoReg2
133 NanoMILE
134 Sharma *et al*, 2009, *Toxicology Letters*, 185.3, 211-218
135 Sotiriou *et al*, 2014, *Environmental Science: Nano*, 1.2, 144-153