MODELLING ENVIRONMENTAL RISKS AND CONCEPTUALISING 'RESPONSIBLE INNOVATION' FOR NANOTECHNOLOGY ENABLED MEDICAL APPLICATIONS

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A thesis submitted to the University of Birmingham

for the degree of

DOCTOR OF PHILOSOPHY

School of Geography, Earth and Environmental Sciences

University of Birmingham

March 2016

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Abstract

Medical products based on nanomaterials can revolutionise disease diagnosis and management modalities via faster, non-invasive diagnostic techniques and targeted therapeutic delivery and will be used extensively in coming years. The central goals of this thesis was to understand environmental risks that could potentially arise from mass production and wider use of nanotechnology enabled medical products and to gather insights from experts' perceptions on "Responsible Innovation". The research presented here uses a mixed methods approach to answer the research questions. By applying probabilistic mass flow modelling concept, prospective environmental concentrations of nanomedicine was estimated and a preliminary environmental risk assessment was done using gold nanoparticles in medical applications (potential of commercialisation and marketed) as a case study. This demonstrated that environmental risks from gold nanoparticles for the two major compartments (sludge applied soil and water) are likely to be minimal in the near future. The second component of the research involved 38 interviews with academics and 28 interviews with representatives from regulatory bodies, industry and funding bodies to understand their perceptions on environmental hazards and risks from nanomedicine and their views on the meaning of the concept of "Responsible Innovation". This revealed that risks from nanomedicine can be compared with risks from existing chemicals and that "Responsible Innovation" is a phrase which can be discussed based on an individual's experience and discipline.

Dedication

I dedicate this thesis

to my parents

and

to Arun and Vinita Kansal

Acknowledgements

I am grateful to Iseult Lynch for stepping in at a crucial time, the 12th hour of a PhD, a gesture of support which can never be from the faint-hearted or the selfish. Her bravery and kindness for offering help without asking despite having a back breaking work schedule are the qualities which I would aspire to emulate throughout life. I am thankful to her for the many subject related discussions, always willing to hear me out, for helping me find temporary work, and for providing financial support.

I am grateful to Jamie Lead for giving me the freedom to explore and shape my PhD and for giving me the time to develop my ideas and for almost always agreeing to my thoughts, for funding me to important conferences which helped me have a clearer picture of the nanomedicine landscape. Without his support I would have been lost in the literature.

I am indebted to Julian Clark for offering the kind of support which one can only dream of in life. I am thankful to him for supporting me with extension requests, for giving me the freedom to explore, for giving prompt feedbacks and inputs. I hope to inculcate the patience he has, patience which is par excellence.

I lack words to express my gratitude for Peter Dobson. The many discussions we had emboldened me to put forth a rounded perspective in this thesis and not confine myself to academic lens. His prompt feedbacks and inputs, over the night in case of urgency, have helped me immensely in moments of quandary. He is inspirational.

I am grateful to Bernd Nowack for his never failing contributions, for being available for discussions and for the encouragement throughout the model development duration and writing of the paper. I am thankful to my colleague and collaborator Tian Yin Sun who patiently did ‘n’ number of corrections to the model code; to

Richard Owen, for giving me the idea to explore responsible innovation which made me delve into the western philosophical literature and helped me understand the differences and similarities between western and eastern philosophy.

I remain indebted to Arun Kansal and Vinita Kansal whose tremendous belief in me made me cross turbulent moments of uncertainty and self-doubt and for their comforting presence and for teaching me selfless dedication and commitment. Their constant support can never be forgotten.

I am grateful to my mother who never failed to express her pride in me for pursuing higher studies and who rarely complained for my inability to visit India. I am grateful to my brothers and sister-in-laws for their support and I am especially thankful to my sister-in-law, Shivani, for her proactive care.

I am grateful to Aksel and Jaideep for always managing to express their belief in me and for their care despite exceptionally hectic schedules and for being my 'all weather' friends.

I am thankful to my friends Marie, Gavkhar, Maria and Christopher, who time and again proved to me the meaning of true friendship. I am grateful to them for their support, care and kindness. The list of gestures is endless, but few very important are - for grocery shopping, for bringing food, for giving me company many late nights, for checking on me. I am grateful to Isaac, Auwal, Mila, and Maurice for their unconditional friendship.

I once again lack words to express my feelings for Pallavi and Gaurav - two gems and brave hearts; ever supporting, kind and generous friends. This thesis would not have been complete on time without Pallavi and Gaurav's support at the 12th hour

with the formatting; Pallavi for making me laugh with all her unique observations and timely financial help from Gaurav is deeply appreciated.

Credit is due to: Neelam, Debasmita and Nitin for their patient care, for not being frustrated at me for neglecting them by doing the disappearing act frequently and repeatedly; Inder for checking on my wellbeing and for the tasty food treats. I remain indebted to my many heart-warming friends (each special in their own way) – Santosh, Maulshree, Sumana, Pranay, Vikash, Ritesh, Harpreet, Ritika, Raj, Michael, and many others - who managed to not let me lose touch with my country, for showering me with laughter and insights, and for their belief in me. I am grateful to Nikolaus for his steady and warm friendship.

I am deeply appreciative of Muna Ali for keeping me on my toes with her thoughtful and encouraging mails and messages.

I am grateful to Steven Emery for making me laugh, for always willing to hear my thoughts, for his insightful comments and for his thoughtful gestures of care.

This research and thesis would not have been possible without the contributions from the interviewees who gave valuable time. The need for anonymity does not allow me to thank them by name; however I am very grateful to them for not making me feel like an outsider and for being as honest and as expressive as one can be.

I remain thankful to Jamie Peart for his unconditional and patient support and for being one of the best trouble-shooters I have come across. He is a reflection of the divine.

I am thankful to Eva Valsami-Jones and Rosie Day for their care and support.

And last, but not least, the funding from the School of Geography, Earth and Environmental Sciences, and Gretchel for her constant support, patience and care.

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Abbreviations

Nanomedicine is a multifaceted field where physics, chemistry, material sciences, biology and biotechnology, electronics and engineering, pharmaceutical sciences, and others have converged to find solutions for disease and strategies to enhance health. The deliberations on shaping innovation, which will result in sustainable public good from nanomedicine, have brought together additional disciplines across the humanities, such as philosophy, history and philosophy of science and medicine, science, technology and society studies, policy studies, risk governance, and business management. Not to forget the interdisciplinary subject of environmental sciences, an important part of this thesis. Hence, acronyms, words and phrases from these individual fields may leave the reader and the uninitiated perplexed. For ease of navigation, I present below the list of abbreviations and their expansions as used in this thesis. I also include a list of those acronyms and words (for example, drugs, pharmaceutical products, therapeutic products, medicine, and human drugs) which have been used interchangeably in the text.

A	
AF	Assessment Factors
AlO_x	Aluminium Oxide (of different valence states)
ANDA	Abbreviated New Drug Application
APCDs	Air Pollution Control Devices
APIs	Active Pharmaceutical Ingredients
Ag-NP	Silver Nanoparticles
Au-NP	Gold Nanoparticles
Au NS	Gold Nanoshells
ATP	Adenosine Triphosphate
B	
BBSRC	Biotechnology and Biological Sciences Research Council
BLA	Biologics License Application
BSA	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalopathy
BSI	British Standards Institution
C	
CA	Cysteamine
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CE	Conformité Européene (European Conformity)
CEO	Chief Executive Officer
CeO_2	Cerium (IV) oxide
CT	Computed Tomography
CTA	Constructive Technology Assessment
CNT	Carbon Nanotube
CNS	Central Nervous System
COSHH	Control of Substance Hazardous to Health
D	
DDT	Dichlorodiphenyltrichloroethane
DEFRA	Department for Environment, Food and Rural Affairs (UK)
DNA	Deoxyribonucleic Acid

