ObservatoryNANO

WP5: Environmental, Health and Safety (EHS) Impacts

Technology Sector Evaluation: Health, Medicine & Nanobio V 1.1 March 2011

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1. Introduction

Nanotechnology has found applications in many industries. Nanomedicine has grown as a discipline in itself and the development of novel structures and advances in nanomaterials are fuelling growth and innovation in the area. The potential of nanotechnology in medicine has been recognised, and a significant amount of funding has been provided to the sector. The number of conferences taking place around the globe on nanotechnology in medicine is an indicator of the interest and potential offered by nanoscience and nanotechnology. The *Cancer Nanotechnology Plan* by the National Cancer Institute in US and the European Technology Platform Nanomedicine have set out plans for the future research activities needed in the area. A roadmap project which sets out the timeframe for nanomedicine applications has been supported by the European Commission (EC). Several other projects relating to nanomedicine have been funded by the EC 6^{th} and 7th Framework programmes. Many national and pan-European networks also exist, with the aim of bringing together stakeholders to discuss and share information. Nanomednet in the UK, Nanoned in Netherlands, the Spanish nanomedicine platform, CC-NanoBioTech in Germany, and the European Foundation for Clinical Nanomedicine (CLINAM) are examples of such networks which aim to bridge the gap between different groups including scientists, industry, clinicians, investors and policy makers.

This report examines EHS aspects relating to developments in nanomedicine as reported in the ObservatoryNANO technology sector report on Health, Medicine & Nanobio (Moore *et al.*, 2009). That report is subdivided in six subsectors:

- Therapeutics,
- Sensors & Diagnostics,
- Regenerative Medicine,
- Implants Surgery & Coatings,
- Novel Bionanostructures, and
- Cosmetics.

In each of the subsector reviews, key technologies and their descriptions are provided. The state of R&D in that particular area is described and additional demands for research are briefly outlined.

The subsector **Therapeutics** discusses drugs and their associated delivery systems used for the treatment of disease. The subsector describes new tools and techniques to achieve a better targeting of drugs, which aim to reduce drug toxicity and improve efficiency of treatment. Also, drugs may be protected from degradation, reducing the number of doses required. Another use of may be delivery of insoluble drugs.

The subsector **Sensors & diagnostics** applies to nanomaterials and tools for measuring nanoscale phenomena both *in vivo* and *in vitro*. The technology has facilitated the development of small, highly sensitive, inexpensive devices for the manipulation and analysis of cells. Improvements in existing techniques due to novel nanomaterials and surface modification methods make it possible to analyse intracellularly in real time, and to detect various analytes simultaneously. More detailed and in-depth analysis of cellular functions is helping scientists and researchers to detect diseases at a very early stage and find suitable cures.

The subsector **Regenerative medicine** describes those nanomaterials and techniques employed to repair or replace damaged soft and hard tissue: tissue engineering. Tissue engineering is the use of cells and their molecules in artificial constructs that compensate for lost or impaired body functions. Scaffolds made of porous biomaterials which mimic the cellular environment are seeded with cells and allowed to grow there. The grown tissue construct is then implanted into the body of the patient where it replaces the diseased tissues and the scaffold degrades. With the emergence of nanotechnology and new characterisation tools, it has become easier to synthesise and characterise materials at the nanoscale to enhance the activities of biological molecules and to mimic the biological functions. A better interaction between extracellular matrix (ECM) and cells is expected which determines the cell growth, mobility and behaviour. The use of nanomaterials in tissue regeneration can help to create an environment which mimics the natural conditions promoting cell adhesion, cell differentiation and cell growth. The delivery of proteins, peptides, genes and other growth factors in a sequential manner is also important in assisting cell growth.

The subsector **Implants, surgery & coatings** describes nanomaterials that can be used in both active and passive implants and in surgical procedures. Nanotechnology has the capability to improve implant biocompatibility, either by coating implants with nanomaterials or by using nanomaterials as implant materials. Different types of coatings can be applied to improve the sustainability of the implants and protect them against bacterial and fungal infection. Coatings have also been applied in synthetic vascular grafts to avoid the deposition of biological material, thereby reducing the chances of occlusion. Nanoscale materials can be used to make lighter and stronger implants that last longer, but also to accelerate cell growth after implantation. The ultimate aim of using these novel technologies in implants, surgery or wound care is to heal the body quickly and efficiently without creating excessive pain or irritation. It may also allow development of biomimetic cures for some of the chronic and degenerative diseases.

In the subsector **Novel bionanostructures**, defined as 'engineered nanoscale structures made from biological material or for biological purposes', the development of such structures and their manipulation for different applications is described. Self assembling molecules which form novel nanostructures have already found applications in different areas ranging from drug delivery to cosmetics. Lipid-based nanostructures like liposomes and nanosomes have been used in the cosmetic industry for the last two decades. While the applications of self assembling molecules are slowly reaching the market, fundamental research on the self assembly of molecules to understand the complex cellular processes as well as next generation electric circuits are gaining pace. The efforts are now on developing molecular switches, e.g. chemically self assembling molecules which can be switched on and off. Complex molecules like catenanes and rotaxanes have been used to create molecular motors.

