

Nanomedicine

new solutions
or new problems?



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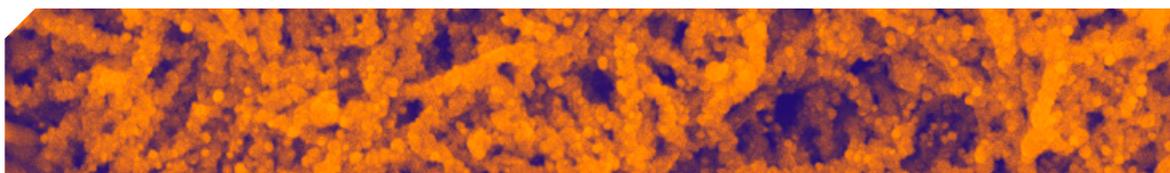
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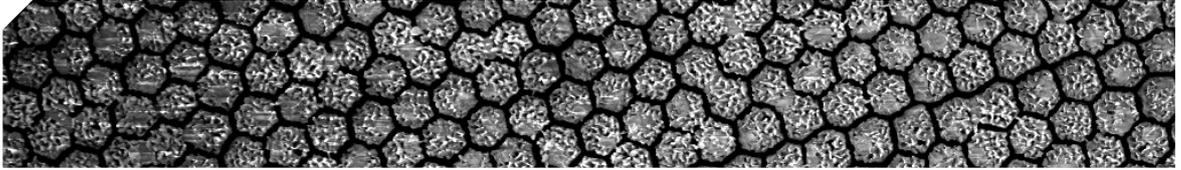
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FOREWORD



“Real knowledge is to know the extent of one’s ignorance.” Confucius

“Doubt grows with knowledge.”
Johann Wolfgang von Goethe

The world of nanotechnology is a fascinating one. The use of nanoscale technology in medicine is already being used in medical devices and medicine. We have learned how to manipulate tiny molecules and take advantage of the novel properties that materials exhibit at this scale, without questioning aspects, such as on human health and the environment. As the field develops, science and commercial interests are leaping forward ahead of our ability in providing a firm regulatory framework. As our understanding and knowledge of the impact of nanoscale products grows we only gradually turn the focus of research towards impacts.

It is already ten years since the UK’s Royal Society and the Royal Academy of Engineering’s report on nanoscience and nanotechnologies pointed out that some regulations would need to be modified on a precautionary basis. Since then many reports on nanomaterials from various institutions have been published with similar calls. Our report on nanomaterials and nanomedicine in healthcare is no different: while acknowledging that nanomedicine may bring some improvements in delivering treatment and in healthcare outcomes, we need to apply some fairly fundamental rules which should govern our handling and development of nanomaterials. Keeping in mind the

precautionary principle, we should improve the European regulation to start covering nanomaterials and nanomedicine, identify and label nanomaterials in products, and prioritise research to address safety concerns of nanomedicine products.

Instead we observe a slow, haphazard approach by the European Commission to identification and management of the risks related to nanomaterials. This report hopes to contribute to the debate in Europe and provide some extra momentum to the processes here. It wants to shine a light on a not very well-known fact: patients and health workers are already exposed to nanomaterials even though we are quite ignorant of the long-term impacts on health and the environment. The potential of and the risks of nanotechnology and nanomedicine need to be openly researched, analysed, debated and regulated.

Health Care Without Harm is a global non-profit organisation whose mission is to transform the healthcare sector worldwide, without compromising patient safety or care, so that it is ecologically sustainable and no longer a source of harm to public health and the environments. This report is part of Health Care Without Harm’s work in Europe to raise awareness about safer products, materials and chemicals in healthcare. We want to ensure that patients and workers have full access to information about chemicals used in healthcare and can participate in decisions about exposure to chemicals.

In a world that is facing an unprecedented global economic, social and environmental crisis we need to question short-term political action, our response to science and regulation and how we conduct science and run businesses.

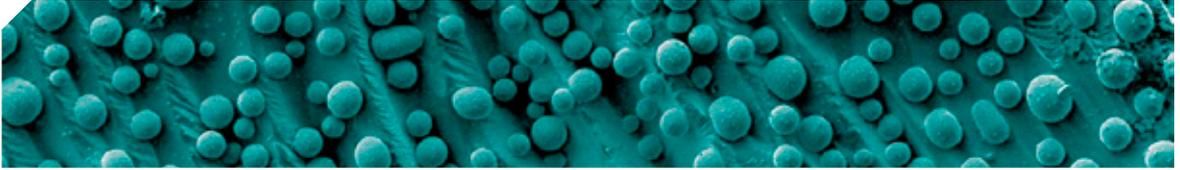
Let's not repeat history with environmental disaster and human cost, such as occurred

with lead, asbestos and DDT. Instead let us learn from mistakes in the past: we need to be transparency on data to manage risks and adapt our legislation speedily to protect humans and the environment. We need action and not delay!

Anja Leetz

Executive Director, Health Care Without Harm Europe

EXECUTIVE SUMMARY



Nanotechnology, the science and business of manipulating matter at the atomic scale, is positioned to initiate the next industrial revolution. Already, nanotechnology products are starting to be used in many areas of everyday life, including in the healthcare sector. A wide variety of commercial applications are already on the market, and continuing investment in research and development will undoubtedly lead to further innovation and a multitude of uses.

In the healthcare sector, nanomaterials offer the prospect of a wide range of medical applications, such as improved drug solubility, drug delivery systems, cellular and tissue repair systems, diagnostic and imaging tools, and therapeutic medicines that can target specific diseased tissues within a patient's body. Nanoscale healthcare and pharmaceutical applications and products (collectively known as nanomedicine) are becoming more prevalent and a number of products have already reached clinical use.

Nanomaterials are engineered to take advantage of unique properties at the nanoscale (where at least one dimension is measured in billionths of a metre). Size is a key property of nanomaterials and nanomedicines because it confers a large increase in surface area, which in turn results in novel properties of the material when compared to the same material at a larger scale. Thus a nanomaterial may have greater chemical and/or biological reactivity or catalytic activity. While these new properties

may be very useful, changing materials at this scale can also result in the introduction of new toxicological risks.

While a greater surface reactivity and solubility or the ability to cross biological barriers such as the blood-brain barrier may be desirable behaviours for a nanoformulated drug, these properties may be less desirable once beyond a specific treatment site within a patient or if the drug enters the environment. It is therefore essential to understand and monitor the bioavailability, bioaccumulation, toxicity and/or environmental transformations and interactions of nanomaterials. Currently, it appears that standard risk assessment procedures are inappropriate for dealing with nanomaterials and tools for environmental monitoring of such tiny materials have not yet been developed.

This report gives an overview of nanomedicine in general with particular emphasis on environmental and human health risks, as well as raising regulatory issues that need to be addressed in order for nanomedicine to deliver on its promises without unduly introducing new risks.

Health Care Without Harm believes that nanomedicine may offer advantages and innovative solutions to some of our current health problems. However, we are also concerned that some of the new properties of nanomaterial products, while desirable from a strictly clinical perspective, can introduce new risks for human health and the environment. It is impossible for

nanomedicines to be completely contained within a clinical/healthcare setting and it is imperative that their whole lifecycle is taken into consideration. Unintentional exposure of workers and associates and environmental contamination may arise during manufacture, use and waste disposal, leading to possible health and environmental impacts which are currently difficult, even impossible, to quantify given the gaps in knowledge, understanding and regulatory control.

The European Union chemical legislation does not specifically refer to nanoscale chemicals and does not explicitly recognise that such materials can have very different properties from the parent "bulk" chemicals. Given the extraordinary characteristics of nanomaterials, Health Care Without Harm believes that they should be regarded as new substances for the purposes of regulation.

A number of specific recommendations are proposed. These are further elaborated in Chapter 6, but are given in summary here:

The **precautionary principle** must underline the regulatory approach to nanomaterials.

The **limitations of EU regulatory frameworks** must be addressed:

- Nanomaterials should be classified as **new substances** in EU legislation;
- Any definition of nanomaterial **should not restrict the size threshold to 100 nm**;
- REACH should take into consideration a **need for lower threshold requirements** for nanomaterials (i.e., less than 100 g);
- REACH should require **specific dossier data for nanomaterials**;
- Nanomedicines that combine **both pharmacological and mechanical functions** should be regulated strictly, recognising the risks of both intentional and unintentional releases;
- **Waste management legislation and guidance** should be reviewed in light

of the need for safe waste disposal of nanomaterials.

Nanomaterial characteristics need to be identified and categorised to ensure appropriate testing methodologies.

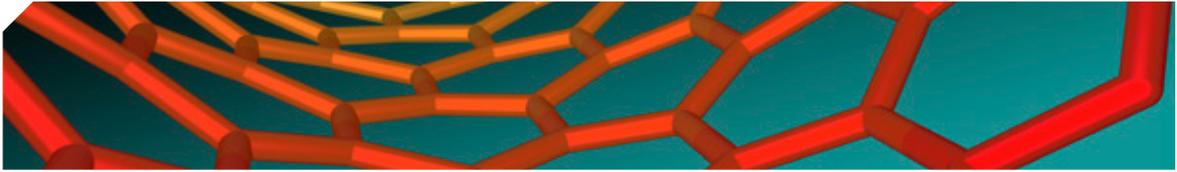
Research is necessary to both address **scientific knowledge on the safety, fate and persistence** of nanomaterials in humans and the environment; and to develop **standards, guidelines and tools** for the detection and monitoring of nanomaterials and their effects on human health and the environment.

The **entire lifecycle of nanomedicines**, including manufacture, disposal and possible environmental impacts, must be taken into account when considering their benefits and risks. For example:

- Guidelines to assess **end-of-life management options** are needed, taking into account toxicity and environmental fate;
- The use of **nano-based cleaners and disinfectants should be discouraged** wherever feasible as their use will contribute to the exacerbation of antibacterial resistance, along with other unknown consequences for the environment.

Patients, workers and communities need **full access to information and to be included in decision-making processes**. This would include:

- An **EU register** listing the production, import and use of nanomaterials;
- **Compulsory labelling** of all nanomedicine products;
- **Public participation** in decisions relating to the exposure of patients, workers and communities to nanomaterials.



1.1 The promise of nanotechnology

Nanotechnology, the science and business of manipulating matter at the atomic, molecular and macromolecular scale¹, is positioned to initiate the next industrial revolution. Billions of euros are being funnelled into research and development around the world, including in the EU², with the prospect of nanoscale technologies and materials being used in many diverse applications. Indeed, consumers are already in contact with nanomaterials – products with nanoscale components include self-cleaning windows, sunscreen lotions and cosmetics, anti-bacterial deodorising socks, fuel additives for motor vehicles, DIY coatings, glues and cleaning products.

In the healthcare sector, nanotechnology has already been put to use in many ways and nanomedicine is now a recognised field. Nanomedicine can be defined as the application of nanotechnology for the diagnosis, monitoring, prevention and treatment of clinical conditions. Applications include nanoscale drugs and targeted drug delivery systems, anti-microbial medical dressings and textiles, *in vivo* imaging, bone substitutes and dental materials, coatings for *in vivo* implants and tissue repair structures³. Nanotechnology is also providing tools to help in the identification and understanding of biomarkers involved in the different stages of diseases³. Future developments in this area are expected to provide solutions to many of modern medicine's unsolved problems by focusing on personalised, targeted

and regenerative medicine. Proposed European development priorities include insulin measurement and delivery by nano-enabled devices, 3-D nanomaterials for stem cell immobilisation at site of injury and image-guided implantation of advanced neurostimulators, to name just a few⁴.

But with new technologies come new responsibilities, such as the need to assess the overall impacts of nanoscale products during manufacture, use and disposal. Concerns have already been raised about certain nanomaterials and their potential detrimental effects on humans. Notable issues include asbestos-like pathogenicity induced by the inhalation of carbon nanotubes⁵ and reduced sperm counts associated with the inhalation of carbon black and nano titanium dioxide⁶. The environment may also be adversely affected, as many nanomaterials may be toxic to non-target organisms or enter the food chain⁷.