DPPC:Cholesterol:DMPC:PEG	1,2-dipalmitoyl-sn-glycero-3-phosphocholine:Cholesterol:1,2-dimyristoyl-sn-glycero-3-phosphocholine:Polyethylene glycol
E	
EA	Environment Assessment
EA	Environment Agency (England and Wales)
ECHA	European Chemicals Agency
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHS	Environment, Health and Safety
EMA	European Medicines Agency
EC	European Commission
EE	Ethinyl estradiol
EGF	Epidermal Growth Factor
EHS	Environmental, Health and Safety
ELSA	Ethical, Legal and Societal Aspects
ELISA	Enzyme Linked Immunosorbent Assay
ENM	Engineered nanomaterials
EPR	Enhanced Permeation and Retention
EPSRC	Engineering and Physical Sciences Research Council (UK)
EQS	Environmental Quality Standards
ERA	Environmental Risk Assessment
ESPs	Electrostatic Precipitators
ETP	European Technology Platform
EU	European Union
F	
FD&C Act	Federal Food, Drug, and Cosmetic Act
FeO_x	Iron oxide (of different valence states)
FP-7	7^{th} Framework programme of the European Commission (2007-2013)
G	
GHTF	Global Harmonization Task Force (now known as The International Medical Device Regulators Forum)
GMOs	Genetically modified organisms
GMP	Good Manufacturing Practices
GS	Glutathione
GRI	Global Reporting Initiative
H	
H&B	Healthcare and Biological
HIV/AIDS	Human Immunodeficiency Virus or Acquired Immunodeficiency Syndrome
HMCIW	Hazardous Medical/Clinical/Infectious Waste
HMSNPs	Hollow Mesoporous Silica Nanoparticles
HONEC	Highest-Observed-No-Effect-Concentration
Horizon 2020	EU Research and Innovation programme (2014-2020) with nearly €80 billion of total funding
HSE	Health and Safety Executive
HSPC/Chol/PEG	Hydrogenated Soybean Phosphatidylcholine / Cholesterol/ Polyethylene Glycol
hTf	Human Transferrin Protein

I	
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICT	Information and Communication Technology
IDE	Investigational Device Exemption
IND	Investigational New Drug
INDA	Investigational New Drug Application
ISO	International Organization for Standardization
K	
K_{oc}	Soil Organic Carbon-Water Partitioning Coefficient
K_{ow}	Octanol-Water Partition Coefficient
L	
$L(E)C_{x)}$	Lethal (adverse effect) Concentration, when x% of the test organisms die or are adversely effected
LOEC	Lowest Observed Effect Concentration
Log k_{ow}	Octanol-water partition coefficient
Log D_{ow}	Octanol-water distribution co-efficient
M	
MAA	Marketing authorisation application
MDIC	Medical Device Innovation Consortium
MHRA	Medical and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MWIs	Municipal Waste Incinerators
N	
NanoKTN	Nanotechnology Knowledge Transfer Network
NAS	New Active Substance
NCs	Nanoclusters
NCE	New Chemical Entity
NDA	New Drug Application
NEPA	National Environmental Policy Act (USA)
NEST	New and Emerging Science and Technologies
NGO	Non-Governmental Organisation
NICE	National Institute of Health and Care Excellence
NHS	National Health Service (UK)
NIEA	Northern Ireland Environment Agency
NIR	Near-infrared
NIOSH	National Institute of Occupational Safety and Health
NME	New Molecular Entity
NOEC	No Observed Effect Concentration
NOM	Natural organic matter
NP	Nanoparticle
NSE	Nanoscale science and engineering
NSF	National Science Foundation
NWO	Netherlands Organisation for Scientific Research
O	
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-Counter
P	
PAMAM	Polyamidoamine
PBT	Persistence, Bioaccumulation, Toxic
PDMAEMA	poly(2-(dimethylamino) ethyl methacrylate
PDMAEMA: DNA	poly(2-(dimethylamino) ethyl methacrylate complexes with

	deoxyribonucleic acid
PEC	Predicted Environmental Concentration
PEI	Polyethylamine
PEI: DNA	Polyethylamine deoxyribonucleic acid complexes
PEG	Polyethylene glycol
PhAC	Pharmaceutically Active Compounds
PhATE™	Pharmaceutical Assessment and Transport Evaluation model
PIs	Principal Investigators
PLA	Polylactic acid
PLGA	Polylactic-co-glycolic acid
PLK-1	Serine/threonine-protein kinase or polo-like kinase 1
PP	Pharmaceutical product
PMA	Premarket approval
PMF	Probabilistic Mass Flow (Model)
PEC	Predicted Environment Concentration
PNEC	Predicted No Effect Concentration
PPCP	Pharmaceuticals and Personal Care Products
pSSD	Probabilistic Species Sensitivity Distribution
Pt-NP	Platinum Nanoparticles
Q	
QD	Quantum Dots
QSAR	Quantitative Structure Activity Relationship.
R	
RBC	Red Blood Cells
RCs	Research Councils (UK)
R&D	Research and Development
REACH	Registration, Evaluation, Authorisation & Restriction of Chemicals
RES	Reticuloendothelial system
RI (and RRI)	Responsible Innovation (and Responsible Research and Innovation)
ROS	Reactive Oxygen Species
RTTA	Real time technology assessment
S	
SCENIHR	Scientific Committee of Emerging and Newly Identified Health Risks
SEER	Surveillance, Epidemiology, and End Results Program Database
SEPA	Scottish Environment Protection Agency
SiO_2	Silicon dioxide
SME	Small and Medium Enterprises
STPs	Sewage Treatment Plants
STS	Science, Technology and Society
STIR	Science and Technology Integration Research
SPIONs	Superparamagnetic Iron Oxide Nanoparticles
T	
TC	Transfer coefficient
TF	Transfer Factor
TGA	Thioglycolic acid
TNF	Tumor Necrosis Factor
TiO_2	Titanium Oxide
TOC	Total Organic Carbon

TPPMS	Mono-sulfonated triphenylphosphine
TSB	Technology Strategy Board (renamed as InnovateUK)
TRL	Technology Readiness Levels
U	
UK	United Kingdom
UNAIDS	United Nations Programme on HIV and AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
US	United States of America
USDA	United States Department of Agriculture
USFDA	United States Food and Drug Administration
USEPA	United States Environmental Protection Agency
USGS	Unites States Geological Survey
USPIOs	Ultrasmall superparamagentic iron oxides
W	
WB	World Bank
WBC	White Blood Cells
WEEE	Waste Electrical and Electronic Equipment
WHO	World Health Organisation
WIPs	Waste Incineration Plants
WPMN	Working Party on Manufactured Nanomaterials
WTPs	Waste Treatment Plants
WW	Waste water
WWTPs	Waste Water Treatment Plants
Z	
ZnO	Zinc Oxide

Words and acronyms alternatively or synonymously used in the thesis

1. PPs, APIs, drugs, medicine, therapeutic products, pharmaceutical, Pharmaceutically active compounds
2. Nanovectors, nanocarriers
3. Responsible Research and Innovation (RRI) and Responsible Innovation (RI)
4. Nanoparticle (NP), Nanomaterial (NM) and engineered nanomaterial (ENM)
5. Nano, nanotech, NSE, nanotechnology, nanotechnologies
6. Nanomedicine, nano-enabled medical products, nanotechnology enabled medical products, nanotherapeutics

Units

mg L^{-1} : milligram per litre
µg L^{-1}: microgram per litre
ng L^{-1} : nanogram per litre
pg L^{-1} : picogram per litre
µg kg^{-1} : microgram per kilogram

Nanotechnology is an area which has highly promising prospects for turning fundamental research into successful innovations. Not only to boost the competitiveness of our industry but also to create new products that will make positive changes in the lives of our citizens, be it in medicine, environment, electronics or any other field."

(European Commissioner for Science & Research, Janez Potočnik)

Chapter 1: Introduction

Or, why to explore potential environmental implications of nanomedicine and what can be done pre-emptively to reduce adverse implications

1.1 Background

Nanotechnology is the development and practical application of structures at a nanometre scale by exploiting the distinctly different physical, chemical, and biological properties of materials and devices at that scale (EC, 2007). At the nanometre scale, materials may exhibit different physical, chemical, mechanical, and optical properties compared to their bulk counterparts. These novel properties can be used to impart desired characteristics to various products used in different sectors, such as textiles, electronics, medicine, food, and specialised chemicals. Nanotechnology is a convergent and multidisciplinary field (Porter and Youtie, 2009; Milojević, 2012), which is growing rapidly worldwide—as has been shown by many bibliometric and patent analysis studies (see e.g., Grieneisen, 2010; Wang and Guan, 2012). This enabling technology is expected to usher in the next 'industrial revolution' (Anonymous, 2000) and to help in dealing with the most serious challenges of the 21st century such as climate change, food security, energy security, and ageing populations. The emergent field is driven by utopian visions of

what nanotechnology can do in future and what kind of nanomaterials are likely to be designed (Tour, 2007; Roco et al., 2011b). Product and process innovations of nanotechnology are seen as an economic driver in the US and EU and specific funds have been earmarked for the required research and development (R&D) to maintain a competitive edge in the global research arena (NSTC, 2000; EC, 2013b). Other countries such as India, Japan, China, Brazil, and many member-countries of the Organisation of Islamic Cooperation (OIC) have also earmarked funds for nanoscience and nanotechnology (Hassan, 2005; Roco, 2005; Islam and Miyazaki, 2010; Shapira and Wang, 2010; Bajwa et al., 2012) to be in the 'nano-race'. Worldwide investment in research on nanotechnology during 2000–2015 is estimated at 0.25 trillion US dollars (EC, 2013b). Figure 1.1 shows the number of companies active in nanotechnology in 2011 in sixteen countries (OECD, 2013a).