The subsector **Cosmetics** covers different products applied to skin or hair. The applications of nanotechnology and nanomaterials can be found in many cosmetic products including moisturisers, hair care products, make up and sunscreen. Almost all the major cosmetic manufacturers use nanomaterials in their products. The European Commission estimated in 2006, that 5 % of cosmetic products contained nanoparticles. The use of nanomaterials in cosmetic products has been the subject of continuous discussion in the media, scientific circles and among policy makers for the past few years. There are a number of classes of nanoparticles used, or proposed for use, in cosmetic applications. In cosmetics there are currently two main uses for nanotechnology. The first of these is the use of nanoparticles, like titanium dioxide (TiO_2) and zinc oxide (ZnO), as UV filters. The second use is nanotechnology for delivery, e.g. liposomes and niosomes. For both uses newer applications are being investigated. The section on cosmetics provides an overview of current activity on nanotechnology in the cosmetic industry.

The key common knowledge gap across all nanoparticle applications is the lack of exposure measurements. As the ObservatoryNANO Project progresses, it is expected that this knowledge gap will be addressed (at least in part). This, coupled with additional information on nanomaterial toxicology should in future enable more resolute conclusions on the risks posed by those nanomaterials in consideration.

2. General Considerations for the Environment, Health & Safety Impact of nanomaterials

The key benefit from nanotechnologies is the ability to exploit the specific, novel and sometimes unpredictable properties that arise from structuring matter at this scale. Over the last 10 years, nanotechnologies have received extensive investment, and have emerged as major drivers of science based innovation and industry. This has led to the development of new processes, products and materials for a wide range of applications.

In 2004 the UK's Royal Society and the Royal Academy of Engineering (RS/RAEng) published a seminal review of the "opportunities and uncertainties" presented by nanotechnologies (Royal Society & Royal Academy of Engineering, 2004). Whilst indicating that for many nanotechnologies, there were no foreseeable risks to health or to the environment, the report concluded that for "nanoparticles and nanotubes" there were potential risks, and that not enough was known about them. This conclusion was based on evidence gained from many years of research that exposure to particles can cause ill health within individuals or exposed populations. For example, within the occupational setting, exposure to coal dust is evidentially linked to the onset of lung diseases including pneumoconiosis and chronic obstructive pulmonary disease (COPD), and exposure to asbestos is causative of asbestosis, mesothelioma and lung cancer. In an environmental context, evidence suggests that exposure to the particulate component of atmospheric pollution may be associated with increased hospitalisation rates and cardio-vascular disease (Seaton *et al.*, 2009).

Publication of the RS/RAEng report led to a huge increase in research activity concerning both human health and environmental consequences (Aitken *et al.*, 2009a). For example, in Europe the Framework 7 NMP programme has funded more than 20 major projects, with a total budget of more that €50million. This research activity has addressed *inter alia* the toxicity and ecotoxicity of many types of nanoparticles, the kinetics of nanoparticles within biological and environmental systems, the extent to which individuals or the environment can become exposed and the level of risk which would result. These investigations have examined numerous mechanisms, end points and processes and materials, and have generated an extensive body of literature, particularly in relation to toxicology and ecotoxicology.

2.1. Establishing a knowledge on the potential hazard and exposure to nanomaterials

Scientific data compiled to date demonstrates that adverse health effects due to exposure to nanoparticles cannot be ruled out (Aitken *et al.*, 2009a, Aitken *et al.*, 2009b, Van Zijverden & Sips, 2009). However, although awareness for the importance of risk research has increased, critical information still is lacking to enable estimation of the risks posed by nanoparticles with equal certainty to those of other non-nano substances. Nevertheless, hundreds of products containing nanomaterials are currently available commercially, a situation which clearly necessitates investigation of the exposure and toxicity of these materials in the near future. Unfortunately, the research questions to be answered are so numerous that it will take years to compile the relevant data.

The potential for nanoparticles to cause damage has also been implicated within the environment, both directly via uptake into plants or organisms (including soil bacteria, eukaryotes, invertebrates and vertebrate species), and indirectly via changes in environmental variables such as pH of aquatic systems, ionic strength or dissolved organic carbon content (Aitken *et al.*, 2009a). Carbon nanotubes (CNT) and silver nanoparticles have been shown to cause detrimental effects in zebrafish development (Cheng *et al.*, 2007), and copper nanoparticles have been shown to be highly toxic to fish, daphids and algae (Griffitt *et al.*, 2008), and to induce stunting of exposed plant seedlings (Lee *et al.*, 2008).

Man and the environment can come into contact with the use of nanotechnology through a wide range of application areas. Some of these applications are produced only with the aid of nanotechnology, others contain nanomaterials. For the risk assessor, this second category is important, particularly when the applications contain non-degradable, insoluble, and freely available nanoparticles. For this category of products there are already a great many different areas of potential use, including medical applications, food, and consumer products as well as environmental and energy technology. These applications can improve the quality of life and the environment and can also lead to significantly more sustainable products, but for which it is of particular importance to understand and control potential risk.

There are already hundreds of nanotechnology applications on the market. For example, nanoparticles of titanium oxide and zinc oxide are regularly used as UV reflectors in sunscreen creams. Nanotechnology is also used to make clothing crease- and dirt-resistant, and to make electronics ever smaller, faster and more multifunctional. However, the majority of potential applications for nanotechnologies are currently still in the research and development phase and are expected to appear on the market over the coming years.

Understanding and effective management of potential risks posed by manufactured nanoparticles and nanomaterials is pivotal for responsible and sustainable development of nanotechnology. This in turn is mandatory for societal acceptance and exploiting the significant economic potential of this technology to the full.