This report provides a brief overview of nanomedicine with particular regard to patient and worker safety and environmental protection. Whilst the use of nanotechnology in the healthcare sector is likely to offer a number of advantages over conventional methods, the full range of risks and benefits is currently not well-identified. The report takes a look at the regulatory and legislative issues that need to be addressed in order for nanomedicine to deliver on its promises without unduly introducing new risks for patients, workers and to the environment.

1.2 What are nanomaterials?

Nanomaterials are materials that have been engineered to have one, two or three dimensions measured in nanometres (see Box 1). These include items such as carbon wires and tubes, and even tiny mechanical devices. This nanoscale world is breathtakingly small – one nanometre is a billionth of a metre or a millionth of a millimetre. To put this into context, a strand of DNA is 2.5 nm wide. At the micrometre scale, a red blood cell measures 7,000 nm across (i.e., 7 microns) and a human hair is 80,000 nm wide – still small but much larger than nanomaterials (see Figure 1).

A critical point is that this scale confers novel properties on nanomaterials⁸. The European Commission has explicitly recognised this in its definition of nanotechnology as:

“...the study of phenomena and fine-tuning of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale”¹.

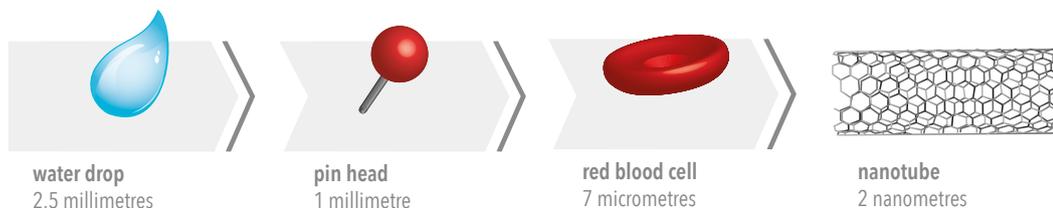


Figure 1 | The relative size of a nanomaterial

Box 1 | Disentangling nano terms

NANOMATERIALS

Nanomaterials have one, two or three external dimensions measured in nanometres (nano-objects) or have an internal structure or a surface structured at the nanoscale (nanostructured materials).

NANOPARTICLES

When all three dimensions of a nano-object are at the nanoscale it is called a nanoparticle. Nanoparticles have various shapes, such as rods, needles, spheres, etc. Nanoparticles can be “hard” such as those made of iron oxide, silver or carbon, or “soft”, such as micelles, liposomes or protein nanostructures.

NANOCRYSTAL

A nanocrystal is a nanoparticle with a crystalline structure, i.e., a structure that is arranged in a regular, periodic manner.

While many of these new properties may be extremely useful, using materials at this scale can also result in the introduction of new risks. Nanomaterials have a very large surface area compared to their bulk counterparts (see Figure 2). This typically results in greater chemical reactivity, biological activity and catalytic behaviour when compared to larger particles of the same chemical composition^{9,10,11}. Such attributes can be very useful but at the same time they may result in greater toxicity^{12,13}. Nanomaterials may also more readily penetrate biological membranes and gain access to cells, tissues and organs of living organisms^{9,14}. This can be highly desirable for therapeutic purposes but detrimental when unintentional exposure occurs.

Other properties of nanomaterials that influence their hazardousness include chemical composition, shape, surface structure, surface charge, catalytic behaviour, extent of particle aggregation or disaggregation and the presence or

OTHER NANO-OBJECTS

Nano-objects with only two external dimensions in the nanoscale include nanofibres, nanotubes (hollow), nanofilaments or nanorods. Nano-objects with one external dimension in the nanoscale include nanofilms, nanolayers and nanocoatings.

NANOMEDICINE

In this report, nanomedicine is defined as the application of nanotechnology for the diagnosis, monitoring, prevention, and treatment of clinical conditions. In this context, nanoscale or nanostructured materials are engineered to have unique medical effects based on their size and structure³. (More specific terms used in nanomedicine are defined below in Boxes 2 and 3.)

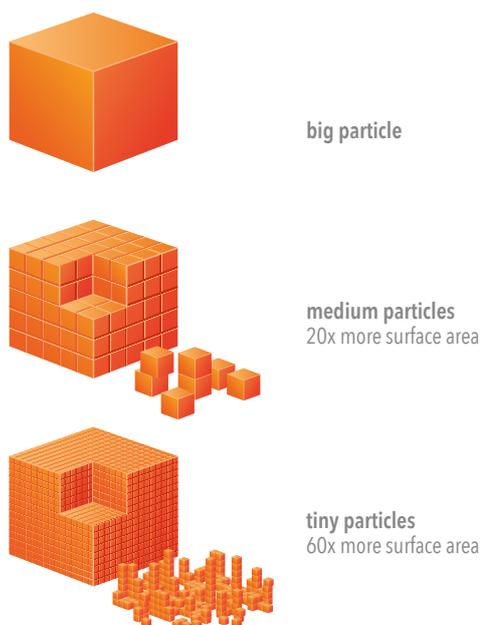


Figure 2 | The increased surface area provided by nanomaterials

absence of other chemicals attached to the nanomaterial^{15,16,17,18}. Because these properties are often different from the parent compound, it is imperative that nanomaterials should be considered as “new” chemicals rather than a variant of the parent compound.

1.3 Nanomedicine has the potential to revolutionise healthcare

The promise of nanomedicine is far reaching, ranging from improved, less toxic, more targeted and even personalised medicines, to more sensitive and cheaper diagnostic tools, innovative structural materials and the prospect of cellular and tissue repair systems (see Table 1). Nanoscale or nanostructured materials have unique medical effects based on their size and structure and include nanoformulations of existing drugs and new nanosized drugs, as well as a variety of medical devices. Much research effort is focused on drugs that are difficult to formulate when using conventional techniques due to their low water solubility, and thereby improve bioavailability.

The creation of structurally engineered nanocarriers capable of delivering drugs more effectively and specifically targeting diseased cells and tissues is another area with huge potential¹⁹.

HEALTHCARE AREA	APPLICATION	EXAMPLE
Diagnostics	<i>In vitro</i> tests using biosensors to specify molecules (biomarkers) associated with a specific disease	Detection of heart disease via DNA-coated gold nanoparticles combined with a biosensor chip to read protein values.
Diagnostics	<i>In vivo</i> measurement of biomarkers using imaging techniques with nanoparticles as contrast agents	Visualisation of small tumours by magnetic resonance imaging (MRI) using magnetic iron oxide nanoparticles attached to carriers.
Diagnostics	Diagnostic “lab-on-a-chip”	Monitoring of lithium levels in the blood at home.
Therapeutics	Passive drug delivery	Delivery of a therapeutic drug to tumours via hollow nanostructures such as liposomes.
Therapeutics	Active drug delivery	Injection of nanocapsules equipped with molecular antennae that release their content on contact with certain disease structures.
Therapeutics	Thermotherapy	Nanoparticles accumulating in the blood vessels of tumours are activated with light, sound or magnetic waves. The particles generate heat and destroy tumour cells.
Tissue regeneration	Regeneration of tissue with nanoscale structured biomaterials	Insertion of nanofibres, peptides and other nanomaterials to provide a matrix within which cells can grow and tissue can be formed.
Tissue regeneration	Regeneration of tissue with cell-based therapies	Insertion of cell-based therapies first created outside the body to promote self-healing properties of cells.

Table 1 | Examples of nanomedicine applications

Adapted from Walhout et al²⁵.

A number of nanomedicine products are already on the market. At present the majority of products are nanoformulations of existing or new drugs (58%) or nanobiomaterials (25%)²⁰. It has been claimed that the worldwide nanomedicine market reached €37.4 billion by 2011 and that the market may double by 2016²¹. In 2011, the largest market share was held by central nervous system products worth €10.4 billion, followed by anti-cancer products at €4.1 billion²¹. Both these areas continue to be the two most rapidly growing sectors²². In geographical terms, currently North America is the major nanomedicine market, followed by the European region; however, the Asia-Pacific region (especially India and China) is expected to exhibit the fastest growth rate in the near future²¹.

Commonly used nanomaterials for medical purposes include carbon nanotubes and nano forms of silicon, gold, platinum, silver and a number of metal oxides. These materials may occur in a range of sizes and shapes, and are often encapsulated or coated with other materials to improve their performance.

Other materials used include quantum dots, dendrimers and liposomes (see Boxes 2 and 3 for definitions). Dendrimers, while promising as carriers of a variety of drugs such as anti-cancer, anti-viral and anti-bacterial drugs, may have limited use currently because of their cytotoxicity (see Box 6)^{23,24}.

1.4 Defining nanomedicine - crucial for regulation

A critical question when assessing the regulation of nanomaterials is their precise characterisation and definition. The International Organization for Standardization (ISO) defines the nanoscale to be in the range of "approximately 1 nm to 100 nm"⁸. Similarly, the European Commission has adopted a recommendation on the definition of a nanomaterial to mean

"A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm"²⁶.

Box 2 | Nanomedicine: drugs, diagnostics, imaging and materials

NANOSCALE DRUGS

Nanoscale particles that have unique medical effects due to their small size and structure (and so excluding traditional drugs comprised of small molecules).

NANOSCALE FORMULATIONS OF EXISTING DRUGS

Produced by a variety of methods including milling, high pressurised homogenisation, etching and lithography. The aim of these production methods is to overcome common pharmaceutical problems by increasing solubility and bioavailability, enabling easier administration and reducing dosage rates. This helps limit systemic toxicities and improves immuno-compatibility and cellular uptake³⁴.

DRUG DELIVERY SYSTEMS

Nanoscale particles/molecules developed to enhance the bioavailability and pharmacokinetics of therapeutic drugs. Examples of drug carriers include liposomes, polymer nanoparticles, nanoshells and dendrimers.

IN VIVO IMAGING

Nanoparticle contrast agents, particularly for MRI and

ultrasound, provide improved contrast and favourable distribution through tissue.

BIOMATERIALS

Nanomaterials that improve the mechanical properties and the biocompatibility of materials for medical implants, including nanocomposite materials used as dental fillers and nanohydroxyapatite used for implant coatings and bone substitutes. Some biomaterials can actively stimulate biological processes such as cell growth.

ACTIVE IMPLANTS

Nanomaterials that improve electrode surfaces and the biocompatibility of device housings. Examples include magnetic nanoparticle-based coatings that make medical implants safe for use with MRI, and nanomaterials used for retina implants to improve the charge transfer at the electrode-tissue interface.

IN VITRO DIAGNOSTICS

The use of nanotubes, nanowires, cantilevers or atomic force microscopy applied to diagnostic devices and sensors with the aim of improving the sensitivity or measuring novel analytes and/or reducing production costs.

Classification adapted from Wagner et al³⁵.

But limiting the definition of nanomaterials to a nanoscale of between 1 nm and 100 nm is inappropriate, especially for nanomedicine applications, as size is only a crude index of novel properties. Indeed the biological behaviour of materials between 100 nm and 1000 nm (in one, two or three dimensions) can pose novel risks, as at this scale they may share many of the characteristic behaviours of nanomaterials below 100 nm in size. These shared properties may include very high reactivity, bioavailability, increased influence of particle surface effects, strong particle surface adhesion, strong ability to bind proteins and very high bioavailability^{9,27,28,29,30}.

Many nanomedicine products do not fall neatly into the conventional size definition for nanomaterials of approximately 1-100 nm. For instance, nanomedicines that aim to passively target sites are typically between 100 nm to 200 nm in size, but particles up to 400 nm have also been used successfully³. Nanomaterials being developed for a variety of clinical applications include liposomes measuring 100-200 nm, nanoshells measuring 60-400 nm³¹ and drug delivery systems measuring 100-200 nm³². A recent survey of nanomedicine products noted that most were sized up to 300 nm, but that some were larger still³. Perhaps this is the reason why both the European Medicines Agency and the US Food and Drug Administration Office of Pharmaceutical Science define nanotechnology as

“... the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties”^{3,33}.

1.5 Regulatory uncertainties may expose humans and the environment to risks

While nanotechnology in general and nanomedicines in particular promise new and innovative solutions to many of our current health problems, regulation of these new approaches is largely unresolved. Are the

current regulatory approaches sufficient? Do we need to adapt and fine-tune existing regulations and directives? Or do we need a new regulatory approach to assess toxicological risks and more directly involve all concerned in decision-making?