The nanoscale is particularly important for applications in the life sciences because the building blocks of life are in that size range, and systems (such as complex proteins and drug–polymer conjugates) and materials can be designed to interact with the receptors on the surface of cells as well as with sub-cellular components. Additionally, the unique electronic and optical properties and large surface areas of nanomaterials can be harnessed for both diagnosis and to develop new treatment modalities. The main application areas of nanotechnology in health care are thus *in-vitro* and *in-vivo* diagnostics, implanted devices, vaccines, regenerative medicine, and drug delivery (Boisseau and Loubaton, 2011; Duncan and Gaspar, 2011). Nanotechnology can help to overcome the traditional problems associated with the solubility (or lack of it) of pharmaceuticals, can limit systemic toxicities by improved

targeting and cellular uptake, and can increase drug bioavailability and immuno-compatibility.

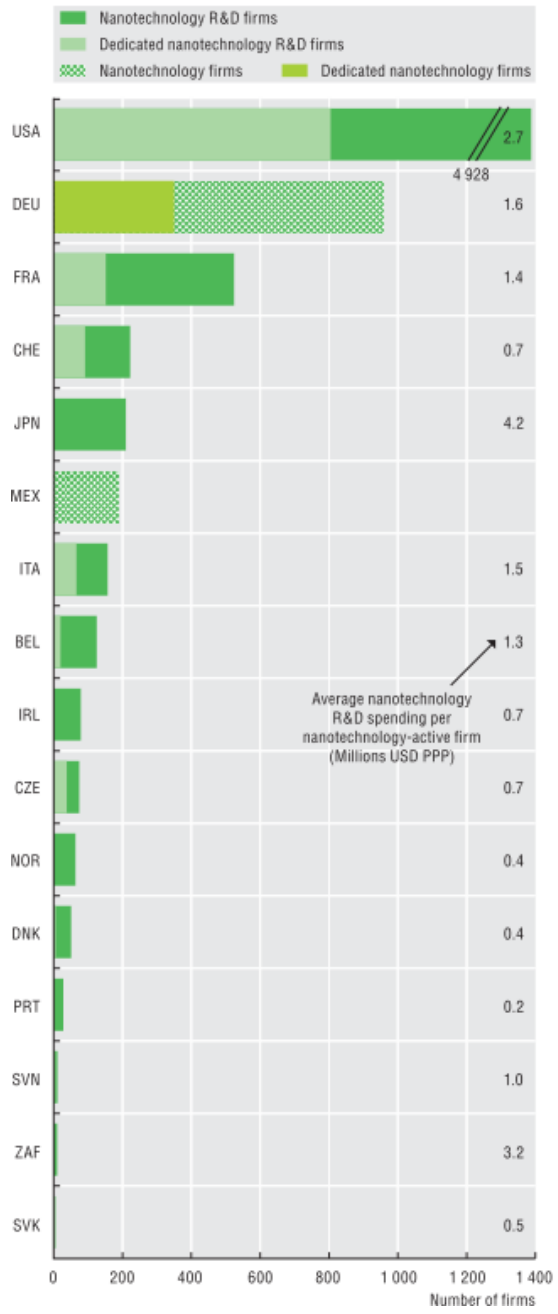


Figure 1.1: Number of firms active in nanotechnology (Taken from OECD 2013a).

Nanotechnology can also help in enhancing the outcomes of various types of treatment such as photothermal therapy, thermal ablation, and hyperthermia, and

can function as combined drug and diagnostics devices, or ‘theranostics’ (reviewed in Duncan and Gaspar, 2011). Nanotechnology in life sciences provides not only immense opportunities for developing novel therapeutics and diagnostics but also tools to enhance our understanding of biological mechanisms and pathways, identify robust biomarkers and thereby increase the efficacy of medicines, tracking of cells, and advance the progress towards stratified and personalised medicine. Scientific publications and patent analyses published during 1990–2012, retrieved by using key search terms related to ‘nanoscale science and engineering’ (NSE), show that research is moving towards health care and electronics and some of the often-repeated words and phrases related to health care included the following: nucleic acid, pharmaceutical composition, functional group, amino acid, therapeutic agent, pharmaceutically acceptable salt, and fatty acid (Chen et al., 2013b). Under the 7th Framework Programme (FP-7) of the European Commission (2007–2014), 116 nanomedicine-related projects with a cumulative value of 550 million euros were funded under the themes Health and Nanosciences, Nanotechnologies, Materials, and New Production Technologies (ETP, 2015). Various strategic programmes and road maps have been created to pursue research in nanomedicine (ETP, 2006; 2009) at the EU level. Figure 1.2 is a timeline of the most important publications related to nanomedicine.

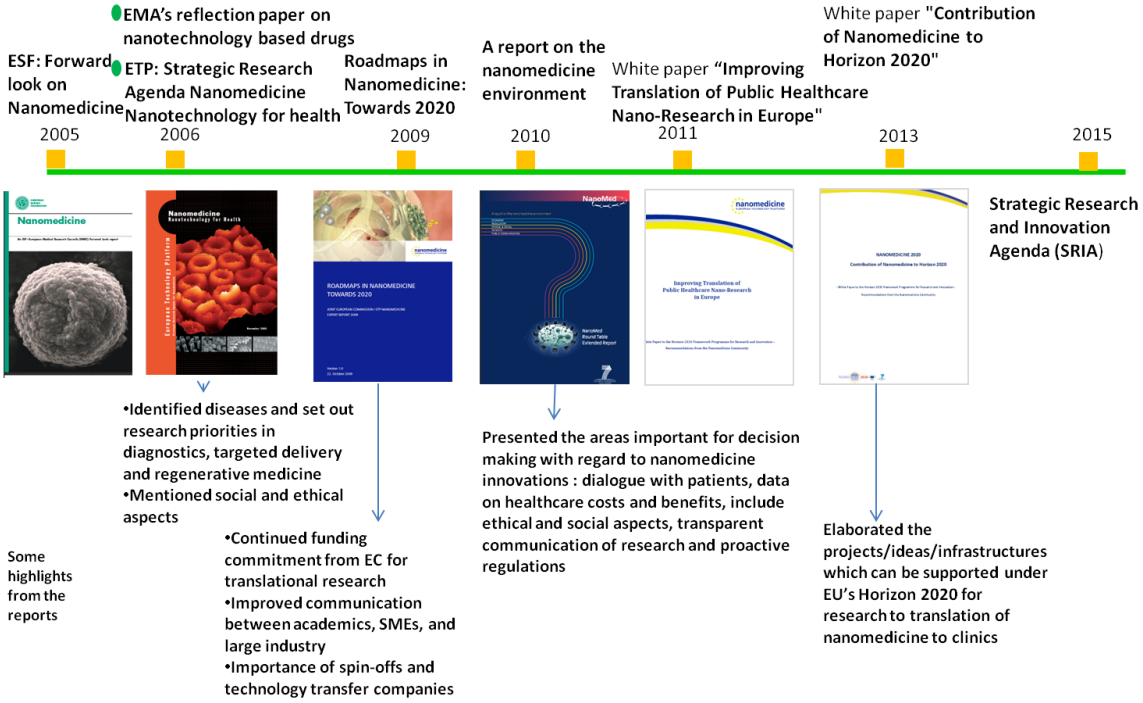


Figure 1.2: Key publications related to nanomedicine in the EU.

The European Technology Platform for Nanomedicine was set up, a partnership between industry and academia, to develop research directions, priorities, and strategies and to promote coherent research in nanomedicine. The platform published many documents over 10 years. Early on, the European Medicines Agency published a reflection paper on nanomedicine.