2.2. Risk Assessment considerations for nanomaterials

In assessing the risks of non-nano chemical substances and nanomaterials alike, the following general approach is applied:

RISK = HAZARD (TOXICITY) x EXPOSURE

The intrinsic hazard (toxicity) of a nanomaterial is determined by a number of factors, such as the ability of a nanoparticle to pass through certain barriers in humans, plants or animals and cause damaging effects. The actual exposure is also determined by various factors such as the form in which the nanomaterial occurs (*e.g.*, either bonded or as 'free' particles) he specific setting in which the nanoparticle is being manufactured applied or used (and thus likelihood of contact). Thus, a specific nanomaterial may be hazardous, but if the level of exposure is very small, the ultimate risk will always be limited. For example, a specific nanoparticle bound within ultra-high performance concrete used to construct a bridge will pose less of a potential risk to consumers (*i.e.* those using the bridge), than the same NP used within antimicrobial food packaging, where the potential for consumer exposure may be increased due to their close contact with the product in which the NPs are bound.

Two areas can be distinguished within risk research for nanotechnology. One area aims at risks related to exposure to nanomaterials and the second area aims at risks related to the rest of nanotechnology and its products. There is consensus that the uncertainties about these risks need to be addressed most urgently.

In 2009, the Dutch Knowledge and Information Point "Risks of Nanotechnology" (RIVM/KIR nano) recommended to focus research primarily on those questions that provide information critical to the assessment of risks to man and the environment

(Van Zijverden & Sips, 2009). Depending on the perspective – worker, consumer, patient, or the environment – the starting points can then be defined for controlling or limiting the risks.

From this and other literature on the topic, there may be identified several key challenges for the EHS appraisal and risk management of nanomaterials:

1. *There is a high urgency for relevant risk information:* One of the pitfalls of emerging technologies is the imbalance between technological development and attention for human health and environmental safety issues as is the case for nanotechnology. Risk information needs to be generated and shared as quickly as possible for products on the market, underpinning the societal acceptance of further applications of this technology.
2. *Validity of known test systems is questionable, and detection of nanomaterials still problematic.* Nanomaterials create a challenge for risk research as they (might) behave differently in regular assessment and testing systems. Equipment and methods to detect nanomaterials allowing large-scale application are lacking.
3. *National, international and interdisciplinary integration is a prerequisite.* A large variety of research questions need to be addressed before uncertainties about risks for man and the environment are at the same level as for other chemical substances.

Whilst this brief introduction provides an outline of the key issues, it is impossible to outline the current knowledge on the hazard, exposure and risk assessment for nanoparticles in full. Instead the reader is directed towards the ObservatoryNANO Baseline Studies (Ross *et al.*, 2009) where many of the seminal studies from the last few years are identified and described.

2.3. The ObservatoryNANO Approach: Integrating EHS considerations with development of novel applications for nanotechnologies

ObservatoryNANO is concerned with mapping scientific and technological development across 10 core technology sectors, and a key task of WP5 is to undertake an appraisal of these reports and to identify potential emerging environment, health and safety issues therein, thus integrating the development of novel applications with risk research, an approach which is urgently required.

There is considerable overlap between those nanoparticles used across these 10 sectors – what differs is their use, which varies according to the application. Therefore the aspect which is specific to the technical sector in considering those novel risks which may arise from development of novel applications, is the potential for exposure. For this reason, the approach which we have adopted is to consider the potential exposure which may arise from the new applications identified.

As far as possible, we have considered the life cycle of the applications identified, whether there were possible exposures within the occupational setting, or to consumers or release to the environment. We also considered whether there was the potential for release from disposal.

Our review process involved extraction of information from each technology sector report & gathering of additional information from their lead authors. This data was then analysed, and our findings outlined within the subsequent sections of this report. In addition to a short summary of the key exposure issues identified from our analysis, our report includes three key tables as follows:

1. A table summarising all information gathered together with consideration of the potential for exposure arising throughout the lifecycle of each application
2. A table outlining those nanoparticles/nanomaterials in use within each technology sector, according to application
3. A table highlighting those applications where we consider there to be a high potential for release.

Detailed information of the type required to make strong evidence judgments about possible exposures was only very rarely available, and this is indicated in table. In none of the scenarios was actual exposure data available. However, for some applications additional information was available from the peer reviewed literature, and where this has been used this is again indicated within the table. In the majority on settings identified, due to the paucity of data assessment of whether or not exposure is plausible is based on expert judgement and information available from other similar scenarios. In this respect, these judgements should be considered provisional and where possible, effort should be placed on collecting relevant specific primary exposure data. As the ObservatoryNANO Project progresses, it is expected that these knowledge gaps will be addressed (at least in part) and thus that later EHS reports will be able to reach more resolute conclusions on the risks posed by those nanomaterials in consideration.

3. Summary of materials which have potential EHS impact

Table 1 below outlines and ranks the exposure potential for nanomaterials in the different subsectors of the Health, Medicine & Nanobio sector. In the absence of real exposure data, it is based primarily upon expert evaluation of the information provided in the technical reports. As a default we have indicated that there is a high potential for exposure in all occupational settings associated with the manufacture of nanomaterials unless adequate control measures are applied. In applications where the hazards (toxicity) of the nanomaterials are similar, those with the highest potential exposure will have the highest potential risks.
The exposure potential is subdivided for the different users (manufacturer, professional user, consumer and environment) and the disposal phase. It is assumed that when nanomaterials enter the environment there is human exposure via the environment as well, including exposure via fish and drinking water. In the table only those environmental compartments are mentioned that are initially exposed to the nanomaterials (*i.e.* possible distribution of nanomaterials from one environmental compartment to another is not included).