In Europe (and elsewhere), key points of dissension in terms of regulatory issues are whether to define nanomaterials as new chemicals and how to properly conduct risk assessments. While the European Commission itself believes that REACH (the EU legislation on Registration, Evaluation and Authorisation of Chemicals) in its current form is sufficient, various Member States, the European Parliament, non-governmental organisations (NGOs) and trade unions have all called for changes to the main text of REACH and have demanded specific nanomaterials regulations^{36,37,38,39,40}. Calls for an up-to-date public inventory of nano products have also been increasing.

A key issue in Europe is the regulatory distinction between medicinal products and medical devices, with different regulatory approaches for market access. This makes the need for clear definitions of nanomedicine products as medicines or devices crucial. Some nanomedicine products will fall into both areas, reinforcing the need for firm and clear regulatory rules to ensure products are assessed using rigorous procedures.

Other issues that remain largely unexplored are the fate and possible transformation of nanomedicines after use if they enter the environment, for example during waste disposal⁴¹, and the exposure of workers. The same qualities that make nanomedicines highly desirable for the healthcare sector, such as increased solubility and enhanced bioavailability, may increase the risk of toxic effects on public health and/or the environment^{34,41}.



Nanomedicine, while often positioned as revolutionary, has been under development for a considerable time. Many of the technologies anticipated in the literature or currently in the research stage may take 20 or more years before becoming available in a clinical setting. It is for this reason that this report focuses on applications and products that are already in commercial use or which are already being tested in clinical studies (taking 1 to 7 years before commercial availability), as these are likely to have a significant impact on industry and society, including with implications for regulation, in the relatively near future.

A recent international review of nanomedicine products yielded 147 products in various

stages of clinical study and 100 commercially available products, including anaesthetics and treatments for cancer, hepatitis, cardiac and vascular disorders, inflammatory/immune disorders, endocrine/ exocrine disorders and degenerative disorders³. Nanomedicines for cancer treatment are by far the most common nanomedicines approved or under development³.

2.1 Nanoscale formulations and targeted drug delivery systems

Nanoscale formulations

Drug delivery and the introduction of new medical properties may be optimised by

Box 3 | Nanomedicines come in many guises

POLYMER NANOCOMPOSITES

A polymer or copolymer with nanoparticles or nanofillers dispersed in a polymer matrix. These nanocomposites may have different shapes such as platelets, fibres or spheroids. They have been used in the construction of drug delivery vehicles and also in tissue engineering to provide scaffolding.

MAGNETIC NANOPARTICLES

Nanoparticles that can be manipulated using a magnetic field. Typically the particles are made of iron, nickel, cobalt or other metals. They may be used in their metallic or oxide forms.

QUANTUM DOTS

Quantum dots are semiconductors whose electronic characteristics are closely related to the size and shape of the individual crystal (nano cadmium or nano zinc). Medical applications include disease diagnosis and screening technologies such as cellular imaging⁴², real-time tracking of molecules and cells over extended periods of time⁴³, *in vitro* imaging of pre-labelled cells⁴⁴ and tumour targeting⁴⁵ (also see Box 7).

CARBON NANOMATERIALS

Carbon molecules such as fullerenes (hollow spheroids) and carbon nanotubes (CNTs) may be used in medical applications, such as coatings for prosthetics and surgical implants (e.g., vascular stents), as well as in drug delivery mechanisms and to assist neuron growth and regeneration⁴⁶.

DENDRIMERS

Dendrimers are tree-like branched molecules. Discovered in the early 1980s, dendrimers have been extensively used as contrast agents, in drug delivery systems for anti-cancer drugs and as gene vectors²⁴.

NANOSHELLS

Nanoshells are spherical nanoparticles made of a dielectric core (made of for example silica) covered by a thin metallic shell (usually gold) and are used in biomedical imaging and *in vivo* cancer therapies⁴⁷.

LIPOSOMES

A liposome is an artificially prepared small bubble enclosed within two layers of lipids (fats). The inside space can be utilised for transport purposes. Once at the target site liposomes may fuse with the cell membrane and deliver molecules inside the cells.

MICELLES

Micelles are nanosized spherical colloidal particles with a hydrophobic interior (core) and a hydrophilic exterior (shell). They are especially useful in encapsulating water-soluble pharmaceuticals.

NANOFILLER

Nanosized particles added to and distributed in the matrix of a composite material to improve its properties.

production of nanoscale versions of existing drugs²⁶. Nanoformulations of existing drugs can overcome common pharmaceutical problems by increasing solubility, limiting systemic toxicities, increasing bioavailability and improving immuno-compatibility and cellular uptake³⁴. Bioavailability, i.e., the absorption of a drug that reaches systemic circulation, is by definition 100% when a drug is administered intravenously and may be much reduced in oral and other formulations.

Nanoscale formulations of a drug enable the bioavailability of this drug to be greater when compared to the bulk formulation. However, increased bioavailability, while on one hand desirable to treat diseases, may be a problem for organisms in the environment⁷.

A number of nanoformulations of existing drugs are already on the market. Commercial products include an anti-organ rejection drug in tablet form, which is easier to administer and has higher bioavailability in comparison to the oral solution⁴⁸, a drug used to prevent nausea and vomiting caused by chemotherapy⁴⁸ and a nanocrystal drug used to improve cholesterol levels⁴⁸.

Targeted drug delivery systems

Nanotechnology has also been heralded as the cornerstone of targeted drug delivery mechanisms which will allow controlled drug release at just the right place and dose, improving patient safety and compliance and reducing side effects. Targeted drug delivery involves a transport device and an active ingredient. Drug delivery vehicles under investigation vary widely and include objects known as polymeric particles, dendrimers, nanoshells, liposomes, micelles and magnetic nanoparticles (see Box 3)⁴⁵. Most targeted drug delivery mechanisms have focused on cancer treatment where these advantages are of great importance.

Particles that have been used extensively are made of nano cerium oxide with a thin coating of fatty oleic acid. These particles act as anti-oxidants and have potential in the treatment of traumatic brain injury, cardiac arrest and Alzheimer's disease, and they could alleviate radiation-induced side effects suffered by cancer patients⁴⁹. They are also viewed as having great potential for treating cancer and other diseases such as macular degeneration and hepatitis⁵⁰.

The features and advantages of a targeted system are various. Encapsulation of a drug (such as in a liposome or micelle) can avoid local irritation and decrease local and systemic toxicity, partly because less drug might be needed⁴⁵. One of the early delivery systems was built from nanoparticles of (non-toxic) polyethylene-glycol designed to carry antibiotics in their cores, reducing immunogenicity and prolonging plasma half-life³⁵.

While targeted drug delivery often reduces the side effects of drugs, the drug delivery mechanisms may also introduce toxicities of their own and have unintended side effects. After the drug is released into the target cells it is often unclear what happens to the carriers. They may move through the body

Box 4 | Finding out more about nano pharmaceuticals

Obtaining information on what nanoscale drugs and drug delivery systems have been approved and what is in the clinical pipeline at the European level is not easy²⁰. Once pharmaceuticals have been approved they can be searched for in the European Medicines Agency database (www.ema.europa.eu). However, results are limited if the name of the pharmaceutical is not known.

Databases of clinical trials are also maintained, but, in Europe, pharmaceuticals are not categorised as involving nano constituents and the database is not easy to search. The EU clinical trials database (www.clinicaltrialsregister.eu) only showed two current trials (as of July 2013) while the US equivalent (www.clinicaltrials.gov) listed 53 studies using the term "nano" in a search. Searches for the term "liposomal" resulted in 126 studies in the European database and 616 studies in the US database.

and accumulate in other organs, or carriers may be excreted and end up in the environment or may accumulate in the body and perhaps cause damage⁵¹.

BENEFITS

- Ease of administration for the patient.
- Preferential accumulation at the desired site of action (such as a tumour).
- Reduced toxicity and side effects for the patient.
- Smaller amount of drugs being excreted and released into the environment.
- Increased bioavailability and solubility.

RISKS

- Increased bioavailability of nanoformulations may prove hazardous for the environment⁷.
- The transport device itself may be toxic or have unintended side effects for the patient.
- Health workers that produce or administer nanosized pharmaceuticals may be subject to unintended exposure of toxic nanomaterials.
- The environment may be exposed to toxic nanomaterials from releases that could occur during production, use or disposal.

2.2 Regenerative nanomedicine, implants and nanomaterials used in dentistry

Regenerative medicine

Regenerative medicine comprises a number of technical approaches, ranging from tissue engineering and wound repair to various futuristic visions of full-scale cell therapy. It focuses on the improvement, repair or

replacement of tissue and organ function and it is expected that nanotechnology will substantially contribute to this. Nanomaterials for tissue regeneration are in the very early stages of development. Currently only two applications related to tissue regeneration, both implantable soft tissue scaffolds with nanostructured surfaces, are in clinical trial or on the market³.

Further developments in this area can be expected for the near future. For instance, the use of nanoparticles in implant cement is expected to overcome many of its current limitations such as breakdown of material, inflammatory responses, etc. This research is currently in the preclinical research stage⁵². Other more futuristic applications include the prospect of artificial organs. For instance, a first artificial kidney containing thousands of nanoporous silicon membranes to selectively filter toxins has been created recently although it is not yet commercially available⁵².

Risks associated with regenerative nanomedicine not only include health and safety considerations such as toxicity and carcinogenicity, but also the long-term stability and excretion pathways of artificial nanostructures. It will be essential

Box 5 | Nanomaterials in dentistry

A variety of nanomaterial-based oral health-care products are used on a daily basis in dentistry, either as nanomaterial-based fillers or for biofilm control and re-mineralisation of sub-micrometre sized enamel lesions⁵⁵.

NANOMATERIAL-BASED FILLERS

Cited advantages for nanomaterial-based fillers include improved optical properties and increased filler level, resulting in reduced amounts of resin, reduced polymerisation shrinkage, and dramatically improved physical properties of nanocomposites⁵⁶. However, wear and abrasive use in the case of dental fillings may release some of the filler into the mouth from where it could be absorbed into the body⁵⁵. The question of toxicity of dental fillers is in general a controversial area and the use of nanocomposite dental fillers needs to be addressed in light of the overall potential issues with other dental fillers. There are some indications that nanocomposites and especially biomimetic nano-fillers (which are still in the research phase) may be less cytotoxic⁵⁵.

BIOFILMS

Cariou lesions in teeth are caused initially by bio-films, encouraged by the consumption of acidic foods and beverages as well as gastric juices, causing surface demineralisation and leading to enamel erosion. Amorphous calcium phosphate nanocomplexes stabilised with casein phosphopeptides (CPP-ACP) can be used successfully for biofilm management, helping prevent demineralisation as well as remineralisation of enamel lesions⁵⁵. These are readily commercially available, for instance in toothpaste. A number of other approaches (using varieties of apatite nanoparticles) have also been tested for remineralisation purposes, but clinical trials have not been conclusive⁵⁵. Nevertheless, commercially available dental prophylactic products containing carbonate hydroxyl apatite nanoparticles are available in some European markets⁵⁵. And, while the application of CPP complexes appears to mimic natural processes and is considered safe, potential risks of these treatments are unknown, as they have never been tested.

to identify the hazards associated with novel nanotechnology-based therapies and characterise the associated risks, while involving relevant stakeholder groups such as health professionals and patients. Key questions are whether the materials used are themselves toxic and their fate when they are released from the product. Inevitably, release may occur even when compounds are tightly bound in a matrix, for instance through abrasion and during waste disposal⁵³.

Implants

Nanomaterials used for implants fall into the categories of metals, ceramics, polymers and composites. Nanocomposites and nanomaterial coatings have been developed commercially for both bone and dental implants⁴⁶. Typical examples include composites for dental restoration and self-etch adhesives containing nanofillers of silanised zircon⁴⁶. Synthetic bone replacement products with a similar calcium and phosphate composition as bone, i.e., as hydroxyapatite and tricalcium phosphate, are also becoming available in nano form⁴⁶ (and see Box 5). Nanostructured metallic alloy implants – for instance hip prostheses made of titanium – are thought to overcome problems of chemical contamination that may occur with conventional prostheses and offer mechanical advantages. Different nanocoatings, e.g., nanosilver, are thought to further enhance these products and items such as bone cement due to their antimicrobial properties⁴⁶. The use of silver nanoparticles with antimicrobial properties in bone cements may also become feasible⁴⁶.

