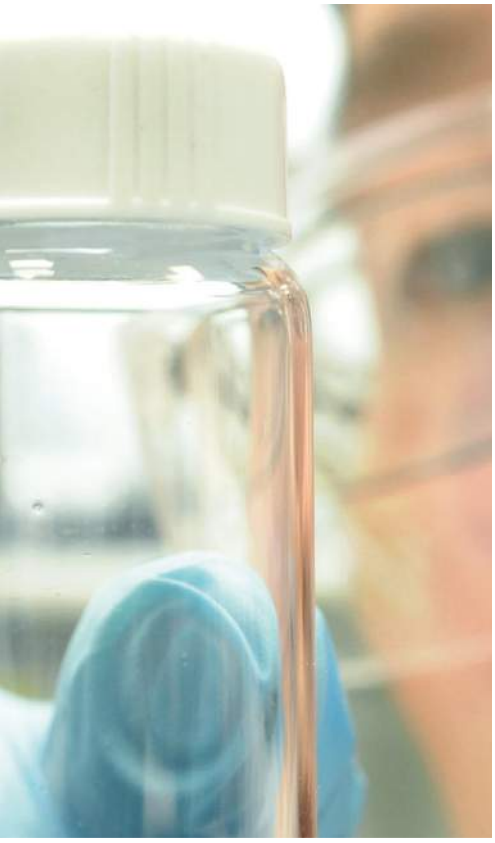
Health Care Without Harm

[How innovations in healthcare research can lead to uncertainties in public health]

The era of nanomedicine



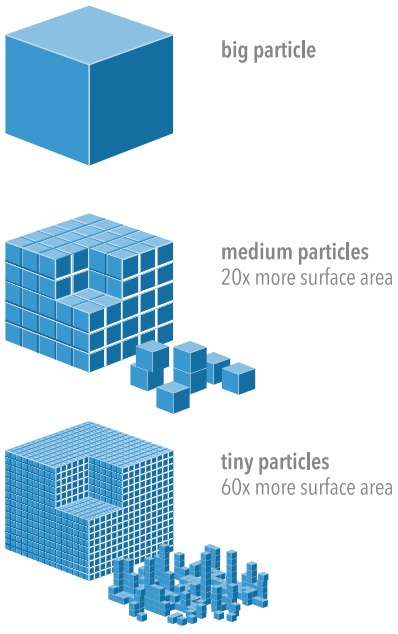
Nanomedicine offers innovative solutions for the diagnosis, monitoring, prevention and treatment of clinical conditions. However, the new properties of nanomaterial products, while desirable from a strictly clinical perspective, can create new risks for human health and the environment. As the European Union chemicals legislation does not yet recognise that such materials have very different properties from the parent chemicals, it does not provide a framework for the monitoring of bioaccumulation and persistence of nanomaterials in the environment or for their toxicity to human health and the environment. Precautionary action should therefore be taken and a regulatory framework put in place in order for nanomedicine to deliver on its promises without introducing new risks for patients, workers and the environment.

What is nanomedicine?

Nanomedicine is an application of nanotechnology. Nanotechnology refers to nanoscale or nanostructured materials (with one, two or three dimensions measured in nanometres), which are engineered to have unique medical effects based on their size and structure. Nanoscale materials present novel properties, such as increased surface area, that cause them to have greater chemical reactivity, biological activity and catalytic behaviour. They also have better penetration of biological membranes and better access to cells, tissues and organs of living organisms[1,2]. Although such attributes can be highly desirable for therapeutic purposes, they may result in greater toxicity if unintentional exposure occurs[3,4]. Nanomedicine has the potential to revolutionise healthcare.

> Nanomedicine products are already on the market

Nanomedicine products are already on the market, reaching €37.4 billion in 2011 and foreseen to double by 2016[5]. A 2010 international review yielded 100 commercially available products and 147 products in various stages of clinical study[6]. These products are mainly anaesthetics and treatments for various disorders such as cardiac and vascular, immune, and degenerative disorders[6] as well as cancer.



The increased surface area provided by nanomaterials

Human Health Concerns

Despite the beneficial applications of nanomedicine, there are potential risks to human health due to the uncertain interaction between nanomaterials and living systems. While their key function of being able to cross biological barriers is desirable in a clinical context, this can be highly toxic to non-target organisms. Ultrafine particles are easily inhaled and can cross the air-blood barrier in the lungs before gaining access to the rest of the body. They can also pass through the skin and the gastrointestinal track. Crucially, nanomaterials, such as gold nanoparticles[7] and quantum dots[8], have been shown to cross the maternal-foetal barrier.

Besides patients, healthcare workers may be at risk of accidental exposure. The European Agency for Safety and Health at Work warns that nanomaterials, including silver, gold and titanium nanoparticles and carbon nanotubes, pose potential health hazards and occupational health and safety risks. Safety Data Sheets generally contain little or no information about nanomaterials such as where they are present, what their characteristics and risks are, or how to prevent exposure[9].

Environmental Concerns

Components of nanomedicine products mainly enter the environment through human metabolism and excretion into the sewage system. A 2013 study of the global lifecycle of engineered nanomaterials estimated that, in 2010, between 260,000 and 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 %)[10]. A recent review of toxicological research on nano metal oxides – silver, copper and zinc – reported that they are extremely toxic to freshwater aquatic organisms, including fish and algae, with crustaceans most affected[11]. Different plant communities experience reduced growth or biomass after taking up nanosilver from soil[12,13]. 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[14]. Synergism may be a source of risk as well. For instance, the presence of nano titanium dioxide may increase the accumulation of cadmium in carp (*Cyprinius carpio*)[15]. Understanding of the environmental exposure risk is hampered by lack of data relevant to soil and sediment behaviour, especially in relation to metal oxides and carbon nanotubes.