In table 2, the nanoparticles carrying potential EHS impact are summarized according to application.

Table 1: Overview of the exposure potential for nanomaterials in the six different subsectors of the Health, Medicine & Nanobio sector.

Table 1.1: SECTOR Health, Medicine & Nanobio – Therapeutics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
Therapeutics	Delivery systems	Polymer-protein conjugates	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Parenteral	Very low - Surface water, soil	Very low	Low – Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.1: SECTOR Health, Medicine & Nanobio – Therapeutics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
		Polymer-drug conjugates Polyketal NP* Dendrimers & Hyperbranched Polymers	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Nanogels Liposomes & niosomes Micelles	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous, topical	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Solid lipid NP, nanostructured lipid carriers, lipid drug conjugate NPs	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Topical	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Nanoemulsions Lipid nanocapsules Protein NPs	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.1: SECTOR Health, Medicine & Nanobio – Therapeutics									
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Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
		Chitosan and lectin NPs	Unbound	High - Dermal, inhalatory	Low - Dermal	High - oral	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Gold NPs, can be PEGylated Magnetic NPs Nanoshells	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Ceramic NPs Aptamers-NP conjugates	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous	low - Surface water, soil	Very low	Low - Air Incineration, wate (STP), soil (landfill); [only unused stock]
		Nanosuspensions & Nanocrystals	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous oral	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.1: SECTOR Health, Medicine & Nanobio – Therapeutics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
		Carbon nanotubes; carbon nanohorns; nanodiamonds	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Intravenous	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Cyclodextrin nanosponges	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Parenteral	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Drug Carrying Implantable Thin films	Unbound	High - Dermal, inhalatory	Low - Dermal	High - Parenteral	Very low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

[1)] known to be on the market indicated by *

Table 1.2: SECTOR Health Medicine Nanobio - Sensors & Diagnostics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
Sensors & diagnostics	Nanosensors In vitro e.g. detection of antibodies, proteins, RNA, DNA, viruses, glucose, cholesterol also in lab-on-a-chip and microscopy	- Nanowire - (boron-doped) silicon, carbon, conducting polymer - Carbon nano-tubes - SW, MW, many varieties through composites of functionalisation - Carbon nanofibres -lipid membrane - Fullerenes - Silver - Cantilever - polymer SU- 8, silicon - gold	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Negligible	Negligible	Very low, recyclers	Low - Air Incineration, water (STP), soil (landfill)
	Nanosensors In vitro e.g. detection of diverse biological targets including small ionic analytes and O2	- Nanoshell - metal, gold - Magnetic np, Fe_2O_3, Fe_3O_4, Fe - silver np on optical fibre -Semiconductor, CdS - Quantum Dots ZnS, CdS, PbS, Cd - Gold	unbound	High- in case of release during manufacture, dermal/ inhalation exposure	Low, dermal, in case of spilling	Negligible	Negligible	Very low	Low - Air Incineration, water (STP), soil (landfill)

Table 1.2: SECTOR Health Medicine Nanobio - Sensors & Diagnostics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
		- PEBBLE - Fullerenes - Cantilever - polymer SU- 8, silicon							
	Nanosensors In vivo	- type np not specified, to be printed on larger devices, e.g. on stents for plaque monitoring, on catheters for fibrillation detection, radiation dose or drug delivery control	bound	High- in case of release during manufacture , dermal/ inhalation exposure	Very low, dermal, in case of release from device	low, parenteral, in case of release from device	Negligible	Very low, recyclers	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Nanosensors In vivo e.g. detection of breast cancer, small analytes	- Magnetic np, Fe_2O_3, Fe_3O_4, Fe - PEBBLE - silver np on optical fibre	unbound	High- in case of release during manufacture , dermal/ inhalation exposure	Low, dermal/intradermal, in case of spilling/puncture accident	High, parenteral	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.2: SECTOR Health Medicine Nanobio - Sensors & Diagnostics									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
	Contrast agents for molecular imaging In vitro	- organic dyes - gold – pure, with silver or functionalized - silica, with dye, gold or silver inside - quantum dots	unbound	High- in case of release during manufacture, dermal/ inhalation exposure	Low, dermal, in case of spilling	Negligible	Negligible	Very low	Low - Air Incineration, water (STP), soil (landfill)
	Contrast agents for molecular imaging In vivo	- Gd-DTPA - Magnetic np, Fe_2O_3, Fe_3O_4, Fe - quantum dots	unbound	High- in case of release during manufacture, dermal/ inhalation exposure	Low, dermal/intradermal, in case of spilling/puncture accident	High, parenteral	low - Surface water, soil	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

[1)] known to be on the market indicated by *

Table 1.3: SECTOR Health, Medicine & Nanobio – Regenerative Medicine									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
Regenerative medicine	Enhancing capabilities extracellular matrix	Nanophase materials	Highly porous, grain sizes less than 100 nm; bound	Dermal, inhalatory, oral	Low - Dermal	High to bound - Bone, oral low to free NP	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]
		Nanocomposite scaffolds	Combination of nanophase materials with polymers; bound	Dermal, inhalatory, oral	Low - Dermal	High to bound - Bone, low to free	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]
		Nanofibre scaffolds	Fibres of synthetic or natural materials; bound	Dermal, inhalatory, oral	Low - Dermal	High to bound - Soft tissue low to free	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]
		Bioactive scaffolds*	Nanopatterned to increase surface, bound	Dermal, inhalatory, oral	Low - Dermal	High to bound - Bone, vascular grafts, low to free	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]
		Carbon nanotubes	Enclosed, coated	Dermal, inhalatory, oral	Low - Dermal	High to bound - Extracellular matrix, low to free	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]