Coronary heart disease associated with narrowing of the vascular network (stenosis) is often treated with the implantation of a stent device to keep the artery open. The main complication is intra-stent restenosis, a re-

narrowing of the blood vessel within the stent. A number of manufacturers have addressed this by using nanoscale coatings of ultrafine hydroxyapatite, polymer or nanoporous ceramic to inhibit re-narrowing⁴⁶.

Retinal implants to treat retinitis pigmentosa have become available in clinical settings, using silicon photodiodes or a series of platinum electrodes on a silicon plate. Both treatments are considered medical devices and have CE labelling⁵², a declaration of conformity with EU standards.

The application of nanotechnology may also lead to improvements in the ability, control and precision of neuro-stimulation to the brain. Brain implants may be usefully applied to neurodegenerative diseases such as Parkinson's disease, movement disorders such as dystonia or tremors, psychiatric disorders such as depression, obsessive disorders and pain⁵⁴. Risks associated with implants are similar to regenerative nanomedicine and include health and safety considerations such as toxicity and carcinogenicity, but also the long-term stability of the implant. Safe waste disposal may also be an issue.

BENEFITS

- Improved function, repair or replacement of tissues and organ functions, with reduced breakdown and reduced inflammatory response.
- Possible overcome of chemical contamination problems that occur with conventional prostheses.
- Mechanical advantages, such as lighter, stronger material when compared to conventional prostheses.
- Nanomaterial based dental fillers exhibit improved material properties when compared to conventional materials.
- Potential reduced toxicity when compared to conventional materials.

RISKS

- Long-term stability and excretion pathways of artificial nanostructures and the potential toxicity of these to the environment.
- The potential carcinogenicity and toxicity of the nanomaterials used in implants.
- Environmental risks of the material from manufacturing and in relation to wear and tear or disposal.

2.3 Nanotechnology-based diagnostics, medical instruments and imaging tools

A number of nanotechnology-based diagnostics, including imaging tools and some nanoscale medical instruments, are already well developed and are available in clinical and healthcare settings. This area of nanomedicine enables the early diagnosis of diseases, decentralisation of healthcare and more effective treatment methods. The overall economic impact of the use of nanotechnology in these areas can be considerable, as the application of nanotechnology to diagnostics has resulted, for example, in high throughput screening, and will ultimately lead to point-of-care diagnostics and personalised medicine⁵⁷.

Diagnostic tools

Currently *in vitro* diagnostics are costly and it is hoped that new generation “lab-on-a-chip” with nanoscale componentry will offer advantages including reduced costs, portability, and shorter and faster analysis. Applications may include point-of-care measurements of saliva for periodontitis, heart disease, insulin detection and improving healthcare accessibility³⁸. For example, gold particles can be used *in vitro* to detect early

heart disease by identifying biomarkers such as the levels of certain protein enzymes which may indicate that a patient has had an undetected heart attack²⁵. Carbon nanotubes have been used in a subcutaneous device for monitoring blood sugar levels *in vivo*⁴⁶. While many of these applications are still in the research or preclinical stage, a lab-on-a-chip the size of a postage stamp is already commercially available and is used to monitor medication levels for manic depressive patients at home at much lower cost and with greater convenience²⁵.

Other diagnostic applications using nanotechnology and already on the market include: colloidal gold particles which, due to their stability, have been widely used to rapidly test for pregnancy, ovulation, HIV and other indications³⁵; magnetic nanoparticles used for cell sorting applications in clinical diagnostics³⁵; and superparamagnetic iron oxide nanoparticles for magnetic resonance imaging - first approved in Europe in 1993³⁵. Magnetic iron oxide nanoparticles also show great promise in the detection of Alzheimer plaques⁵⁸.

The toxicity risks both for humans and the environment are as yet unclear and will of course very much depend on the specific



nanomaterials in use. For instance, the use of quantum dots to illuminate organs and detect tumours may pose additional toxicity risks should they diffuse into surrounding organs and disrupt cellular function⁵⁹. It is also unclear whether diagnostic tests could have adverse effects on medical staff applying the tests and how disposal of diagnostic tests will be undertaken safely.

Medical instruments

Medical instruments are also being increasingly miniaturised, with nanomaterials used for enhanced efficiency. For example, carbon nanotubes may be used instead of glass pipettes for delivery into cells⁴⁶. Nanosilver is increasingly incorporated into catheters and other instruments as a coater because of its antimicrobial effects^{46,60}. Wound dressings may also incorporate some sort of nanosilver, either in the form of silver salts, metallic silver nanocrystals or nanoparticles for the same purpose⁴⁶.

Another area of great development in medical devices is that of thermotherapy, a form of cancer treatment that uses heat to destroy cancer cells. By using nanoparticles to generate the heat, the treatment can be more successfully localised and result in fewer side effects. A number of devices are either at the clinical study stage or are already on the market. The devices use a number of different nanomaterials including nanosized iron oxides, gold-coated silica nanoparticles and hafnium oxide nanoparticles. For instance, iron oxide nanoparticles are interstitially or intravenously delivered then heated by applying an alternating magnetic field to provide hyperthermia treatment localised to a tumour⁵⁹. Iron oxide nanoparticles are also used for magnetic detection of cells *in vitro*⁵⁹. A key question will be if this therapy constitutes a device (for bursting the tumour

cells) or should be classified as a drug (given the ensuing metabolism of the burst cells).

Imaging tools

Nanomaterials are being used extensively as contrast agents in non-invasive medical imaging tools, including computed tomography, magnetic resonance, positron emission tomography, single photon-emission computed tomography, ultrasound, and optical imaging. The use of nanosized metal oxides, dendrimers, quantum dots, etc., as contrast agents may lead to better understanding of biological processes at the molecular level, as well as having the advantage of better photo-stability, higher quantum yield and increased *in vitro* and *in vivo* stability. However, the inevitable issues of waste management and potential toxicity issues have rarely been discussed⁶⁰, despite the need to address them with some urgency.

BENEFITS

- Diagnostic tools may become cheaper, more portable and produce less waste.
- Faster and earlier disease analysis can be enabled, including at point of care.
- Nano-enabled imaging tools allow earlier and more accurate detection and hence more effective treatment of diseases.
- Thermotherapies offer less invasive treatments and alternatives to chemical cancer treatments.
- More effective antimicrobial coatings for implants and medical devices.

RISKS

- Health and safety considerations such as toxicity and carcinogenicity of nanomaterials (especially metals and metal oxides).
- Safe waste disposal of nanomaterials used in medical devices.
- Potential resistance to antimicrobial nanomaterials if overused.

2.4 The future of nanomedicine - fusing therapy and diagnostics?

At the more visionary end of the scale are the plans for "theranostics," a fusion of therapy and diagnostics. Rather than wait for a disease to manifest itself on a more conventional time scale, nanomedicine raises the possibility of using ultra-sensitive diagnostic abilities combined with treatment at a very early stage. Theranostic platforms envisage the targeting of a disease, diagnosis and administration of a treatment in one single step. Much work in this area has focused on cancer treatment, especially in the utilisation of electromagnetically-activated nanoparticles. Several of these platforms are currently nearing or are progressing through clinical development.

Theranostics may in the future predict risks of contracting a disease, diagnose disease, assist in stratifying patients, and monitor therapeutic responses and hence enable earlier and more effective treatment. But this approach also raises ethical issues surrounding the starting point of "disease" and the use of treatments before "illness" begins. Some of the materials used are also potentially acutely toxic and there are risks of environmental contamination and unintentional exposure.

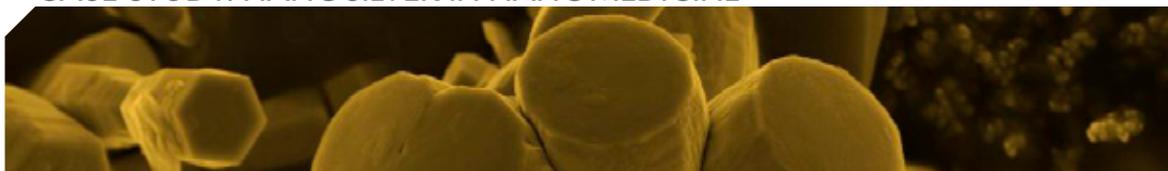
For example, quantum dots are extensively used as fluorescent imaging agents, but can also act simultaneously as drug delivery vehicles. In this dual role, i.e., as imaging agents and drug delivery vehicles, they have played a key role in theranostics⁶¹. However, questions have been raised regarding the use of quantum dots in their current form due to their potential acute toxicity.

BENEFITS

- Identification and treatment of diseases in one step may be cheaper, more effective and less invasive.
- Earlier treatment may be facilitated.

RISKS

- Ethical issues surrounding the starting point of "disease" and the use of treatment before "illness" begins.
- Some materials are intrinsically toxic.
- Risks of environmental contamination and unintentional exposure.



The fungicidal, bactericidal and algicidal properties of silver have been known for a long time. For centuries silver has been known to be effective in killing harmful bacteria contaminating various commodities, including milk and water. In recent years, nanosilver has increasingly been used in consumer and industrial products. It has become one of the most commonly used nanomaterials in consumer products, predominantly as a bactericide. It can be found in a range of products, including disinfectants, cleaning agents, powder coatings (e.g., on door knobs), wall paints, air conditioning, clothes especially sportswear, toothbrushes, baby bottles, etc. The biocidal effect is used not only for preservation of materials but more often against the real or supposed risk of infection or only against unpleasant odours caused by bacteria.

In hospital settings, nanosilver is used extensively for wound management, particularly for the treatment of burns, ulcers (rheumatoid arthritis-associated leg ulcers, diabetic ulcers, etc.), toxic epidermal necrolysis, healing of donor sites and for meshed skin grafts⁶², with claims of improved infection management⁶³. Silver-coated catheters are also used to prevent the growth of slime-containing biofilms that encourage bacterial infection⁶⁴. For instance, silver-coated urinary tract catheters reduce the frequency of urinary tract infection⁶⁴. Nanosilver is also used in textiles and other essential medical equipment⁶⁵. Other proposed applications of nanosilver

in medical devices include in infusion ports, orthopaedic protruding fixation devices, endovascular stents, urological stents, endoscopes, electrodes, peritoneal dialysis devices, subcutaneous cuffs and in surgical and dental instruments⁶². Silver nanotechnologies are also claimed to improve battery performance in implantable medical devices by reducing biofilm growth and so protecting conductivity⁶².

Nanosilver is a more effective antimicrobial than bulk silver

The comparatively large surface area of silver nanoparticles increases their reactivity, which increases their toxicity, typically from oxidative stress caused by the release of silver ions⁶⁶. Given the rate of ion release is generally proportional to the surface area of a particle, nanosilver is more efficient than bulk silver at generating silver ions and therefore is a more efficient antimicrobial⁶². Additionally, increased toxicity to bacteria results from the ability of nanosilver to cross many biological barriers, increase production of reactive oxygen species and its capacity to deliver silver ions efficiently to the surface of bacteria⁶⁷.

Induction of bacterial resistance

A number of concerns have been raised regarding the use of nanosilver including the possibility of adverse effects on patient cells which could delay wound healing or pose localised toxicity⁶⁸. A bigger concern is that the overuse of nanosilver in consumer

products may induce bacterial resistance and make it difficult to use in legitimate medical applications. Several reports describing resistance to silver in hospital settings have already emerged, especially in hospital burn wards⁶³. A recent study reported for the first time that *Bacillus* spp. could develop resistance to nanosilver cytotoxicity upon exposure⁶⁹. A key issue here is the problem that selection of bacteria with the ability to resist silver also selects for other antimicrobial resistance genes. Resistance genes to silver have been found on a range of plasmids, notorious for containing multiple antibiotic resistance genes^{70,71}. The widespread and indiscriminate use of nanosilver in healthcare settings may further contribute to the induction of resistance.