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 uptake.

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 al*

Case study

Nanosilver

Nanosilver is used extensively for wound management and prevention of bacterial infections. It can be found in plasters, silver-coated catheters, textiles and other essential medical equipment, as it is more effective than bulk silver. However, overuse of nanosilver in consumer products may induce bacterial resistance. A recent study reported for the first time that *Bacillus* spp. could develop resistance to nanosilver cytotoxicity upon exposure[16]. In addition, the widespread and indiscriminate use of nanosilver in healthcare settings may further contribute to the induction of resistance. Elevated concentrations of silver nanoparticles in wastewater effluents can lead to silver resistance in environmental bacteria, damage beneficial soil microbes or exert toxic effects on aquatic organisms such as algae[17].

Regulatory Challenges

The International Organization for Standardization (ISO) defines nanoscale to be in the range of "approximately 1 nm to 100 nm"[18]. In 2011, the European Commission also adopted a recommended definition of nanomaterial using this size range. Notably, many nanoparticles in nanomedicine products are larger than 100 nm: liposomes are 100-200nm, nanoshells 40-600nm, and drug delivery systems 100-200nm. However, these larger nanoparticles still share many of the characteristic behaviours and novel risks of nanoparticles smaller than 100nm; therefore the Commission's recommended definition will not be appropriate or sufficient enough to deal with many new nanomedicine products.

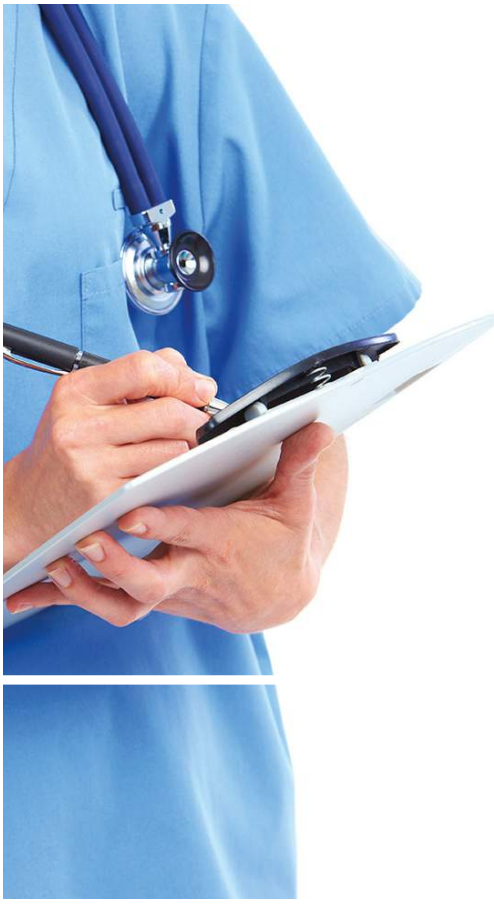
In addition, some nanomedicine products fall into both the medicinal products category and medical devices category. These categories follow different regulatory approaches for market access, mainly regarding the degree of testing and clinical trials required. An example of such a cross functional nanomedicine product is nanosilver, used as coatings on implants and catheters and also as wound dressings, which can be argued to combine mechanical (protecting a wound) and pharmacological functions, and could be considered as both a medical device and a medicinal product.

Moreover, The Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals, (REACH) applies only to materials produced in total quantities of over 1 tonne/year, which would exclude the majority of nanomaterials from needing to be registered[19]. As nanomaterials usually occur in low concentrations in the final product, further exclusion could also occur since no registration is required when the concentration of a substance in the final product is lower than 0.1%, which may be difficult to determine for nanoformulations. A manufacturer that is subject to REACH registration does not have to submit a dossier of hazard information, including specific data on nanomaterials, and current test guidelines in REACH do not contain specific tests for assessing the risk of bioaccumulation or environmental concentration thresholds for nanomaterials.

Policy recommendations

Given the challenges to address and control nanomaterials and nanomedicine at the EU level, HCWH Europe recommends the following actions in order of responsibility and challenges that nanotechnology presents:

1. Form an appropriate definition of nanomedicine products that includes nanoparticles larger than 100 nanometres and takes into account the risks associated with the larger particle size.
2. Define nanomaterials as new chemicals within REACH, subject to specific regulatory requirements that take into account novel properties and hazards of nanomaterials.
3. Create a potential regulatory category for the market authorisation of nanomedicine products that exhibit both pharmacological and mechanical functions so such products are properly scrutinized before entering the market.
4. Overcome the scientific gap on safety, fate and persistence of nanomaterials in humans and the environment by developing appropriate tools for their detection as well as monitoring and adopting specific standards and guidelines.
5. Establish an EU Register of nanomaterials used in products and/or of products containing nanomaterials in order to increase the sustainability of nanotechnology while providing confidence and transparency to the general public and workers.
6. Extend labelling requirements at the EU level; information on the presence of nanomaterials in products and the potential risks should appear on a label in order to improve workers safety.
7. Increase public participation in decisions regarding the exposure of patients, workers and communities to nanomaterials and nanomedicine.
8. Include specific provisions in EU waste management legislation to address nanowaste. The entire life-cycle (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.



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