Table 1.3: SECTOR Health, Medicine & Nanobio – Regenerative Medicine									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human (e.g. recyclers)	Environment
		Cell sheet engineering	Polymer sheets covalently attached to surface	Dermal, inhalatory, oral	Low - Dermal	High to bound - Soft tissue low to free	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill); [only unused stock]
		Magnetic NP	In stem cells unbound-	Dermal, inhalatory, oral	Low - Dermal	High - parenteral	Very low - Surface water, soil	Low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Bioreactors, biocapsules and biochips	*In vitro* growth of tissues	Low	Low	Low	Very low - Surface water, soil	Low	Low - Air Incineration, soil (landfill)

[1)] known to be on the market indicated by *

Table 1.4: SECTOR Health Medicine Nanobio – Implants, Surgery and Coatings

				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
Implants, Surgery and Coatings	Dental implants	TiO_2 Al_2O_3 Hydroxyapatite Calcium-phosphate Diamond Zirconia	Bound Mostly coatings or composite pastes to be cured in situ	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, oral, due to wear; care to be taken in applying composite High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]
	Bone implants	TiO_2 Ti Ti6Al4V CoCrMo Al_2O_3 Hydroxyapatite Calcium-phosphate HA-PLLA HA-Ta Diamond Zirconia	Bound Mostly coatings or bone filler composite	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear; care tobe taken in applying composite High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]
	Cartilage implants	Ti HA-PLGA Peptide-hydrogel Poly(e-capro-lactone) Carbon-nanotubes	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]

Table 1.4: SECTOR Health Medicine Nanobio – Implants, Surgery and Coatings									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
	Bladder implants	PLLA PLGA PU PS PA-PGA Fibrinogen Cellulose-acetate	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]
	Vascular implants	Ti CoCrMo Al2O3 Hydroxyapatite Polydi-oxanone PLGA PCL-PLA Collagen Elastin Polysac-charide	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]
	Vascular implants	Magnetic NP	Unbound in cells coated on implants	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	High to free NP, parenteral	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]

Table 1.4: SECTOR Health Medicine Nanobio – Implants, Surgery and Coatings									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
	Neural implants	Peptide-hydrogel Carbon-nanotubes Carbon-nanofibres Gold-diverse-monolayer-substances Si/SiO2-diverse-monolayer-substances Silicon	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers (only unused stock)	Very low - Air Incineration, soil (landfill); [only unused stock]
	Surgical blades	Diamond Silicon	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Very low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers	Low - Air Incineration, soil (landfill); [only unused stock]
	Nanoneedles /nanotweezers	Carbon-nanotubes Silicon	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Very low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers	Low - Air Incineration, soil (landfill); [only unused stock]

Table 1.4: SECTOR Health Medicine Nanobio – Implants, Surgery and Coatings									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Subsector	Application specific	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer/ patient	Environment	Human	Environment
	Catheters	Carbon-nanotubes Ag	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Very low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers	Low - Air Incineration, soil (landfill); [only unused stock]
	Wound care/smart textiles	TiO2 Peptide-hydrogel Carbon-nanotubes PU Silk Ag	bound	High- in case of release during manufacture, dermal/ inhalation exposure	Very low, dermal, in case of release from device	Low to free NP, parenteral, due to wear High to bound NP	Negligible	Very low, recyclers	Low - Air Incineration, soil (landfill); [only unused stock]
	Wound care/smart textiles	Ag	unbound	High- in case of release during manufacture, dermal/ inhalation exposure	Low, dermal	High, parenteral	Negligible	Low, recyclers	Low - Air Incineration, soil (landfill); [only unused stock]

[1)] known to be on the market indicated by *

Table 1.5: SECTOR Health, Medicine and nanobio - Novel Bionanostructures -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer	Environment	Human (e.g. recyclers)	Environment
Novel Bionanostructures	Synthetic cells	Liposomes Niosomes Nanosomes Cubosomes Solid lipid NP Nanostructured lipid carriers Polymers Polymer-protein-hybrids Nanoemulsions Carbon-nanofibres Carbon-nanotubes	Unbound, various forms	High- release during manufacture is possible, dermal/ inhalation exposure	High- dermal/ inhalation exposure	In vivo applications: High- direct dermal use of product. In vitro applications: not applicable	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Delivery systems in drugs and cosmetics	Liposomes Niosomes Nanosomes Cubosomes Solid lipid NP Nanostructured lipid carriers Polymers Polymer-protein-hybrids Nanoemulsions DNA-nanocages Rotaxane+SiO2 DNA/ RNA-selfassem-bled structures	Unbound vesicular structures/ particles in cream/ liquid	High- release during manufacture is possible dermal/ inhalation exposure	High- dermal/ inhalation exposure	High- direct dermal or parenteral use of product. By using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.5: SECTOR Health, Medicine and nanobio – Novel Bionanostructures –									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer	Environment	Human (e.g. recyclers)	Environment
	Regenerative Medicine	Carbon-nanofibres Carbon-nanotubes Polymers	Bound, providing scaffold for cell/tissue growth	High- release during manufacture is possible, dermal/ inhalation exposure	High- dermal exposure	High to bound via parenteral use of product; low to free NP	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Molecular switches/motors for Electronics	Carbon-nanotubes Rotaxanes Catenanes Carbon/silicon-nanowires DNA/ RNA-selfassembled structures	Bound, e.g. in IC's	Medium - release during manufacture is possible, however, manufacture takes place in controlled environments	Very low	Very low	Very low	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Molecular switches/motors for Drug discovery/drug design	DNA/ RNA-selfassembled structures Nanoemulsions	Unbound/bound	High- release during manufacture is possible	Very low	Very low	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Molecular switches/motors for Sensors/diagnostics	DNA/ RNA-selfassembled structures	Bound, in vitro	High- release during manufacture is possible	Very low	Very low	Very low	Very low	Low-STP, landfill, incineration