Environmental risks

The distribution of silver nanoparticles into the environment and the possibility of adverse environmental effects have only recently been researched in some detail. Key routes into the environment are through elevated concentrations in wastewater effluents and through the use of sewage sludge as fertiliser or as organic soil improver⁷². The sludge or biosolids from wastewater treatment can also reach the environment through dumping in

landfills or oceans or via incineration⁶⁹. All exposure routes may ultimately lead to silver resistance in environmental bacteria⁷³. And, once in the environment, exposure to humans or non-target organisms may occur through a variety of mechanisms including inhalation, dermal contact and ingestion⁷⁴. For instance, nanosilver used in some clothing has been shown to leak rapidly and quickly into the water during washing and easily reach wastewater treatment plants⁷⁵.

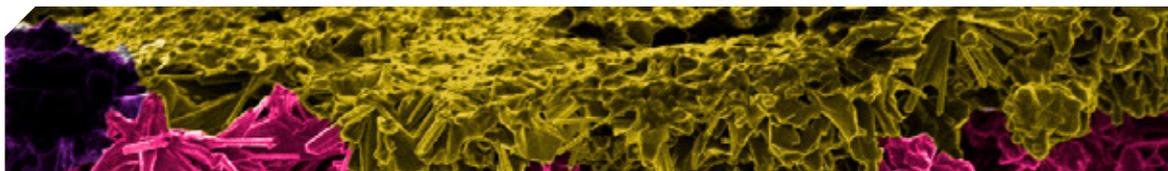
In addition to induced bacteria resistance, nanosilver can also damage beneficial soil microbes depending on the soil type⁷⁶. Changes in microbial community composition, biomass and extracellular enzyme activity, as well as effects on some above-ground plant species, have been observed after the application of sewage biosolids containing low doses of nanosilver during a long-term field experiment, along with significant increases in nitrous oxide (N₂O) fluxes⁷⁷. This is significant since nitrous oxide is a notorious greenhouse gas, with 296 times the global warming potential of carbon dioxide. It is also the dominant stratospheric ozone-depleting substance. A number of studies have also investigated nanosilver's toxicity to aquatic organisms. For instance, nanosilver particles have been shown to



accumulate inside algal cells, where they exerted toxic effects⁷⁸. They have also been observed to aggregate and be transferred transgenerationally in nematodes⁷⁹ and to accumulate in fathead minnow embryos⁸⁰.

There are considerable human health and environmental risks associated with the indiscriminate use of nanosilver in consumer and health products. Evidence to date suggests that precautionary action is advisable due to nanosilver's environmental

toxicity⁸¹. The clinical use of nanosilver should be limited to applications of most value (wound management, medical devices) where alternative disinfectants or antimicrobials are not effective. Hospitals and healthcare providers should establish guidelines to restrict the clinical use of nanosilver to critical applications and patients. Nanosilver textiles should only be used where substantial therapeutic effect can be demonstrated.



The potential risks for human health and the environment of nanomedicine products will depend on the nanomaterial that is used, as well as on the environmental processes and exposure routes that control the fate, transport and transformation of the nanomaterial⁴¹. In the first instance, exposure to nanomaterials in nanomedicine products is intentional. However, the desirable effects may also lead to unintentional exposure to other organs in the patient's body, other people, non-target organisms and the environment⁵¹.

A key issue for nanomaterials toxicity is their ability to bind and interact with biological matter and as a result change their own properties⁴⁶. However, in the case of nanomaterials the interaction mechanisms between nanomaterials and living systems are not yet fully understood⁴⁶. Furthermore, one of the greatest potential dangers may be the propensity of some nanomaterials to cross biological barriers in a manner not predicted from studies of larger particles of the same chemical composition⁸².

The common assessment paradigm for toxicological assessment is that there is a correlation between mass and toxicity, but a number of studies have shown that this may not be the case for nanomaterials. Other properties such as surface area, surface chemistry, etc., may give a better indication of toxicological endpoints⁸³. Furthermore, given that bioavailability may be enhanced in some nanomaterials, particularly those devised for medical purposes, this will result in a change

of biological effects and it may be difficult to predict or to include in existing environmental risk assessment schemes⁸³. Table 2 provides a summary of nanomaterials commonly used in medicine, their applications and their potential toxicity and ecotoxicity.

4.1 Human health concerns

A vital question in considering the toxicology of nanomaterials to human health is how they change and act depending on the specific biological compartment (in the body or within a cell) in which they find themselves. Indeed, one of the key features of nanomaterials and

Box 6 | Toxicity of dendrimers

Dendrimers are branched tree-like and highly symmetric molecules. Their unique physical characteristics such as symmetry, water solubility, encapsulation ability and the possibility for large numbers of functional peripheral groups makes them ideal as drug delivery vehicles. In this role they have been utilised as carriers of anti-cancer, anti-viral and anti-bacterial drugs. Additionally, they have been used as contrast agents, as catalysts to create organic light-emitting diodes and in gene therapy²³.

Currently the clinical use of dendrimers is limited due to their significant *in vitro* cytotoxicity and their ability to disrupt red and white blood cells. These characteristics are due to cationic groups on the dendrimer surface interacting with negatively charged biological membranes. This causes membrane disruption through the formation of nanoholes, membrane thinning and membrane erosion, followed by leakage of cytosolic enzymes and cell death²³. In order for dendrimers to be used safely and more widely under clinical conditions this behaviour will need to be overcome. Some possible strategies to tackle inherent toxicity issues include developing biodegradable and/or biocompatible dendrimers and surface engineering. The latter approach will not only reduce inherent toxicity, but may also lead to improved drug encapsulation, biodistribution and pharmacokinetic properties, an increase in solubility, improved targeting to specific sites, better transfection efficiency, improved sustained and controlled drug release, improvement in stability profiles and improved therapeutic potential of anti-viral and anti-bacterial activity²³.

one of their greatest potential dangers may be their ability to cross biological barriers, not seen in studies of larger particles of the same chemical composition⁸². This also highlights a key paradox for nanomedicine: the desirable effects observed in nanomedicines may at the same time be highly toxic to other persons, the environment or non-target organisms⁵¹.

The harmful effects of inhaling ultrafine particles are well documented. For example, the industrial pollutant carbon black is known to cause cancer through inhalation in rats and under certain circumstances in humans¹⁰¹. Similar concerns have been raised in relation to certain carbon nanotubes¹⁰². A further major concern is whether nanoparticles can cross the air-blood barrier in the lungs and gain access to the rest of the body⁷. There is

evidence that nanomaterials can translocate from the lung into the liver, spleen, heart and possibly other organs¹⁰³. Access via the olfactory bulb has also been reported¹⁰⁴.

Another potential exposure route in humans is through the skin. Access by fullerenes and quantum dots has been reported, dependent on size and surface coatings¹⁰⁵. Gastro-intestinal assimilation and movement from there into the blood stream has also been demonstrated¹⁰⁶. Nanomaterials have been found to accumulate in low concentrations in the liver, spleen, heart and the brain¹⁰⁷. The possible effects of nanomaterials on the developing foetus are of special concern, with gold nanoparticles¹⁰⁸ and quantum dots⁹⁸ having been shown to cross the maternal-foetal barrier.

NANO COMPONENT	HUMAN AND MAMMALIAN TOXICITY	ECOTOXICITY
Carbon nanomaterials	Asbestos-like pathogenicity induced by carbon nanotubes (CNTs), depending on shape, length and state of aggregation ⁵ .	Inhibition of growth in freshwater algae ⁸⁴ and of root elongation in different vegetables depending on CNT structure ⁸⁵ .
Cerium oxide	Conflicting <i>in vitro</i> data regarding toxicity, but apparent lack of toxicity in animal models ⁵⁰ .	Oxidative stress in cereal seeds ⁸⁶ .
Dendrimers	Acute and chronic toxicity ^{23,24} .	Reduced growth and development effects on freshwater fish at sublethal concentrations ⁸⁷ . Decreased cell viability in freshwater ⁸⁸ .
Nano gold	Zebrafish accumulated gold nanoparticles (via feed) in brain, liver, spleen and skeletal muscles ⁸⁹ .	Decrease in colony formation of soil microbial communities ⁹⁰ . Reproductive performance decreased in fruit flies ⁹¹ . Oxidative stress in marine invertebrates ⁹² .
Nano iron oxide	Low direct cell toxicity, but immune cells showed impaired functioning, i.e., struggled to engulf pathogenic bacteria ⁹³ .	Hydroponically grown pumpkin plants (<i>Cucurbita maxima</i>) translocated and accumulated nanoparticles ⁹⁴ . Nano-Fe2O3(m) enhances the toxicity of arsenic (As) in <i>Ceriodaphnia dubia</i> when ingested. The bioaccumulation of nano-Fe2O3(m) is affected by time, nanoparticle concentration and pH ⁹⁵ .
Nanosilver	Potential local toxicity issues ⁶⁸ .	Toxic to beneficial soil microbes ⁵⁹ . Altered microbial community composition, biomass and enzyme activity ⁶⁰ . Increased resistance in environmental bacteria and plasmids ^{69,70,71,73} .
Quantum dots	Acute and chronic toxicity ⁸² . Can translocate from the lung into liver, spleen, heart and possibly other organs ⁹⁷ . Can cross the placental barrier ⁹⁷ .	Little is known about the fate of dots excreted from living organisms on the environment ⁹⁸ .
Silicon dioxide	Low direct cell toxicity, but immune cells showed impaired functioning, i.e., struggled to engulf pathogenic bacteria ⁹³ .	Decrease in growth rate in freshwater algae ⁹⁹ . Capacity to bind may alter the availability of other contaminants for environmental organisms ¹⁰⁰ .

Table 2 | Example of potential human health and environmental toxicity risks of selected nanomaterials used in nanomedicine

The key pathways through which humans may be unintentionally exposed to nanomaterials are through inhalation, ingestion and dermal exposure, with possibility for further translocation to secondary organs⁷. For instance, dental procedures may involve the milling, drilling, grinding and polishing of applied medical materials containing nanomaterials, which may then be inhaled inadvertently, make contact with skin or be ingested¹⁰⁹.

A number of parameters will affect the overall toxicity of nanoparticles. In general, it has been observed that size is very important, in particular for cellular uptake of nanoparticles. Additionally, the greater the intracellular dose of nanoparticles, the greater the effect generated (whether toxic or otherwise). Shape, and perhaps more importantly surface charge, can also have a determining effect on toxicity⁹⁷. Other physiochemical characteristics that may have toxic effect in cells depending on the nanomaterial include agglomeration⁸², the Trojan horse-type uptake mechanism¹¹⁰ and zeta potential¹¹¹.

Box 7 | Toxicity of quantum dots

While quantum dots show great promise in medical applications for imaging procedures⁶¹, a key problem remains their acute toxicity, as they are typically inorganic fluorescent nanocrystals, typically consisting of cadmium selenide, cadmium telluride, indium phosphide or indium arsenide semiconductor materials⁶¹. For example, cadmium quantum dots dissolve under UV irradiation to release toxic cadmium ions into culture medium¹¹³. Various methods to reduce leakage of quantum dots have been developed, but little is known about the environmental fate of quantum dots excreted from living organisms¹¹³.

The toxicity of quantum dots arises either from the semiconductor core material (typically cadmium or selenium), which may leach, and/or the generation of free radicals during excitation. Quantum dots may cross the blood-brain barrier, may accumulate in adipose tissue, may be toxic to liver and kidneys and are considered possible teratogens (i.e., causing abnormalities of physiological development) and carcinogens¹¹⁴. Their complicated physiochemical characteristics may introduce additional toxicity. All synthetic precursors of quantum dots are toxic, possible pyrophoric, and some are toxic on ingestion or prolonged exposure¹¹⁴.

The generation of reactive oxygen species has been shown to be greatly affected by catalytic effects at the nanoparticle surface¹¹. The presence of other contaminants, mode of action of the chemical and differences in species physiology all influence toxicity¹¹².