In July 2015, under the Horizon 2020 programme, infrastructure money was allocated for characterisation of nanomedicine to advance its translation[1] to clinics. The component for health in FY 2015 – about 440 million dollars – in the National Nanotechnology Initiative budget was the highest (NSTC/CoT/NSET, 2015) in the US and increased from about 60 million dollars in FY 2002 (Roco, 2003).

Global sales from nanotechnology-enabled medical products in 2011 was estimated at 73 billion dollars (BCC Research, 2012) and is likely to double by the end of this decade. The development and commercialisation of such novel and complex

[1] See https://ec.europa.eu/jrc/en/news/eu-ncl-launched

materials will most likely result in exposure to these materials at the workplace (Lee et al., 2012) and their release into the environment (Kiser et al., 2009).

Such high activity in research on nanomedicine and its many potential uses necessitates that researchers explore proactively the uncomfortable questions of possible risks and the motivation and purpose of research and innovation to help create and shape appropriate governance structures in parallel with product development before such products become part of the very fabric of society and also for deriving sustained benefits from them. Moreover, due to the complexity, ambiguity, and uncertainty inherent in such emerging technologies (Renn and Klinke, 2004), it is better to assess and characterise possible risks associated with the technologies to help establish adequate regulatory control.

The title of the thesis reflects its dual aims of exploring environmental risks arising from nanomedicine, and assessing the current discourse on shaping research and innovation and applying it to nanomedicine research and innovation in the face of 'known and unknown unknowns'. The first aim was to inquire into the possibility of future environmental hazards and risks associated with use of nanomedicines and their release (excretion and disposal) into the environment. This aim was achieved by conducting "exploratory or curiosity driven" horizon scanning (Amanatidou et al., 2012) to identify the research and development trends in nanomedicines. Applications of gold nanoparticles (Au-NP) in nanomedicines and devices were found to be potentially important developments. Thereafter, an extensive review of literature was done to estimate their consumption and release, and a probabilistic mass flow modelling study was done to predict the environmental concentrations of this select group of nanomedicines and then, using those as a base, to conduct an

environmental risk assessment. The probabilistic mass flow modelling study (Gottschalk et al., 2009; Gottschalk et al., 2010) of Au-NP (used or potential to be used in medicines and medical devices) was done in collaboration with Bernd Nowack's group at EMPA, the Swiss Federal Laboratories for Materials Science and Technology. The novel contribution of this aspect of the thesis is that it expands the ambit of this work to the specific and unexplored topic of the release of nanomedicines into the environment by using the bottom-up approach of estimating prospective consumption. To complement the theoretical modelling, 66 experts[2] involved in research and development in nanomedicine and nanotechnology were interviewed to provide a qualitative perspective on possible hazards and risks from nanomedicine. The interviews were conducted to ascertain experts' views/ thoughts on the possibility of future environmental risks from nanomedicine and on the adequacy of the current regulatory framework to assess such risks for emerging nanomedicine.

The second aim refers to and builds upon the collected body of work by Richard Owen and others (Owen et al., 2013a) on 'responsible innovation' (RI), which is described in greater detail in the literature review chapter (Chapter 2), and perceptions of experts from academia, regulatory bodies, industries, and funding bodies on RI, which are discussed in Chapter 6. The idea was to conceptualise a framework for RI that would be meaningful for nanomedicine and allow targeted

[2] I define experts here as individuals who are identified as 'specialists' in their field of study, are professionally established and well-recognised in their professional networks. However, as argued by Wynne (1998) and others (e.g., Stilgoe, 2006, 2009; Rabeharisoa and Callon 2004) people with science education or education in a particular discipline need not be the only experts. I too believe that there are different forms of expertise (and all such expertise might not be necessarily achieved via certification) which can be termed as experiential expertise. WYNNE, B. 1998. *May the Sheep Safely Graze? A Reflexive View of the Expert–Lay Knowledge Divide. Risk, Environment and Modernity: Towards a New Ecology. SAGE Publications Ltd,* London, SAGE Publications Ltd. STILGOE, J., IRWIN, A. & JONES, K. 2006. The received wisdom: Opening up expert advice. London: DEMOS, STILGOE, J. 2009. Citizen Scientists: reconnecting science with civil society. London: DEMOS.. RABEHARISOA, V. & CALLON, M. 2004. Patients and scientists in French muscular dystrophy research. *In:* JASANOFF, S. (ed.) *States of Knowledge: The Co-Production of Science and Social Order.* Routledge.

dissemination strategies to be designed. This was achieved by interviewing various expert stakeholders from the nanomedicine innovation chain to understand their views on likely environmental hazards and risks from nanomedicines, the current regulatory framework, and what the term RI means to them. Fulfilling these aims to contribute to a sustainable nanomedicine industry in service of society required a truly interdisciplinary research approach combining quantitative and qualitative methodologies and accessing literature across a broad spectrum of subjects /fields. The literature accessed for this thesis covered a wide range of disciplines, to name a few: nanomedicine; environmental effects of nanoparticles (including publications by academics and documents from policy making organisations); environmental fate and transformation of pharmaceuticals, (eco)toxicity of pharmaceuticals; toxicity of nanoparticles; public understanding of science, legal and regulatory studies; philosophy of science; science, technology and society studies; risk assessment and governance; technology and innovation management.

Before explaining the context and objectives of the research, it is important to discuss briefly the matter of definitions so as to justify my interpretation of a term, my choice of not defining it, or of using some terms interchangeably. Nanotechnology is considered both new and old technology, and so is nanomedicine,[3] however, going by the literature I accessed, I consider nanotechnology as a new and emerging technology and treat it as such throughout the thesis.

[3] As one scientist from the 66 interviewed experts shared: "*And if you look at the review ……., you'll see …a list of a table of products which are in the market place already since the 1980s, 1990s. So, it is although, nano became very fashionable in the last 10 years, it's something which has been evolving in many ways and although the new materials coming get ever more sophisticated, there are nano materials as medical products for a long time being used safely."* (NMS 08)

1.2 Definitions

1.2.1 Nanotechnology or nanotechnologies?

The Royal Society and the Royal Academy of Engineering proposed that the term nanotechnologies be used instead of nanotechnology (RS/RAE, 2004) due to the plurality of the field and the range of approaches and applications encompassed. Similarly, Duncan and Gaspar (2011) preferred nanomedicines to nanomedicine because of the range of interventions (diagnostic, therapeutic, and regenerative) and the range of nanomaterials that can be utilised. However, instead of delving into the semantics, I use the singular forms – nanotechnology and nanomedicine – throughout, following the predominant usage by the interviewees and for simplicity, although I agree with the arguments in favour of the plural forms nanotechnologies and nanomedicines.

1.2.2 Nanomaterials: can they be defined uniformly?

There is no globally accepted regulatory definition of nanomaterials; moreover, the definition may depend on the context. A cursory review of definitions suggested by various agencies in the EU and US indicates that nanomaterials are those materials that have one or more dimensions in the range of 1–100 nm and are specifically designed to be in that size range to exploit their novel properties. The European Commission proposed the following definition to be used in legislations and for policy-making: “Nanomaterial means 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. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1% and 50%" (EC, 2011a). However, the Commission mentioned that "special circumstances prevailing in the pharmaceutical sector should not prejudice the use of the term 'nano' when defining certain pharmaceuticals and medical devices", and hence refrained from defining nanomedicine. This definition poses problems in implementation, because the methods of measurement to distinguish the nano-fraction in products are yet to be developed and validated; though funds have been allocated to overcome this problem, for example, the NanoDefine project in FP-7.

This thesis does not focus on natural or incidental nanomaterials but discusses only those nanomaterials that have been specially designed in the nanoscale for medical purposes, which, according to ISO, are referred to as engineered nanomaterials.

1.2.3 Nanomedicine: no regulatory definition yet

As mentioned earlier, nanomaterials in health care were treated as a special case in the EC recommendations (EC, 2011a). The European Medicines Agency (EMA) has recently come up with a working definition of nanomedicine, which is as follows: "Nanomedicines are purposely designed systems for clinical applications, which have at least one component at nano-scale size resulting in definable specific properties and characteristics". The agency also emphasises that "the nanomedicine should

have the expected clinical advantages of nano-engineering and should meet the definition of a medical product".

This definition is not in any document published by the EMA but its representatives present the definition at various conferences. The agency shies away from defining what the nanoscale size range is and alludes to the suggested definition by the EC (Ehmann et al., 2013).