Table 1.6: SECTOR Health, Medicine and nanobio - COSMETICS -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer	Environment	Human (e.g. recyclers)	Environment
Cosmetics	Vesicular delivery systems	Liposomes	Unbound vesicular structures/ particles in cream/ liquid	High- release during manufacture is possible, dermal/ inhalation exposure	High- dermal/ inhalation exposure	High- direct dermal use of product. By using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Transferosomes	Unbound vesicular structures/ particles in cream/ liquid	High- release during manufacture is possible dermal/ inhalation exposure	High- dermal/ inhalation exposure	High- direct dermal use of product. By using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Niosomes	Unbound vesicular structures/ particles in cream	High- release during manufacture is possible, dermal/ inhalation exposure	High- dermal exposure	High- direct dermal use of product	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.6: SECTOR Health, Medicine and nanobio - COSMETICS -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Profession al user	Consumer	Environm ent	Human (e.g. recyclers)	Environment
		Nanoemulsions	Nanostructur ed liquids, dispersions of nanoscale droplets of one liquid within another	High- release during manufacture is possible, dermal exposure	High- dermal exposure	High- direct dermal use of product	Very low	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Delivery systems (carriers)	Solid Lipid NP (SLNs)	Unbound particles with a solid lipid matrix in cream/ liquid	High- release during manufacture is possible	High- dermal/ inhalation exposure	High- direct dermal use of product. By using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Nanostructured Lipid Carriers (NLC)	Unbound particles/ mixtures of solid lipids with liquid lipids in cream/ liquid	High- release during manufacture is possible	High- dermal exposure	High- direct dermal use of product	Very low	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.6: SECTOR Health, Medicine and nanobio – COSMETICS -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Profession al user	Consumer	Environm ent	Human (e.g. recyclers)	Environment
		Dendrimers and hyperbranched polymers	Unbound uni-molecular, monodispers e, micellar nanostructur es in cream/ liquid/ gel	High- release during manufacture is possible	High- dermal exposure	High- direct dermal use of product	Very low	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Nanocrystals	Unbound aggregates of atoms in cream/liquid	High- release during manufacture is possible	High- dermal exposure	High- direct dermal use of product	Very low	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
	Nanoencapsu lation and controlled release	Nanocapsules and hollow silica nanoshells	Unbound particles with shell and interior in cream/ liquid	High- release during manufacture is possible	High- dermal/in halation exposure	High- direct dermal use of product. Using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Cubosomes*	Unbound discrete sub-micron,nano-structured particles	High- release during manufacture might be possible	High- dermal/ inhalation exposure	High- direct dermal use of product. Using spray product also inhalation exposure	Very low- possibly air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.6: SECTOR Health, Medicine and nanobio - COSMETICS -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer	Environment	Human (e.g. recyclers)	Environment
	UV filters	TiO_2 TiO_2 with 1% manganese	Unbound particles in cream	High- release during manufacture is possible	High- dermal/inhalation exposure	High- direct dermal use of product to large parts of body / hair. In spray product also inhalation exposure	Low- surface water, air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		ZnO	Unbound particles in cream	High- release during manufacture is possible	High- dermal/inhalation exposure	High- direct dermal use of product to large parts of body / hair. In spray product also inhalation exposure	Low- surface water, air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]
		Hollow styrene acrylate copolymers	Unbound particles in cream	High- release during manufacture is possible	High- dermal/inhalation exposure	High- direct dermal use of product to large parts of body / hair. In spray product also inhalation exposure	Low- surface water, air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

Table 1.6: SECTOR Health, Medicine and nanobio - COSMETICS -									
				Exposure potential Use (e.g. activity, exposure route, what)				Exposure potential Disposal (e.g. incinerated, landfilled, recycled, STP)	
Sub sector	Application	Types of NP [1)]	Incorporation in products	Manufacturer	Professional user	Consumer	Environment	Human (e.g. recyclers)	Environment
		Novel broad spectrum organic UV filter	Unbound particles in cream	High- release during manufacture is possible	High- dermal/inhalation exposure	High- direct dermal use of product to large parts of body / hair. In spray product also inhalation exposure	Low- surface water, air in case of spray	Very low	Low - Air Incineration, water (STP), soil (landfill); [only unused stock]

1) known to be on the market indicated by *

Within table 2, the nanoparticles carrying potential EHS impact are summarized according to application.

Table 2: Nanoparticles carrying potential EHS impact, according to application, for the six subsectors.