A further complication is that nanomaterials may also acquire new “biological identities” (and thus new properties) via the adsorption of biomolecules onto their surface, giving what is termed a “bio-corona”. Toxicological studies need to assess the interaction between the bio-corona and the nanomaterials and how they might interact with each other, as well as assessing the physiological response of the organism to the bio-corona⁸².

4.2 Occupational Health and Safety issues in healthcare facilities

Nanomedicine can pose a risk to others beside patients. The manufacture, use of and exposure to nanomaterials in any workplace is a recognised matter for concern, but as yet not resolved. The European Agency for Safety and Health at Work has cited a number of specific nanomaterials – such as silver, gold and titanium nanoparticles and carbon nanotubes – as posing potential health hazards and occupational health and safety (OHS) risks¹¹⁵.

While the application of nanotechnology and nanomaterials has the potential to offer many benefits to patients, it remains unclear what risks healthcare workers are exposed to in the process of using, administering or involuntarily coming into contact with nanomedicine products. Many healthcare workers are unaware that they may be handling these materials on a day-to-day basis and of the potential toxicity of nanomaterials.

For healthcare workers, accidental exposure to nanomaterials may occur through a number

of exposure scenarios. While inhalation of airborne nanoparticles may be the most common exposure route in the workplace, ingestion through unintentional hand-to-mouth transfer from contaminated materials is also possible. Dermal exposure is another possible pathway for entry into the human body, in particular via cuts and damaged skin or through unintentional needle-stick injuries. Exposure can occur in a variety of situations, such as disposal of excreta from patients receiving nanoscale drugs, handling of nanomaterial-contaminated items and spillages, consumption of food and beverages that have come into contact with nanoscale drugs, and cleaning and maintenance of areas where nanoscale drugs are handled^{34,109,115}. Healthcare workers with a particularly high risk of exposure are those that prepare or administer medicines containing nanomaterials or who work in the areas where these medicines are used.

Although some particular health issues have been identified (such as unintended exposure), more generally there are gaping holes in the available information concerning OHS issues. Despite the focus of this report in healthcare environments, workers involved in the manufacturing of nanomaterials may also suffer substantial exposures. The nature of their exposure may also be different; for example,

particles that are used in a liquid matrix may be present in the atmosphere in the factory, presenting inhalation rather than topical exposure hazards. Manufacturing sites may also generate wastes with high concentrations of nanoparticles, which differ in nature and effects from the products, being by-products of the synthesis procedures. These all need to be considered in the overall assessment of the nanomaterials before licensing.

Key OHS issues include a lack of data on the health impacts of nanomaterials and their potential environmental toxicity, combined with a continuing inability to monitor any adverse effects¹¹⁵. The lack of technologies and protocols for environmental and health monitoring, detection and remediation is still considerable, despite some efforts being made to address the problem¹⁰⁹. For instance, Safety Data Sheets (SDS) generally contain little or no information about nanomaterials, including whether they are present, what their characteristics and risks are, nor how to prevent exposure¹¹⁵.

Preventive measures are therefore currently the only available tools to protect the health of workers. To minimise risks of exposure to nanomaterials in workplaces in the healthcare sector the European Agency for Safety



and Health at Work suggests the following measures¹¹⁵:

Substitution

- Avoiding the presence of nanomaterials that could become airborne by using less hazardous forms or modifying their surface properties.

Workplace design and monitoring procedures

- Instituting engineering controls such as clean benches with high-efficiency particulate air (HEPA H14) or ultra-low penetration air filters.
- Supplying separated, clearly signed and dedicated workplaces for handling nanomaterials.
- Minimising the number of personnel being exposed and the duration of exposure.
- Prohibiting access by unauthorised personnel.

Collective preventive measures

- Instituting a health surveillance program for workers handling nanomaterials.

Personal protective equipment

- Using personal protective equipment when exposure cannot be reduced effectively enough. Equipment should be adequate to prevent exposure and minimise the risk while being suitable for the worker. This can include respiratory protection, gloves and protective clothing.

Given the general lack of coordinated, publicly available information about specific nanomaterials, including who produces them, where they are being produced and used and what their potential risks may be, it is not clear that the risks are being taken into consideration in healthcare facilities. Provision of information to workers and their

participation in the management and risk assessment processes of nanomaterials is fundamental to elimination or reduction of the risks posed by nanomaterials. Doctors, nurses and other healthcare professionals need to know the risks involved in their work and be able to contribute to improvements in workplace practices at all levels.

Box 8 | Ethical issues

“Personalised medicine”, both in the context of theranostics and targeted drug delivery systems, has emerged as a key goal of many researchers. By adapting the use of pharmaceutical agents to an individual's genome, great efficiencies and hence lower healthcare costs are predicted to be achieved. But there are a number of ethical implications, including privacy and values issues.

Given the opportunities for combining early diagnosis with therapy, appealing as it may seem, this raises a number of questions. For example, at what point does a person's illness start? Does it start when the person's genetic predisposition is discovered (perhaps even before birth), when the first cancerous cell appears in the body (detected during a future “daily health check-up” at home) or when the tumour has started developing but no symptoms have appeared? At what point does one intervene?

Nano implants may also introduce ethical issues such as the ability of a patient to consent, the difficulty of continued self-determination (i.e., is it the person or is it the device that is inducing the person to act?), unanticipated mood changes and other personality changes⁵⁴.

A full discussion of ethical issues falls outside the scope of this report but they need urgent and careful thought before the use of such early diagnosis becomes widespread.

4.3 Environmental concerns

Globally, hundreds of thousands of tonnes of nanomaterials are being released into the environment, both intentionally and unintentionally, throughout the lifecycle of nanomaterial production, use and disposal. Possible entry routes for nanomaterials into the environment include waste disposal (waste water treatment, storm water run-off, landfill, incineration) and unintended release such as through abrasion and wear as well as emissions from manufacturing and accidental spills³⁴. A 2013 study into the global lifecycle of engineered nanomaterials estimated that, in 2010, 260,000–309,000 tonnes of

nanomaterials ended up in landfills (63–91%), soils (8–28 %), water bodies (0.4–7 %), and the atmosphere (0.1–1.5 %) ¹¹⁶. Nanomedicine is increasingly, albeit on a small scale, contributing to this problem.

For components of nanomedicine products, a major route of entry into the environment is through human metabolism and excretion into the sewage system. The fate and ultimate removal of these compounds depends very much on the appropriate design of waste water treatment facilities and it is at present unclear whether these will be able to adequately remove nanomedicines. Unsatisfactory removal of emerging contaminants in general is a recognised worldwide problem and nanomedicines may exacerbate this issue. Other possible transfer routes into the environment include the improper disposal of nanomedicine products at end-of-life (especially of *in vitro* diagnostic materials) ³⁴.

Environmental impacts are uncertain

When nanomedicine products enter the environment it becomes crucial to understand their fate and effects in terms of bioavailability, bioaccumulation, toxicity, environmental transformation and interaction with other environmental contaminants. A key question is whether current environmental fate and transport models are even applicable ⁸³. What happens to nanomaterials once they reach the environment depends on numerous environmental conditions, including their aggregation, dissolution, oxidation/reduction and adsorption properties ¹¹⁷.

Nanodrugs in particular may present bioaccumulation issues as many are stable in aqueous solution ¹¹⁸. This implies that they will be able to travel for long periods in the external environment, will contaminate soils via sewage and spills and ultimately migrate into groundwater and river systems and into

the food chain ¹¹⁹. Simulated experiments have shown that physicochemical properties of the aquatic environment such as pH, ionic strength, salinity, mineral content, natural organic matter and extracellular polymeric substances can influence the toxicity and bioavailability of nanomaterials ^{120,121}.

A recent review of toxicological research on nano metal oxides (silver, copper and zinc oxide) reported that they are extremely toxic (as defined by EU Directive 93/67/EEC) to freshwater aquatic organisms including fish and algae, with crustaceans being most affected ¹²². Freshwater may stabilise nano metal oxides and make them more persistent and hence increase availability for fish and algae filter feeders, while sea water appears to facilitate aggregation and settling and hence reduce toxicity ¹²³. This report confirms the need for strict assessment and regulation of the use and disposal of nanomaterials in general and nanomedicines in particular.

Nano metal oxides have also been shown to contaminate soils and enter the food chain via plant uptake. Recent studies reported that different plant communities experience reduced growth or biomass after taking up nanosilver from soil ^{124,77}. Soya beans, a major human and animal food source, have been shown to absorb and be adversely affected by nano zinc oxide and nano cerium oxide from contaminated soils ¹²⁵. Cerium oxide nanoparticles (despite conflicting *in vitro* and *in vivo* toxicity data) are viewed as having great potential as a cancer treatment and treatment for other diseases such as macular degeneration and hepatitis ⁵⁰. Yet at the same time their interaction with important food crops raises serious issues about how and when they should be used and, very importantly, their disposal ¹²³.

A recent review concluded that risk assessment of nanoparticles in soil will

be difficult because of the varying soil conditions¹²⁰. However, nanosilver, nano copper oxide and zinc oxide nanoparticles have been shown to damage beneficial soil microbes to varying extent depending on the soil type⁷⁶. Exposure to carbon nanoparticles may harm earthworms by slowing population growth, increasing mortality and damaging tissue¹²⁶. Data for many other nanoparticles used in nanomedicine is still lacking or sketchy.

Possible synergistic effects

An often overlooked aspect of environmental contaminants is that they usually exist as part of a complex mixture of chemicals in the environment. The composition of this mixture may increase or decrease the bioavailability of individual components and hence toxicity to organisms. For instance, the presence of nano titanium dioxide may increase the accumulation of cadmium in carp (*Cyprinus carpio*)¹²⁷. To date, little research has been done in the area of ecotoxicological effects of engineered nanoparticles in chemical mixtures and more research is urgently needed¹²⁷.

Lack of knowledge is hampering assessment of ecotoxicity

Ascertaining the ecotoxicity of nanomaterials and how they are distributed in the environment and the effect they may have on organisms is currently not only challenging, but also beset with limitations due to a lack of suitable monitoring equipment and extensive knowledge gaps¹²⁸. Currently no actual environmental monitoring of nanomaterials in the field has been reported, but this may change in the near future. In the interim, environmental models of the effect of nanomaterial release into the environment are being calculated and reported³⁴.

An extensive review of the potential health impact and environmental safety of

engineered nanoparticles was conducted in 2010, as part as the EU's 7th Framework ENRHES project¹²⁸. This review recognised that understanding of the environmental exposure risk of engineered nanomaterials was hampered by the general lack of data relevant to their soil and sediment behaviour, especially in relation to metal oxides and carbon nanotubes¹²⁹. A further key issue identified was the lack of comparability of research due to different functionalisation of nanomaterials, different experimental approaches and different levels of attention given to the characterisation of the nanomaterials used¹²⁹.

Given the novel properties and the novel ways that nanomaterials interact with living organisms and the environment, it is clear that all nanomaterials must be considered new chemicals.

4.4 Nanomedicine waste management

Nanomaterials may occur in a variety of products that are used in healthcare settings and that ultimately have to be disposed of, including not only nanomedicine products, but also cleaning fluids and paints as well as various items contaminated with nanomaterials (e.g., wipes and syringes). It is inevitable that some of the new nanotechnologies will end up in waste water treatment facilities, landfills or incinerators either as deliberate or accidental waste.

The minimisation of the amount and toxicity of waste generated by the healthcare sector, proper management and segregation of medical waste and the elimination of medical waste incineration by promoting and implementing alternatives has been one of the major campaign goals (and successes) of Health Care Without Harm. Unfortunately, the introduction of nanomedicines and nanomaterials in the healthcare sector

introduces many of the old but also new waste management issues.

Current regulatory guidance on nanowaste management is minimal, whole lifecycle data is largely unavailable, and the application of industrial waste treatment methods to nanowaste is problematic, due to the incomplete physicochemical definition of nanomaterials¹³⁰. Available research comparing methods used to treat nanowaste from research and manufacturing facilities concluded that

“nanowaste should be classified as hazardous waste, and as a minimum, double-bagged, enclosed in a rigid impermeable container and preferably bound within a solid matrix”¹³⁰.