Similarly, liposomal products are generally not included in the search list of nanomedicines in the clinical trials website, although academic literature includes liposomes in nanomedicine. This lack of concrete definition can result in continued lack of certain or verifiable knowledge on nanomedicine products being developed and on the market, total investments in the field, and economic impacts. For example, Provenge® [4] was regarded as nanomedicine by nanotechnology enthusiasts (Roco et al., 2011a) but the label 'nano' may not be used widely (Goldman and DeFrancesco, 2009). Moreover, products can be evaluated and labelled inconsistently across jurisdictions. For example, some background scientific publications mention ferumoxytol as an iron oxide nanoparticle (NP); however, the EMA mentions it as a colloidal iron carbohydrate complex (EMA, 2012) whereas the USFDA mentions it as a NP (USFDA, 2011b).

For the purpose of this thesis, liposomes, various polymeric particles, polymer–protein complexes (with or without small-molecule drugs), micelles, dendrimers, protein–drug conjugates, and antibody–drug conjugates are considered

[4] Provenge® is the first cancer vaccine to receive USFDA's approval (in 2010) for asymptomatic or minimally symptomatic metastatic hormone-resistant prostate cancer. This vaccine is patient specific; dendritic cells and other antigen-presenting cells along with "recombinant protein composed of prostatic acid phosphatise" and granulocyte-macrophage colony-stimulating factor are cultured in patients' own blood. GOLDMAN, B. & DEFRANCESCO, L. 2009. The cancer vaccine roller coaster. *Nat Biotech,* 27**,** 129-139.

nanomedicines based on the mainstream scientific literature. However, neither viral and bacterial vectors, virus-like particles, which are currently at the R&D stage as potential drug-delivery agents, nor regenerative medicine where nanomaterials can act as scaffolding agents, are included in this thesis. *In vitro* diagnostics and various possibilities exploiting the properties at nanoscale has been touched upon and some details are provided in Chapter 2 and in the annexe to Chapter 4.

Historically, innovation has tended to precede discussions over safety by a considerable margin leading to reactive oversight and regulation (Hodge et al., 2010). Even if not reactively, there has been considerable delay between innovation, the products that result from it and subsequent cases of amendment or development of regulation, this delay is called the 'governance gap' (Renn and Roco, 2006). Moreover, time from research to market is getting shorter with each innovation wave (nanotechnology is proposed as the 6th wave). Figure 1.3 illustrates the progressively shortened time of transformative innovation paradigms over the years (Hargroves and Smith, 2005). In order to close this governance gap, there is a need to govern research and technology which provides insights as to what is coming downstream. Different approaches and conceptual frameworks, such as constructive technology assessment, real-time technology assessment, and upstream public engagement, have been used as a means to integrate societal considerations in new technologies or assess societal impacts; however, they have inclined more towards governing technology than research. To reflect on possible innovation pathways and implications before a technology or its applications become entrenched in society, a conceptual framework for governing research and innovation has been put forward by Owen et al. (2013b), known as responsible innovation (RI).

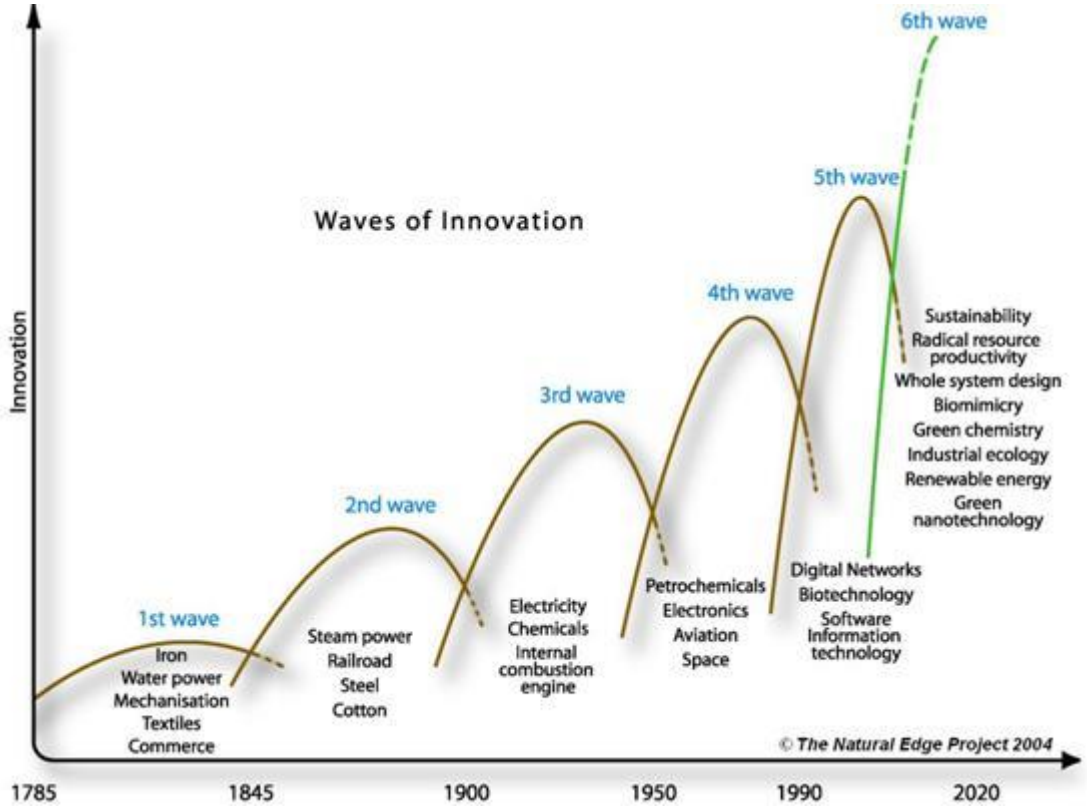


Figure 1.3: Waves of innovation.

Taken from http://www.naturaledgeproject.net/Keynote.aspx

1.2.4 Publics or Public

There have been many arguments made for advocating the use of the word 'publics' instead of 'public' because of the heterogeneity of populations with their myriad cultural beliefs, norms, ideologies and worldviews. 'Publics' is now used extensively but only in academic literature (Nerlich, 2013). However, I have used the term 'public' throughout the thesis to keep to the popular and most frequent usage.

1.3 The research context

The research presented in this thesis started in October 2010. At the time, only one peer-reviewed paper (Baun and Hansen, 2008) that discussed the potential

environmental impacts of nanomedicine had been published. The EMA conducted an international workshop in September 2010, which included a presentation on methodological issues in environmental risk assessment of nanomedicine by the German Federal Agency for the Environment (UBA). Empirical evidence for this research was collected primarily in the UK through semi-structured interviews, conducted either in person or over telephone or Skype. The interviews were done at a time when EPSRC had funded (in 2009) one of its three identified Grand Challenges which focussed on applications of nanoscience and engineering – nanotechnology for healthcare.[5] The academics working on nanomedicine whom I interviewed were in the early phase (first 2 years of the 3-year funding) of implementing their research. The research presented here began at a time when discourses on risks to the environment, health, and safety (EHS) from products of nanotechnology became mainstream and projects, programmes (for example, the EU FP-6 programmes FramingNano and NanoInteract and the various EU FP-7 programmes), and centres[6] were funded to explore EHS risks, develop visions for possible future scenarios, and understand people's views on the developments in nanotechnology (the EU Nanosafety cluster was established in 2008 to support linkages across EU projects, and the EU-US Communities of Research (CoRs) was established in 2012 to support transatlantic cooperation). However, most of the risk research being conducted was for the first-generation, passive or low-end nanomaterials in products advertised or were suggested as nanotechnology enabled. The occupational or environmental risks from 'active' nanomaterials, capable of

[5] The other two EPSRC Grand Challenges were novel applications for renewable energy and carbon capture and utilisation.

[6] For example, Rice University's CBEN, Science Foundation Ireland funded CBNI, National Science Foundation funded Centres of Environmental implications of Nanotechnology at Duke University and at USEPA, Nanotechnology in Society Centres at University of California, Santa Barbara and University of Arizona, Cross Research Council of the UK funded Environmental Nanotechnology Initiative.

changing their structure or properties based on external stimuli such as temperature, pH, and light remained unexplored. One example of such active nanostructures is medicines targeted at specific disease sites or parts of the body or imaging agents targeted to affected sites. However, it is this very promise of making 'stealth' drugs capable of crossing physiological barriers in the body to increase bio-availability and solubility that raises obvious concerns regarding future (unintentional) environmental exposure. Possible environmental implications from these 'active' nanostructures intended for medical uses were not yet on the agenda of nanotechnology researchers, environmental health researchers, policy makers, regulators or industry. It was against this background that medical applications of Au-NP was chosen as a case study to explore potential environmental implications, to identify uncertainties and gaps in existing knowledge, and to assess experts' perceptions on nanomedicine in the environment.