Table 2.1: Nanoparticles within TS Report - Health Medicine Nanobio - THERAPEUTICS

	Polymer therapeutics			Vesicular Delivery Systems: Liposomes, Niosomes	Lipids*	Protein NPs**	Metal(lic) NPs***	Nanosuspensions & nanocrystals	Carbon nanostructures	Others****
	Polymer-protein/drug conjugates	Dendritic Architectures	Polyketal NPs, Nanogels							
Increase protein/drug solubility and stability	•				•			•		•[1]
Drug delivery	•	•	•	•	•	•	•	•	•	•
Treatment							•[2]			
Imaging applications					•[3]		•[4]			

* This group of 'Lipids' consists of the following products: Solid Lipid Nanoparticles, Nanostructured Lipid Carriers, Lipid-drug conjugate NPs, micelles, lipid nanocapsules, nanoemulsions

** This group of 'Protein Nanoparticles' consists of albumin, chitosan and lectin NPs, and aptamer-NP conjugates

*** This group of 'Metal(lic) Nanoparticles' consists of gold NPs, Magnetic NPs, ceramic NPs and nanoshells

****I.e. cyclodextrin nanosponges, drug-carrying implantable thin film

[1] Refers to cyclodextin nanosponges; [2] Refers to gold NPs, magnetic NPs; [3] Refers to micelles: have also been proposed as contract agents in diagnostic applications; [4] Refers to magnetic NPs

Table 2.2: Nanoparticles within TS Report - Health Medicine Nanobio - SENSORS & DIAGNOSTICS

4)	Nanowire - (boron-doped) silicon, carbon, conducting polymer	Carbon nano-tubes, many varieties	Carbon nanofibres	Magnetic np, Fe2O3, Fe3O4, Fe	Nanoshells - metal, gold	Semiconductor, CdS	Quantum Dots - ZnS, CdS, PbS, Cd,	Fulle-renes	Gold	Silver	Cantilever - polymer SU- 8, silicon	PEBBLE, optical fibre	Gd-DTPA	Silica
Nanosensors In vitro 1)	•	•	•	•		•	•	•	•	•	•	• •3)		
Nanosensors In vivo 1)	•	•	•	•		•	•	•	•	•	•	• •3)		
Molecular imaging				•			•		• •2)	• •2)3)			•	• •2)
Nanotechnology on a chip									•					
Microscopy		•												

1) In many instances, it was not clear from the TS report whether nanosensors are intended for use in vitro, in vivo or both. Therefore, for the time being, the two rows are identical. This needs to be clarified, because this information is essential for the EHS analysis.

2) probes for SERS (Raman) – gold / silver core, silica shell

3) probes for SERS (Raman) 30-80 nm - Optical fibre, coated with metallic film, immobilised silver np on the fibres

4) In many instances in the TS-report, general descriptions such as nanomaterials, nanoparticles, nanowires, nanofibres, macromolecule (on surface of nanowire), (targeted) contrast agents, engineered biomarker functionality, nanopores (in various membranes / matrices, nanofluidics, nanochip, fluorescent probes, organic dyes as fluorophores were mentioned – these were not included in this table

Table 2.3: Nanoparticles within TS Report - Health Medicine Nanobio - REGENERATIVE MEDICINE[1]

	Nanophase materials*	Nanocomposite scaffolds	Nanofibre scaffolds	Bioactive scaffolds	Bioactive scaffolds	Carbon nanotubes	Cell sheet engineering	NPs+Stem cells*	Bioreactors, biocapsules and biochips
Scaffold function	•	•	•	•	•		•		
Transport						•			
Cell communication								•	
In vitro tissue regeneration							•		•

* Stem cells should not be classified as NPs. NPs can facilitate cell communication between stem cells.

[1] Regenerative medicine describes those nanomaterials and techniques employed to repair or replace damaged soft and hard tissue

Table 2.4... Nanoparticles within TS Report - Health Medicine Nanobio - IMPLANTS, SURGERY AND COATINGS

1)	TiO2 Ti Ti6Al4V CoCrMo Al2O3	Hydroxyapatite Calcium-phosphate HA-PLLA HA-PLGA HA-Ta	Diamond zirconia	Peptide-hydrogel Poly(e-capro-lactone) Polydi-oxanone	Carbon-nanotubes Carbon-nanofibres	PLLA PLGA PU PS PA-PGA PCL-PLA	Fibrinogen Cellulose-acetate Collagen Elastin Polysac-charide silk	Magnetic NP	Gold-diverse-monolayer-substances	Si/SiO2-diverse-monolayer-substances	Silicon	Ag
Dental implants	•	•	•									
Bone implants	•	•	•									
Cartilage implants	•	•		•	•							
Bladder implants						•	•					
Vascular implants	•	•		•		•	•	•				
Neural implants				•	•				•	•	•	
Surgical blades			•								•	
Nanoneedles/nanotweezers					•						•	
Catheters					•							•
Wound care/smart textiles	•			•	•	•	•					•

1) In many instances in the TS-report, general descriptions such as nanomaterials, nanoparticles, nanowires, nanopores, nanocomposites were mentioned – these were not included in this table

Table 2.5: Nanoparticles within TS Report - Health Medicine Nanobio - NOVEL BIONANOSTRUCTURES

	Liposomes Niosomes Nanosomes Cubosomes	Solid lipid NP Nanostructured lipid carriers	Polymers Polymer-protein-hybrids	Nanoemulsions	Carbon-nanofibres Carbon-nanotubes	DNA-nanocages	Rotaxanes Catenanes Rot.+SiO2	Carbon/silicon-nanowires	DNA/ RNA-selfassembled structures
Synthetic cells	●	●	●	●	●				
Delivery systems in drugs and cosmetics	●	●	●	●		●	●		●
Regenerative Medicine			●		●				
Molecular switches/motors for Electronics					●		●	●	●
Molecular switches/motors for Drug discovery/drug design				●					●
Molecular switches/motors for Sensors/diagnostics									●