Health Care Without Harm recommends a lifecycle approach to deal with nanomaterial waste, with special emphasis on end-of-life management. Nonetheless, virtually no guidelines on how this can be achieved are currently available. A report, funded by the UK Department for Environment, Food and Rural Affairs (June 2010), on lifecycle assessment of consumer products with carbon nanotubes (CNTs), concluded that urgent research is needed

“to address the almost total lack of exposure data for CNT-containing consumer products, and the appropriateness of end-of-life treatments”¹³¹.

The report went on to suggest that appropriate treatment should include separate collection of (spent) CNT-containing products under controlled conditions, and that disposal methods should ensure their complete destruction, which the report suggested could only be achieved by incineration.

Currently, neither European Directive 2008/98/EC nor Directive 1991/689/EEC, which govern waste management, mention nanomaterials at present as it is still too

difficult to assess whether nanomaterials meet the criteria of hazardous waste¹³². Key questions pertaining to the waste disposal of nanomedicines and medical nanowaste will revolve around their potential intrinsic toxicity, their recyclability, their fate and transport in the environment upon disposal, as well as general safety and hazard factors¹³⁰. EU waste management regulations and directives will need to be updated appropriately.

Solid waste treatment

Landfill is one of the major waste disposal options for solid waste. The incidental or known disposal of nanomaterial waste as solid waste raises concern about its effects on anaerobic (waste degradation and leachate treatment) and aerobic (leachate treatment) processes, as well as issues with the potential release of these nanomaterials into the environment through landfill leachate¹³³. A recent study focusing on the effect of water-soluble nano zinc oxide, nano titanium dioxide and nanosilver on biological landfill processes provided inconclusive preliminary results¹³³.

Waste water treatment

Waste water treatment plants will provide key entry points of nanomaterials into soil (via sludge) and freshwater. Some research on the effect of engineered nanomaterials on waste water treatment is starting to emerge. For instance, when sewage, biosolids and liquid effluent from a commercial wastewater reclamation facility were analysed, engineered nano titanium particles in a range of sizes were detected¹¹⁹. This clearly demonstrates the need to monitor waste water liquid effluent for these and other nanoparticles¹¹⁹. Furthermore, research that observed the release of silver ions from silver nanoparticles in natural waters under field conditions found that the particles persisted even after 4 months¹³⁴. The exact nature of the particles is likely to be crucial however -

for example, a polymer coating appeared to affect the fate and behaviour of nanomaterials in waste water treatment plants, with coated silica nanoparticles flocculating more readily than uncoated nano silica¹³⁵.

Incineration

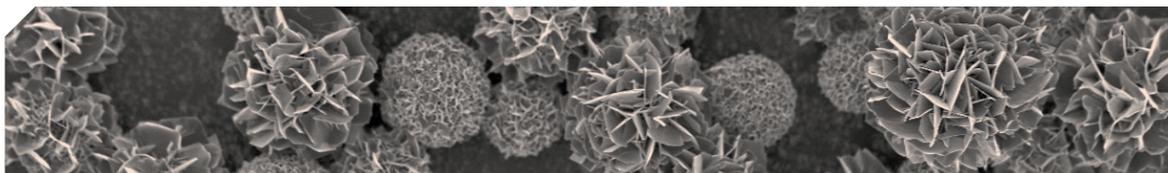
Incineration has been suggested as one of the methods to deal with nanowaste. Incineration of solid waste is still a common way of treating waste in many European countries, either directly into incinerators or via wastewater and then sludge incineration. Incineration is known to produce many toxic by-products including polycyclic aromatic hydrocarbons (PAHs), polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/Fs)¹³⁶. The toxic by-products may then be emitted into the atmosphere either in their gaseous and/or particulate phase.

The effect that nanomaterials contained in the waste may have on the hazardousness of these emissions is largely unknown. However preliminary evidence suggests nanomaterials may undergo physical or chemical transformations, may catalyse the formation and destruction of other pollutants (e.g., dioxins) and may affect the effectiveness of control technology to remove them, as well as affect their transport and impact in the

environment¹³². The interactions are likely to be dependent on the particle composition and available surface area. The limited experimental evidence shows that formation of pollutants can increase in some cases and decrease in others¹³². Some research reported that the total PAH (polycyclic aromatic hydrocarbons) emission factors were on average ~6 times higher for waste spiked with nanomaterials (i.e., titanium, nickel oxide, silver, cerium, iron oxide, fullerene and quantum dots) versus their bulk counterparts¹³⁶. Chlorinated furans were also formed at elevated concentrations when silver and titanium nanomaterials were part of the waste¹³⁶.

Recent experiments, conducted on the fate of nano cerium oxide in a full scale incineration plant, showed that while incineration did not release the nanomaterials into the atmosphere, the residues to which they bound ended up in the solid waste fraction¹³⁷. Further disposal of the nanomaterials bound to the bottom ash and fly ash may require special handling to prevent release into the environment.





The regulation of nanomaterials will remain a complex issue for the next couple of years. The European Commission has adopted a so called “incremental approach”, which focuses on adapting existing laws to include nanomaterials, including the regulations pertaining to medical devices and human medicines. Key issues currently include the classification and identification of nanomaterials, safety data and access to information, including labelling and the establishment of registries of nanomaterials and products. For nanomedicine, one of the big issues will be how to regulate crossover or borderline products, i.e., products that integrate medicines and devices. Finally, the manufacturing and production of medicines and medical devices at the nanoscale will also include worker OHS issues, contamination of the environment and waste management questions, which need careful consideration and may need additional regulations.

5.1 Nanomaterial definition

As discussed earlier, the nanomaterial definition adopted by the Commission in 2011 (2011/696/EU) will not be appropriate or sufficient to deal with many of the new nanomedicine products. The key limitation identified is that many of the products being developed will have a size above the rather arbitrary limit of 100 nm in one or more dimensions, while still having the essential properties of nanomaterials.

5.2 Nanomaterials under REACH

Currently, nanomaterials are not explicitly mentioned in REACH, the EU’s regulation on chemicals and their safe use (EC 1907/2006). Nanomaterials are clearly covered by the definition of a “substance”, however, REACH itself does not mention nanomaterials¹³⁸.

Three key limitations have been identified, which make the regulation wholly unsuitable for the regulation of nanomaterials and fatally weaken its capacity to ensure proper safety for humans and the environment:

- Given its silence on the subject, REACH does not insist that nanomaterials are separately registered. If considered equivalent to the bulk material, a manufacturer does not have to present a dossier of hazard information including specific data on the nanomaterials and acknowledge any novel properties.
- REACH applies only to materials produced in total quantities of over 1 tonne/year, which would exclude the majority of nanomaterials from having to be registered¹³⁹. Furthermore, because nanomaterials usually occur in low concentrations in the final product, further exclusion could occur since no registration is required when the concentration of a substance in the final product is lower than 0.1% w/w - which may be difficult to determine for nanoformulations. A further issue is the general lack of access to information due to commercial confidentiality clauses¹³⁸.

→ Finally, establishing the ecotoxicology of nanomaterials is fraught with limitations and difficulties²³. An overarching problem with EU legislation is that current test guidelines in REACH use conventional methodologies for assessing chemical risks that are most likely inappropriate for risk assessment of nanomaterials¹⁴⁰. For example, some of the standard tests for assessing the risk of bioaccumulation of medical products may not be appropriate^{141,142}. Similarly, environmental concentration thresholds may be inappropriate. Further risk assessment is triggered if surface water concentrations are predicted to equal or exceed 0.01 parts per billion, but this threshold is neither science-based nor can it be interpreted as a safe concentration¹⁴³. Given their increased reactivity and other novel properties, a mass-based concentration may be the wrong approach to describing the environmental profile of nanomaterials^{142,144}.

After five years of implementing REACH, the European Commission concluded that more specific requirements for nanomaterials are necessary but saw no need for specific new legislation¹⁴⁵. The Commission is however considering the modification of some technical provisions in REACH Annexes. Several European Member States,

researchers, NGOs, consumer organisations and workers' representatives have disagreed with this position on the basis that a revision of the annexes will not be sufficient to address all the issues that REACH should properly encompass^{36,37,38,39,40,146}

5.3 Medicinal product or medical device?

As mentioned previously, a key question for nanomedicine is whether nanomedicines are to be regulated as a medicinal product or as a medical device (see Box 9). EU legislation differentiates between medicinal products and medical devices, with different regulatory approaches for risk assessment. Preliminary market authorisation for medicinal products for human use is only issued after suitable clinical trials (Directive 2001/83/EC), while a medical device can be introduced with lesser degrees of testing depending on the risk category the device falls into (Directives 90/385/EEC, 93/42/EEC, 98/79/EC and 2007/47/EC currently under revision: COM(2012)542 final).

In the new proposal for a regulation on medical devices, and taking into consideration the scientific uncertainties about the risks and benefits of nanomaterials used in medical devices, the European Commission proposes that

Box 9 | Medicinal products or devices?

Currently, EU legislation defines medicinal products and medical devices as follows:

A MEDICINAL PRODUCT:

"(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." (Directive 2004/27/EC)

A MEDICAL DEVICE:

"...any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any

accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for medical purposes for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means." (Directive 2007/47/EC)

“All devices incorporating or consisting of nanomaterial are in class III unless the nanomaterial is encapsulated or bound in such a manner that it cannot be released into the patient’s or user’s body when the device is used within its intended purpose”¹⁴⁷.

Class III triggers the most severe conformity assessment procedure. At the time of writing, this specific recommendation is being questioned at the European Parliament level and might be rewritten in the new Regulation to cover only devices which intentionally release nanomaterials.

Some nano products have already been registered in Europe as medical devices, many clearly with mechanical functions such as carbon nanotubes in bone cements, nanopaste hydroxyapatite powder for bone void filling and polymer setting material with nanoparticles in dental cements⁴⁶. However, nanosilver or other nanomaterials used as coatings on implants and catheters and as wound dressings can be argued to combine mechanical (protecting a wound) and pharmacological functions, and could be construed as both a medical device and a medicinal product. The same could be argued of thermo cancer therapy (see above) where

tumour cells are mechanically destroyed by nanoparticles (a device) but which is followed by later metabolism (medicine)⁴⁶. The European Commission’s Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) considered (without coming to a conclusion) that

“the immediate effect is mechanical as the tumour cells burst. On the other hand, one might regard the legislation on medicines applicable as the burst cells are metabolised at a later point in time”¹⁴⁸.

Without specific provisions for products that exhibit characteristics of both, i.e., combining mechanical, chemical, pharmacological and immunological properties, and/or combining diagnostic and therapeutic functions, a potential third category might be needed to regulate these products¹⁴⁹.

It is also unclear at this point whether the currently required toxicological studies are adequate and sufficient. Will, for instance, nanomedicines require new testing models *in vitro* and *in vivo* at the preclinical stage¹⁵⁰? The US National Cancer Institute is standardising and conducting preclinical toxicology, pharmacology and efficacy tests for nanoparticles and devices through its Nanotechnology Characterization Laboratory



in order to prepare products for US clinical approval. The EU has also indicated the intention of establishing such a centre, but this has as yet not progressed any further¹⁵¹.

5.4 Mandatory EU register and labelling

A number of EU member countries and NGOs have recently proposed the establishment of an EU Register of nanomaterials used in products, and/or of products containing nanomaterials. The purpose of such a register is to assure maximum transparency of the use of nanomaterials in all products, including in the medical area. A register could fulfil a number of purposes: monitoring of the potential adverse health and environmental impacts of nanomaterials; improving companies' knowledge of the substances they are manufacturing and using; increasing information and traceability throughout the supply chain for all stakeholders; and increasing knowledge of toxicity and ecotoxicity and resources invested in risk assessments for nanomaterials. Overall, this would increase the sustainability of nanotechnology while providing confidence and transparency for the general public and workers.

While the Commission is not advancing with a EU level register, and has delayed a consultation on this topic to evaluate the potential costs of operating such a system and its impacts on health and the environment, several European countries are initiating or considering national projects. France was the first country to put in place a nano register (January 2013), while Belgium is proposing to start one in 2015 and Denmark is currently consulting interested stakeholders.