During the later part of the decade 2000–2010, the concept of responsible development of nanotechnology led the way to responsible innovation (RI) (Fisher and Rip, 2013). However, when the present research was started in late 2010, the concept of RI was still in the making and not widely known. Owen and Goldberg (2010) used the call for 'nanotechnology grand challenge for carbon capture and utilisation' as a test case to develop a framework for RI. David Guston had proposed the concept of 'centres of responsible innovation at universities' (early 2000s)[7] in response to the emphasis on commercialising the innovations from research in universities under the Bayh Dole Act or the Patent and Trademark Law Amendments Act, 1980. However, the concept of RI was being developed independently in the

[7] See the footnote in page 372 in HELLSTRÖM, T. 2003. Systemic innovation and risk: technology assessment and the challenge of responsible innovation. *Technology in Society,* 25**,** 369-384.

UK, the Netherlands, and the US. From 2010 to 2012, at least eight workshops and conferences[8] were held centred around RI, indicating the rapid integration of RI in policy discourse. This was the right time to gather the perceptions of experts on the meaning of RI to inform the evolving framework on RI and contextualise it for nanomedicine. The dimensions of the framework on RI as conceptualised by Owen et al. (2013b) form the basis of analysing the empirical qualitative data. This framework is elaborated in Chapter 2 and also discussed in Chapter 6. However, a few other definitions of responsible innovation (RI) or its cognate term, responsible research and innovation (RRI), are given below.

1.3.1 Defining responsible (research and) innovation

Here I provide two definitions of RI, one by Renè von Schomberg and the other by the EC. Some more definitions of RI are provided in Chapter 2, wherein I also explain the common conceptual denominator.

Renè von Schomberg defines RRI as "*a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society).*" (von Schomberg, 2013, p.63)

"*RRI refers to ways of proceeding in Research and Innovation that allow those who initiate and are involved in the processes of research and innovation at an early stage (A) to obtain relevant knowledge on the consequences of the outcomes of their*

[8] For details of the six workshops, see FISHER, E. & RIP, A. 2013. Responsible Innovation: Multi-Level Dynamics and Soft Intervention Practices. *Responsible Innovation.* John Wiley & Sons, Ltd. Two other conferences were: Responsible Innovation Conferences held in the Hague in April 2011 and December 2012.

actions and on the range of options open to them and (B) to effectively evaluate both outcomes and options in terms of moral values (including, but not limited to well-being, justice, equality, privacy, autonomy, safety, security, sustainability, accountability, democracy and efficiency) and (C) to use these considerations (under A and B) as functional requirements for design and development of new research, products and services." (EC, 2013d, p.56)

1.3.2 Geographical context of research

The spend in the US on research in the health care sector is the largest in the world, followed by the EU – about 130 billion dollars and about 30 billion euros [about 32 billion dollars][9], respectively – and most of the high-growth innovation firms in the pharmaceutical sector are in the US (Research America, 2012; EC, 2013b; EFPIA, 2015). However, in the EU, the R&D intensity of pharmaceutical and biotechnology sectors is the highest amongst all industrial sectors (EFPIA, 2015). Also, the quantitative data used to do the probabilistic modelling to estimate potential future concentrations of nanomedicine is for the EU and US. Therefore, in this thesis, the US and the EU's R&D policies and regulations are presented where required and necessary. However, the 62 interviews[10] for this research study were mostly those of UK-based experts (very few were from other EU countries), which makes the thesis oriented more towards the EU and UK research and innovation scenario.

[9] Currency conversion for 4 January 2016 using the XE currency converter website.
[10] 62 interviews involving 66 interviewees.

1.4 Style of writing

Theses in the social sciences are typically in the first person; those in the sciences are typically impersonal. Since this is a mixed-methods interdisciplinary thesis, I have used the first-person option throughout for clarity and consistency. Wherever I believed that a particular term needed explanation, I have provided explanatory footnotes where possible; however, due to the diversity of subjects handled, it is acknowledged that it has not been possible to provide explanations of many terms that have been used throughout the thesis (though these terms may be of common knowledge in the particular field).

1.5 Research purpose

Multiple and substantial benefits are claimed for nanotechnology applications in health care. More than 200 nanomedical products have been approved and are in the market or are at their early or late stages of clinical trials (Etheridge et al., 2013), and many more are under development, with focus on designing multifunctional, complex, and 'smart' systems to target disease sites and to cross physiological barriers. Such immense potential contributions to human health, from a new and emerging technological application, necessitate adoption of a critical approach which considers various aspects of R&D in nanomedicine and possible future implications. The overall purpose of the research was to explore how the developing nanomedicine sector could be shaped to contribute sustained benefits to society. Environmental hazards and risks of nanomaterials – especially of nanomedicine – are poorly understood. Hence, an exploratory study was performed to conceptualise whether nanomedicine might create newer forms of environmental hazards and risks.

Knowledge gaps and uncertainties are pervasive in the case of EHS implications of nanomaterials; therefore, besides aspiring to make a novel contribution to discussions on environmental risks of nanomedicine, I gathered the viewpoints of key stakeholders in the nanomedicine innovation chain to help strengthen the discussions on RI. Taking these insights the objective was to conceptualise how RI can be operationalised in the nanomedicine field to help proactively alleviate issues from future implications as such products become embedded into the societal fabric.

1.6 Research Objectives

- To critically review the existing literature on pharmaceuticals and nanomaterials in the environment, to review the current scenario of regulation in medicine and medical devices, and to ascertain the developments in nanomedicine.
- To estimate prospective environmental concentrations of nanomedicine and, based on the predicted releases, perform a risk assessment.
- To ascertain stakeholder views on the potential environmental risks of nanomedicine and the adequacy of current risk governance frameworks to manage these risks.
- To explore the construction of the concept of RI by experts in the nanomedicine innovation chain.

1.7 Organisation of the thesis

In order to address these research objectives, the thesis adopts a mixed methods approach with chapter content structured as follows:

Chapter 2 explores the existing literature and discusses in detail all the above four objectives to help situate the research. The chapter describes R&D interests and gives a snapshot of nanomedicine products in the market or in advanced stages of clinical trials to provide a foundation for the study. Studies on monitored environmental concentrations of pharmaceuticals and ecotoxicology of pharmaceuticals are included because it is important to discuss the findings. Similarly, biodistribution, transformation, fate, and the effect of nanomaterials in the environment are discussed. The selection of literature was limited to the topic of my research, although I have included some studies on the application of nanomaterials in other areas wherever necessary to support the points being made. A brief background of the emergence of the concept of RI is given and the various framings of RI are presented. Innovation in pharmaceuticals and medical devices and the regulatory framework for medicines and medical devices are also covered briefly.

Chapter 3 presents the methodology adopted to investigate the topics of the thesis. The reasons for selecting the spatial boundary of the UK and the US, along with those for selecting quantitative and qualitative methods are discussed. I also justify the choice of the probabilistic mass flow (PMF) model and discuss the reason for building a probabilistic species sensitivity distribution for estimating risks (however, detailed methodology is in Chapter 4). Gold nanoparticles (Au-NP) used in medicine has been selected as a case to predict future environmental concentrations of

nanoparticles from medicine due to the enormous range of potential applications of Au-NP and increased future use. Furthermore, the chapter gives details of the qualitative data and describes how the study participants were selected and discusses the methodological approach and the analytical framework chosen to analyse the qualitative data.

Chapter 4 discusses the quantitative part of the research. I used the well-established PMF model to estimate prospective concentrations of nanomedicine (Au-NP has been used as 'indicative' nanomedicine) in the technical (sewage treatment plants, incinerators, and so on) and environmental (soil, water, sediments) compartments. The various assumptions to arrive at the input data are explicitly stated. Potential risks to the environment are estimated using the ecotoxicity studies of gold nanoparticles. This chapter details the knowledge gaps and uncertainties related to assessing environmental risks from nanomaterials.