Table 2.6: Nanoparticles within TS Report - Health Medicine Nanobio - COSMETICS

	Liposomes Transferosomes Niosomes	Solid lipid NP and nanostructured lipid carriers	Dendrimers and hyperbranched polymers	Nanocrystals	Nanocapsules and hollow silica nanoshells	Cubosomes	TiO_2 (with manganese)	ZnO	Hollow styrene acrylate copolymers, organic UV filter
Vescicular delivery systems	•								
Nanoemulsions									
Delivery systems		•	•	•					
Nanoencapsulation and controlled release					•	•			
UV filters							•	•	•

4. Summary and Conclusions

A great variety of nanomaterials is used in nanomedicine, including structures based on lipids, proteins, DNA/RNA or other naturally occurring materials and substances. Furthermore, many different nanomaterials based on polymers, both degradable and non-degradable are applied. The various known forms of carbon like CNT, diamond, carbon black, fibres, wires are also often used. Furthermore, many different sorts of metals and metal oxides are used, as well as silica, quantum dots and a number of specific types that do not fit easily in a larger category.

The key nanomaterials used in the various nanomedicine subsectors are outlined in Table 2 in Chapter 3 of this report. Potential exposure of manufacturers, professional users and consumers/patients to the nanomaterials, related to their application is shown in Table 1 in Chapter 3 of this report. For further information on the hazards of those nanomaterials listed, readers are directed to the ObservatoryNANO baseline studies document (Ross *et al.*, 2009), which provides key information on toxicity, ecotoxicity, fate and behaviour, and characterisation considerations for each.

The main routes of potential human exposure to the nanomaterials were found to be:

- For manufacturers: dermal exposure during handling of products, or inhalation of powder, or aerosolised nanomaterials during production process;
- For professional users: dermal exposure, and in some cases inhalatory exposure while administering products to patients;
- For patients: depending on intended use oral, dermal, parenteral, intravenous.

The main routes of potential environmental exposure were found to be:

- During use: in case of spray products via air, for other products soil or surface water via excretion by patients;
- At disposal stage: depending on the product, incineration, landfill, or effluent from sewage treatment plants might lead to air, soil or surface water exposure

For personnel involved in the manufacture of the products, the risk of exposure is generally high. For other groups of people, the exposure potential to nanomedicine products varies considerably depending on the application. However, in general it can be said that for therapeutics, sensors/diagnostics for in vivo use, regenerative medicine, implants and cosmetics the intended use of many applications inherently implies high exposure potential for patients. For professional users exposure potential is mostly low, except for some cosmetics applications. In a rather high number of applications, the nanomaterial is used in an unbound state, and will thus potentially spread through the body. For the environment, the exposure potential to nanomedicine products is considered range from low to negligible.

The following list provides some more details for each subsector on exposure potential for patients:

- **Therapeutics:** The intended use of these products is to treat people by having interaction with a specific part of the body. Therefore in all cases, there will be high exposure. Some products are applied at a specific part on or in the body, other products are equipped with features that enable specific targeting. In most cases, the formulation of the products consists of free nanomaterials, which means there is always a potential for systemic exposure, i.e. to the entire body, regardless of the administration route (oral, dermal, parenteral or intravenous).
- **Sensors & Diagnostics:** This is a rather heterogenic group with regard to exposure potential. Contrast agents for molecular imaging *in vivo* are intended to be administered parenterally (mostly intravenously), and thus imply high potential systemic exposure. Nanosensors intended for *in vivo* use can be distinguished in products consisting of unbound nanomaterials and larger products with bound nanomaterials. For unbound nanomaterials, there is again high potential for systemic exposure, while there is low potential in case of bound nanomaterials. Both sensors and contrast agents are also applied for *in vitro* diagnostics. In these applications, diagnosis is performed on samples taken from the body which are not returned to the body. In these cases, exposure potential for patients is therefore negligible.
- **Regenerative Medicine:** Products in this group are intended to repair or replace damaged soft or hard tissue. In most cases, the nanomaterials are bound inside or on the surface of matrices. Local exposure to the bound nanomaterials at the site of administration will therefore be high in all cases, whereas systemic exposure potential to free nanomaterials is low.
- **Implants Surgery & Coatings:** Nanomaterials in products used in surgery are generally contained inside or coated on larger products. The duration of contact with the patient is relatively short. Local exposure to the bound nanomaterials at the site of treatment will therefore be high in all cases, whereas systemic exposure potential to free nanomaterials is very low. Also for implants, nanomaterials are usually bound. Duration of contact is long term. Local exposure to the bound nanomaterials at the site of treatment will therefore be high in all cases, whereas systemic exposure potential to free nanomaterials can be considered low, provided there is only slow generation of wear particles. Care must be taken to avoid exposure during the treatment procedure with dental composite materials cured in situ and bone fillers. An exception is formed by wound dressings with unbound silver nanoparticles, leading to (intended) high exposure.
- **Novel Bionanostructures:** Applications as synthetic cells, in delivery systems for drugs or cosmetics and in regenerative medicine imply high exposure potential. In case of bound nanomaterials in regenerative medicine, this is mostly local, whereas systemic exposure is low. Applications as molecular switches or molecular motors in electronics, sensors or drug discovery lead to very low exposure potential.
- **Cosmetics:** This category of products is intended for direct use on the skin, and consists often of unbound nanomaterials in a cream or liquid. This results in high dermal exposure, and in case of products that are applied by spraying also high inhalation exposure.

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