The French nano register requires companies that manufacture, import and distribute nanomaterials in quantities of ≥ 100 g to submit to the authorities an annual declaration

stating the quantity and information on use. The aim is to better understand how and where nanomaterials are being used; enable traceability; improve knowledge of the market and volume of nanomaterials involved; and collect available information on the toxicology and ecotoxicology of nanomaterials¹⁵². The nano register received more than 3400 registrations in 2013. In the French system, nanomaterials which are intentionally released under normal or reasonably foreseeable conditions due to washing, abrasion or wear do not need to be registered¹⁵⁴.

Belgium is proposing a system in line with the French that would require all manufacturers, distributors or importers of substances at the nanoscale (>100 g/year) to register their products via an online portal from 2015. Unfortunately, cosmetics, biocides, medicines for humans and animals, food contact materials and animal feed would be excluded.

In the new proposal for a regulation on medical devices, the European Commission advanced with mandatory labelling for medical devices containing nanomaterials (as noted above):

"unless the nanomaterial is encapsulated or bound in such a manner that it cannot be released into the patient's or user's body when the device is used within its intended purpose"¹⁴⁹

This would limit the scope of labelling provisions, ignoring materials which might give rise to accidental or unintentional releases.

5.5 Improving worker safety

There are a number of Directives in place and a Health and Safety Strategy implemented in the EU-28 Member States that should in principle provide a measure of OHS preventative measures. Employers are obliged to conduct regular workplace risk

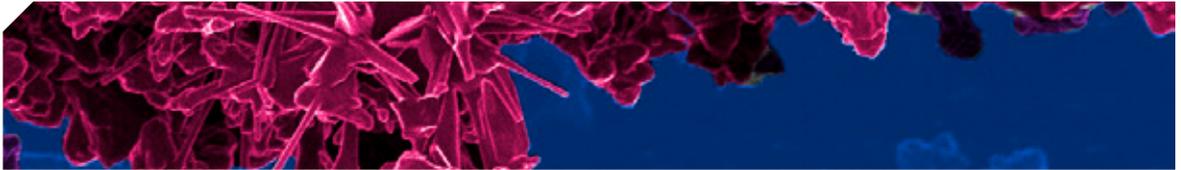
assessments and put in place adequate prevention measures (EU Directive 89/391/EEC). Chemical agents at work are stringently regulated according to Directive 98/24/EC. And of course, if a nanomaterial, or the macro-scale material of the same composition, is recognised as a carcinogen or mutagen, then Directive 2004/37/EC on carcinogens and mutagens at work must be followed.

The European Commission has assumed that these pieces of legislation also protect workers from the risks of nanomaterials. However, these EU Directives do not specifically mention nanomaterials and their provisions are difficult to apply because nanomaterials are not defined as hazardous substances *per se* according to REACH. Furthermore, methodologies to identify nanomaterials are lacking and, with no labelling requirements at European level, information on their presence in products and the possible risks are not available to workers. As such, these Directives do not protect workers, and Trade Unions (namely the European Trade Union Confederation) and the European Parliament have already asked for specific legislation that protects workers from the risks of nanomaterials^{36,40,155}.

5.6 Nanowaste

At present, EU waste management legislation does not have specific provisions to address nanowaste. The European Commission believes that the current legislation also applies to nanowaste. However, this is not always the case and the European Parliament has asked the Commission to review its waste legislation and provide specific guidance on how to manage nanowaste to avoid health and environmental issues, particularly from incineration and landfill activities³⁶.





Nanomedicine is already a reality and has the potential to deliver many advantages for the diagnosis and treatment of many health problems. A number of technologies are already on the market or being tested in clinical studies, using a myriad of nanomaterials. Health Care Without Harm recognises that nanomedicine can bring many benefits to patients and the healthcare professions. However, there are many reasons to consider that new risks may arise to affect human health and the environment.

The basis for these concerns lies with the different properties of nanomaterials, the many gaps in knowledge, the lack of methodologies and tools for assessment and management of any risks, and our conclusion that the regulatory framework is insufficient to protect human health and the environment. The risks will of course be dependent on the specific materials in use and on the exposure routes, but cannot be dismissed while they are not clearly identified. Because of this, Health Care Without Harm believes that legislators have an important role to play in protecting human health and the environment from the potential risk of exposure to nanomedicine and nanomaterials. A strong regulatory framework will give confidence in the use of nanomedicine, and a number of policy recommendations from Health Care Without Harm follow below.

Apply the precautionary principle

The potential of nanotechnology to bring

societal and environmental benefits remains largely unproven. Nanomaterials are essentially new and largely untested chemicals and little is known about their persistence, bioaccumulation and toxicity, although many would fall into the category of toxic materials. Therefore, in view of the potential risks of nanomaterials to human health and the environment and the lack of knowledge, preventive action should be taken and the precautionary principle must be applied. Without a clear knowledge of the risks involved for human health and the environment, products should not be allowed into the market. This is particularly important for dispersive applications such as disinfectants, which do not have a clearly established medical benefit over and above other products.

Address limitations of EU regulatory frameworks

Nanomaterials are new chemicals and should be classified as new substances in EU legislation, placing the burden of proof for safety in the hands of nanotechnology producers and distributors. One of the biggest issues is that of regulating nanomedicine products, as many will be crossover or borderline products with mechanical and chemical functions. Therefore, it is important to:

- Improve the current nanomaterial definition by adopting a more broad definition that does not restrict the size threshold to 100 nanometres in one or more dimensions, in accordance with

the definition of the European Medicines Agency.

→ Amend REACH, maintaining the dictum “no data, no market” and taking into consideration:

- A need for different threshold requirements for registration of nanomaterials.
 - That specific data for dossier information should be required to ensure that the manufacture, marketing and use of nanomaterials in nanomedicine products or others have no harmful effects on human health or the environment during the entire life cycle.
- Specify clear provisions for nanomedicine products that exhibit characteristics combining pharmacological and mechanical functions so that they are regulated as a third category which acknowledges the risks of both intentional and non-intentional release of nanomaterials into patients and healthcare professionals.
- Review EU waste management legislation to take into consideration specific properties and characteristics of nanowaste and to provide guidance on management of nanomaterials in waste, including in landfills, whilst avoiding health and environmental consequences.

Identify and categorise nanomaterial characteristics to ensure appropriate testing methodologies

Testing methods for nanomaterial toxicity are still very much under development, hence knowledge on toxicological and ecotoxicological properties is insufficient to conduct proper risk assessment¹⁴⁰. The recommended testing requirements to ensure the safe use of nanomaterials can be grouped into:

- Substance identification and characterisation based on physicochemical properties;

- Toxicological properties; and
- Environmental fate and behaviour including ecotoxicological properties.

In order for appropriate testing to be carried out all nanomaterials need to be identified in terms of:

- crystal structure
- primary particle size distribution
- agglomeration/aggregation state
- specific surface area
- morphology/shape/aspect ratio
- information on surface modifications
- catalytic properties
- free radical formation potential
- surface charge/zeta potential
- dustiness (i.e., the propensity of a material to generate airborne dust during its handling)
- the fate and properties of nanomaterials in water, and
- photo-degradation potential.

Prioritise research to address safety concerns regarding the risks of nanomedicine products in human health and the environment

Research into nanomaterials and nanomedicine has continued to increase in recent years, but it has been focused towards improving technological innovation and, unfortunately, the potential risks of nanoproducts have remained poorly assessed. When nanomedicine products enter into the environment it is crucial to understand their fate and effects in terms of bioavailability, bioaccumulation, toxicity, environmental transformation and interaction with other environmental contaminants. Also current test guidelines use conventional methodologies that are unlikely to be appropriate for the assessment of risks associated with nanomaterials. Therefore it is important to:

- Fill in the scientific knowledge gaps on safety, fate and persistence of nanomaterials in humans and the environment.

→ Develop nanomaterial-specific standards, guidelines and tools to detect, monitor and measure nanomaterials in the environment and the effects of exposure of these materials on human health and the environment.

Consider the entire lifecycle of products when considering the benefits of nanomedicine

The entire lifecycle (including the manufacture, transport, use, environmental impacts and end-of-life management) of nanomaterials needs to be addressed when considering the potential benefits and risks of nanomedicine. For example it is important to:

- Develop guidelines to assess end-of-life management options for nanomaterials that include:
 - The potential intrinsic toxicity of nanomedicine waste and the hazardous effects of incineration emissions.
 - Prediction of the fate and transport of nanowastes in the environment upon disposal.
 - Assessment of whether nanowaste should be listed as hazardous waste.
 - Research into the current handling, treatment, storage and disposal practices for bulk materials and their appropriateness for the respective nanoform.
- Discourage the use of nano-based cleaners and disinfectants in hospitals. Nano-based cleaners may act as potent antibacterials but may also exacerbate antibacterial resistance. They should only be used in the context of treating serious medical conditions.

Patients, workers and communities need full access to information and to be part of the decision-making process

Transparency, despite numerous stakeholder dialogues and other public relation exercises pertaining to nanotechnology, has not been a hallmark of the emerging nanotechnology industry. In many of the “dialogues” there has been a heavy emphasis on convincing the public of the potential (but as yet mostly unproven) benefits of nanotechnology and very little information on the potential risks associated with substantially unregulated and untested products that have been introduced into the market. In terms of nanomedicine, very little stakeholder involvement has occurred. Perhaps this is because nanomedicine has been perceived primarily as the domain of the medical profession, rather than a range of “products” that has the potential to affect not only patients but also healthcare workers, the wider community and the environment. It is therefore important to:

- Create a mandatory EU register for of the production, import and use of nanomaterials and nanomedicine products.
- Introduce compulsory labelling of all nanomedicine products, so patients and healthcare workers can take informed decisions about the use of such products.
- Increase public participation in decisions regarding the exposure of patients, workers and communities to nanomaterials and nanomedicine.

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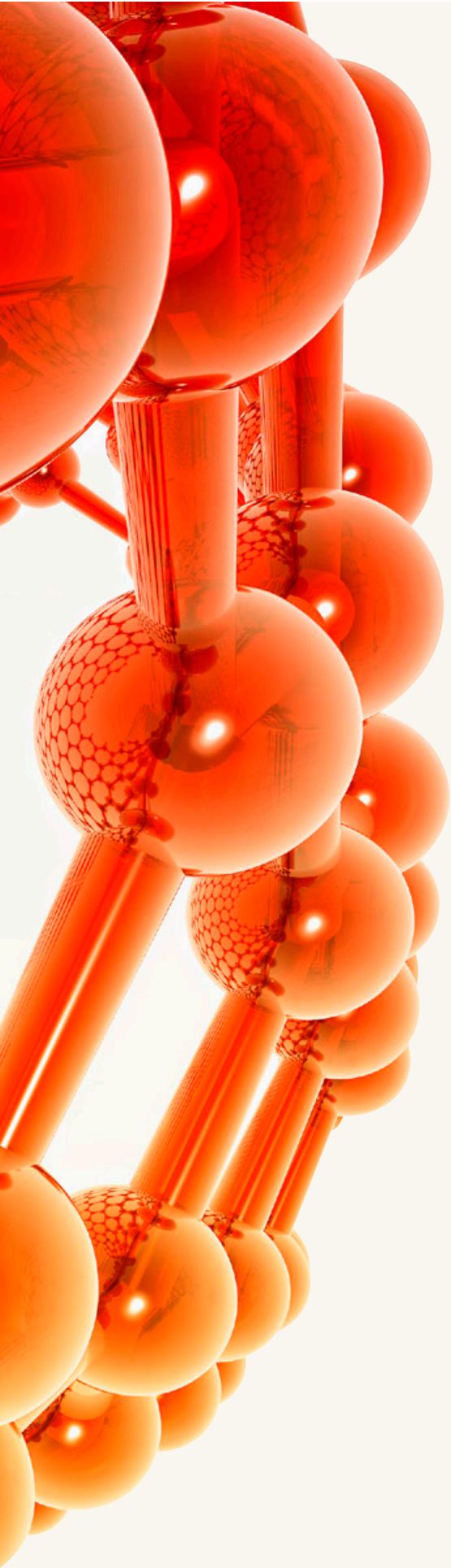
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