Chapter 5 continues from Chapter 4, where the environmental concentration of gold nanoparticles from medical products is presented. In this chapter, I am trying to 'open up' (Stirling, 2008) the debate on nanomedicine, largely confined to ethics (Silva Costa et al., 2011) and risks (Hogle, 2012), by asking neglected questions of potential environmental implications of nanomedicine to experts in the nanomedicine innovation chain. Moreover, in cases of uncertainty or when addressing complex issues, expert elicitation is a preferred strategy. Experts were interviewed to provide a qualitative perspective on possible hazards and risks from nanomedicine. These expert interviews were not conducted with the aim to validate the model results (of Chapter 4) or with the intention to privilege their knowledge over others' knowledge. The perceptions of various stakeholders regarding possible environmental hazards

and risks from nanomedicine and of the adequacy of the governance framework for nanomedicine are discussed in this chapter. I conclude by drawing parallels from studies on the perceptions of experts and the public on the environmental risks of conventional medicine.

Chapter 6 discusses one of the key objectives of the thesis which is about how to guide research and innovation so that better societal and environmental outcomes are achieved, taking into consideration the difficulties, challenges, and uncertainties that often plague innovations at an early stage. The chapter discusses RI as conceptualised by Owen et al. (2013a) and as interpreted by various stakeholders and briefly describes the methodology for coding the interviews. The chapter then goes on to argue that the stage-gated process of developing pharmaceuticals can be used to integrate the dimensions of RI (although the goals of new drug research can be considered to be mainly driven by instrumental and substantial imperatives). I explore ways by which RI can be operationalised by dovetailing the existing concepts, such as business citizenship and stakeholder engagement and tools (e.g., institutional review boards) and voluntary codes of conduct and programmes (e.g. corporate responsibility). I end the chapter by discussing the importance of RI in nanomedicine and with some thoughts on future research directions.

Chapter 7 concludes the thesis by revisiting two central aims of the thesis, namely (1) to explore the possibility of future environmental hazards and risks associated with nanomedicines and (2) to understand the perception of experts about RI. The chapter considers the findings discussed in the earlier chapters to make a case for shared responsibility or collective commitment based on the distributed innovation model used in the pharmaceuticals industry. The concept of RI is flexible enough to

allow institutions, agencies, and actors to imbibe the many facets of RI in many different ways.

Parts of the next chapter are adapted from the following review article published in the Journal Environmental Science: Processes and Impacts:

MAHAPATRA, I., CLARK, J., DOBSON, P. J., OWEN, R. & LEAD, J. R. 2013. Potential environmental implications of nano-enabled medical applications: critical review. Environ Sci Process Impacts, 15, 123-44.

All elements of the research and writing were done by I. Mahapatra under supervision from her co-authors.

Chapter 2: Nanomedicine R&D, 'post-normal' science, and responsible innovation

2.1 Introduction

The attractiveness of nanotechnology for health-care applications lies in its ability to develop and synthesise materials at nano sizes, which allows such materials to interact with receptors on the cell surface as well as with various subcellular components. New properties due to the nano size can enhance uptake of drugs and evade biological barriers of the body. The large surface area of nanoparticles allows attachment of various biomolecules such as antigens, peptides, and amino acids and can help to detect, simultaneously, multiple disease biomarkers, and identify infectious microorganisms present in minute quantities in body fluids, and thus can help in early diagnosis and treatment. Application of nanotechnology, combined with other advanced therapies such as cell therapy and gene therapy, can potentially provide solutions for incurable or difficult-to-cure diseases such as cancer and neurodegenerative diseases, which are expected to increase in the future. Cancer is the second leading cause of mortality worldwide (Lozano et al., 2012) and accounted for an estimated 15% of global deaths in 2013 (Global Burden of Disease Cancer Collaboration, 2015), of which 62% were due to neoplasm[11] in developing countries (WHO, 2006). Neurological disorders including cerebrovascular diseases contributed to 6.3% of the global disease burden and accounted for 11.67% of the deaths in 2005. Alzheimer's and other dementias are projected to increase to 66% by 2030 (WHO, 2006) as a result of the ageing population and longer lifespans. These statistics reflect the unmet clinical needs of these conditions.

[1111] Neoplasms are abnormal growth of tissue in a part of the body, especially as a characteristic of cancer.

The pharmaceutical industry derives its growth from R&D (Tollman et al., 2011) and is currently facing major challenges in the form of revenue loss as patents of a number of drugs having high sales continue to expire (Paul et al., 2010). Moreover not all approved drugs deliver sufficient returns on the investments made on them by the pharmaceutical company (Grabowski et al., 2002). Nanotechnology can help to reintroduce shelved therapeutics and reposition drugs thereby increasing patent life and generating revenues. For example, developing clinical applications of siRNA has been a challenge, mainly because of the rapid enzymatic degradation of the molecule in the body (Reischl and Zimmer, 2009). Recently a team from the US has been successful in conducting a clinical trial on melanoma patients that involved encapsulating siRNA in a 70 nm cyclodextrin-based polymer, with human transferrin protein (hTf) as a targeting ligand and a polyethylene glycol (PEG) polymer as a stabilizing agent for nanoparticles (the clinical name of this nanomaterial is CALAA 01) (Davis et al., 2010). Similarly, use of tumour necrosis factor (TNF) as a chemotherapeutic found limited applications because of systemic toxicities. Currently, Phase I clinical trials for patients with advanced solid tumours are being conducted for TNF-PEG-Thiol colloidal gold nanoparticles of 27 nm (Aurimune®). With intravenous injection of these nanoparticles, it was found that patients were able to tolerate 20 times the usual dose of TNF-α (Zolnik and Sadrieh, 2009; Kim et al., 2010) compared to the non-nanoformulation. By 2019, nanotechnology in medicine is expected to have a global market of $528 billion (BCC research, 2015).

Of the drugs currently in the market, 90% are effective only on 40% of individuals, resulting in ineffectual prescriptions worth $350 billion a year (Jerome, 2012). For neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease

and mood-affective disorders such as depression and schizophrenia, 98% of the small-molecule drugs available in the market have very poor efficacy (de Boer and Gaillard, 2007). Ineffectiveness of drugs can be due to many reasons, including genetic polymorphism (which influences responses to drugs), lack of knowledge of the underlying causes of diseases, many different mutations leading to a particular disease, ineffective dosage, and poor bioavailability. Nanotechnology can ameliorate ineffectiveness of some medicines and create a shift towards more personalized medicine by creating new tools for supporting discoveries in life sciences, e.g. discovery and identification of biomarkers (Liotta et al., 2003; Dasilva et al., 2012), and can provide solutions to the traditional problems associated with poor solubility (Hawkins et al., 2008; Zhang et al., 2011c), cytotoxicity (Davis et al., 2010), limited bioavailability (Allen and Hansen, 1991), immunocompatibility (Gradishar et al., 2005), and limited cellular uptake (Desai et al., 1996) of many therapeutic agents. Table 2.1 summarises some of the potential advantages introduced by nanotechnology for medicine.

Table 2.1: Some possible advantages of nanotechnology-enabled drugs over conventional drugs. Adapted from Kumar et al. (2013).

Physical aspects	Biological aspects
Increase in aqueous solubility	Improves bioavailability
Protects the drug from degradation by enzymes or recognition by the mononuclear phagocyte system	Improves biocompatibility
Makes it possible to encapsulate both lipophilic and hydrophilic drugs or multiple drugs	Improves targeting of disease sites
Enables release of drugs that respond to specific stimuli such as acidity–alkalinity, temperature, and magnetic field	Prolongs circulation time
Ability to reach certain disease sites	Has the ability to reduce systemic toxicity

Although a clear and uniform definition of nanomedicine is yet to be articulated, there are a wide variety of publications, reports, and discussions related to nanomedicine and its potential to improve human health and the economy. A recent study based on a comprehensive search criteria established that there are 247 products approved or in clinical trials that could be labelled 'nanomedicine' (Etheridge et al., 2012). An advanced search undertaken on the website clinicaltrial.gov on 3 November 2015 with 'nanoparticle' as the search term, 'Phase 0,1,2,3,4' as the selected parameters, and excluding studies with unknown status returned 158 records, of which 54 were open studies. Most (113) were conducted in the US, followed by Europe (15) and China (15). The majority of clinical trials were for neoplasms of various types.

Most of the nano-therapeutics are primarily based on PEG or liposomal and albumin encapsulation (Duncan and Gaspar, 2011). The applications in clinical development belong to the categories of liposomal formulations, polymer–protein and polymer–drug conjugates, micelles, antibody–drug conjugates, dendrimers, and metal NP such as iron oxide NP and Au-NP. Nano-therapeutics can be produced either by top-down processes such as milling, high-pressure homogenization (reviewed in Junghanns and Muller, 2008), innovative lithography techniques (reviewed in Rajasekhar et al., 2013), or through bottom-up processes involving synthesis of more sophisticated and complex designs, e.g., create a nano-size drug-delivery platform consisting of a polymer matrix, functional surface moieties, and targeting ligands to deliver related drugs to affected sites in the body (Hrkach et al., 2012).

Polyethylene-glycol-coated therapeutics have been shown to have increased circulation time in the human body (Gabizon et al., 1994), and many PEG-coated therapeutic agents are in advanced stages of clinical trials (Pasut and Veronese,

2009; Duncan and Gaspar, 2011). However, PEG is not easily biodegradable, and not only PEG but also polymeric nanoparticles made of natural polymers such as chitosan and alginates might not be easily degraded by the enzymes in the human body (Gaspar and Duncan, 2009). After internalization by cells, nanoparticles are typically localized inside highly acidic endosomes or lysosomes and can lose their polymer coating, which can subsequently be excreted by the kidneys (Kreyling et al., 2015) or dissolved by the highly acidic environment of lysosomes.

2.1.1 Current landscape: nanotechnology-enabled therapeutics

This section is not a detailed description of all of the developments in nanomedicine; rather, it attempts to set into context the main objective of the thesis. Therefore, only a brief description is given here of the major categories of well-established nanocarriers (either with at least one clinical application or at an advanced stage of development) and of a few promising developments in the field of oncology, central nervous system (CNS) disorders and HIV/AIDS—chosen because of the high global disease burden values, huge future market potential due to future demographics, current market status (57% of the total global nanomedicine sales in 2011 were accounted for by oncology and CNS drugs), or research rankings. Many in-depth reviews of the development of nanomedicine have been published (Alexis et al., 2008; Vicent et al., 2009; Bhaskar et al., 2010; Duncan and Vicent, 2010; Kim et al., 2010; Brambilla et al., 2011; Duncan and Gaspar, 2011; Kateb et al., 2011), and readers may refer to these reviews for details. Carbon-based nanocarriers (e.g. fullerenes, carbon nanotubes, and nano diamonds) have immense potential for

myriad applications for incurable or difficult-to-cure diseases because of the ease of surface functionalisation of these nanocarriers, their hydrophobicity, stability, variability, customizable therapeutic cargo encapsulation and release strategies, their ability to cross various biological barriers in the body or to escape the reticuloendothelial system (RES). However, to the best of my knowledge, none of the disease treatment strategies that have shown their potential either *in vitro* or in proof-of-concept experiments using these materials has moved beyond the pre-clinical stage.

Drug carrier design requirements: The key principles governing rational design considerations of therapeutic delivery carriers (Adair et al., 2010; Petros and DeSimone, 2010) are as follows:

- Physiologically stable vectors / nanoconstructs capable of evading the RES / mononuclear phagocytic system
- Amenability to surface functionalisation with targeting moieties such as aptamers, antibodies, and cell-penetrating peptides
- Ability to cross the biological barriers of the body, i.e., 'right' size, shape, surface property
- Availability of a clearance mechanism
- Ability to release the drug payload at the required site (delivery can also be designed so that it is modulated by pH, oxidation-reduction, and enzymatic cleavage of bonds or activated by external stimuli such as an electro-magnetic field or light)
- Biodegradability and biocompatibility, i.e., low or no immunotoxic, genotoxic, mutagenic, reproductive, or developmental toxic effects.

Nanomaterials are broadly classified into two categories based on the type of interactions exploited for designing the nanomedicine. These two categories are 'hard' and 'soft'. Hard nanomaterials, such as metal and metal oxide nanoparticles, and fullerenes are formed via ionic or covalent bonds, whereas 'soft' nanocarriers use weak interactions (Canton and Battaglia, 2012). The key types of hard nanomaterials currently being investigated for clinical applications and in the market are Ag-NP, Au-NP and Fe_xO_y NP or SPIONs. Ag-NP have an antimicrobial effect and have applications in bandages for burn injuries, catheters and others. Fe_xO_y NP are used because at nanoscale iron oxide exhibits super-paramagnetism[12] and can be used as contrast agents as well as for hyperthermia treatments for cancer (Hadjipanayis et al., 2008; Thiesen and Jordan, 2008). More examples of the use of Au-NP are given in Chapter 4 and the annexe to it.

Nanocarriers, both currently used and under investigation, can also be classified into two major categories: passive and active. The 'passive' or first-generation nanocarriers comprise delivery systems that are simple polymer- or lipid-coated therapeutic agents that release their payload due to specific characteristics of the diseased tissue, e.g., the enhanced permeation and retention (EPR) effect of tumour tissues. The much acclaimed nanotechnology-based oncological drug Abraxane® is a passive nano therapeutic (chemotherapeutic drug paclitaxel bound to human albumin). 'Stealth' NP or PEG-coated NP also fall under this category. Doxil® (liposomal PEG Doxorubicin) and Oncaspar® (PEG–L-asparaginase) are examples

[12] Superparamagnetic particles have single magnetic domain and align themselves with applied magnetic field but lose the magnetisation after removal of the field. Applied alternating magnetic field can be used to generate heat from particles and cause cell death.

of two already marketed drugs using PEG coating, which is used to reduce protein binding to the nanocarriers and thus facilitate their evasion of macrophages.

The 'active' or next-generation nanocarriers are defined as having specific additional functionalities, such as surface decoration with antibodies, aptamers, and receptor proteins, which allow for molecular recognition by the target tissue or have environmentally responsive triggers to release payload at the disease site or have multiple functionalities such as detecting and treating diseases (theranostics). An example of a targeted nanomedicine in advanced stages of development is the mannose-targeted polyethylamine (PEI) polymers containing plasmid DNA as the therapeutic agent for treatment of HIV/AIDS (Phase II clinical trials) (Mamo et al., 2010). Another intriguing nanomedicine is BIND-014, which consists of a polymer matrix, therapeutic payload, functional surface moieties, and targeting ligands and is currently under Phase II trials for solid tumours[13] (Hrkach et al., 2012). Many proof-of-concepts studies showing temperature, pH, redox etc. as stimuli for controlled release of the therapeutic payload exist in the literature. For example, tumour micro-environments have acidic pH and this can be utilized for triggered drug release. In a murine model, it was shown that nanoparticles made from polymer (poly B amino ester) were stable at a physiological pH of 7.4 but became soluble at pH 6.5 associated with the tumour, leading to the release of doxorubicin (Yoo et al., 2011). Another pre-clinical study showed that paclitaxel conjugated to self-assembling recombinant amino acid polypeptides (nanoparticles of about 60 nm) resulted in the release of the drug after uptake into tumour cells, as the polypeptide bond was designed to be responsive to the low-pH environment in the tumour. It was found that the uptake was 2-fold higher than that of Abraxane® (Bhattacharyya et al.,

[13] http://nano.cancer.gov/learn/now/clinical-trials.asp

2015). Similarly, with the aid of stimuli created from external sources, drug release can be achieved. Thermosensitive stealth liposomes (TSLs) composed of DPPC/Chol/DMPC/PEG2000 (54:30:3:3) of ca. 100 nm were designed to carry the anti-neoplastic drug doxorubicin without 'leak' at the physiological temperature. Gold nanorods were injected simultaneously with these TSLs in the mouse model of human glioma and NIR irradiation was applied, increasing the temperature and resulting in release of the drug. The animals showed increased survival when compared to the USFDA-approved liposomal doxorubicin, a non-TSL (Agarwal et al., 2011). Rapid advances in design and synthesis of ENMs can be made by the use of high-throughput technologies and combinatorial libraries of chemicals and materials. For example, such libraries can help to synthesize various shapes of nanoparticles (Kim et al., 2012a) and new polymeric materials (Abeylath et al., 2011). New polymeric therapeutic nanomedicines can be synthesized by combining two or more different types of polymers to give unique properties to help deliver genes (Green et al., 2008), therapeutic nucleotides (Lee et al., 2009a), peptides (for example, siRNA for the serine/threonine protein kinase or polo like protein kinase – PLK-1 - a key regulator of mitosis in mammalian cells conjugated with nucleic acid lipid particle) (NCI, 2011b; Kanasty et al., 2013), or drugs (Hrkach et al., 2012). Figure 2.1 shows a cartoon of a multifunctional polymeric nanoparticle (Schneider et al., 2009) with its various components.

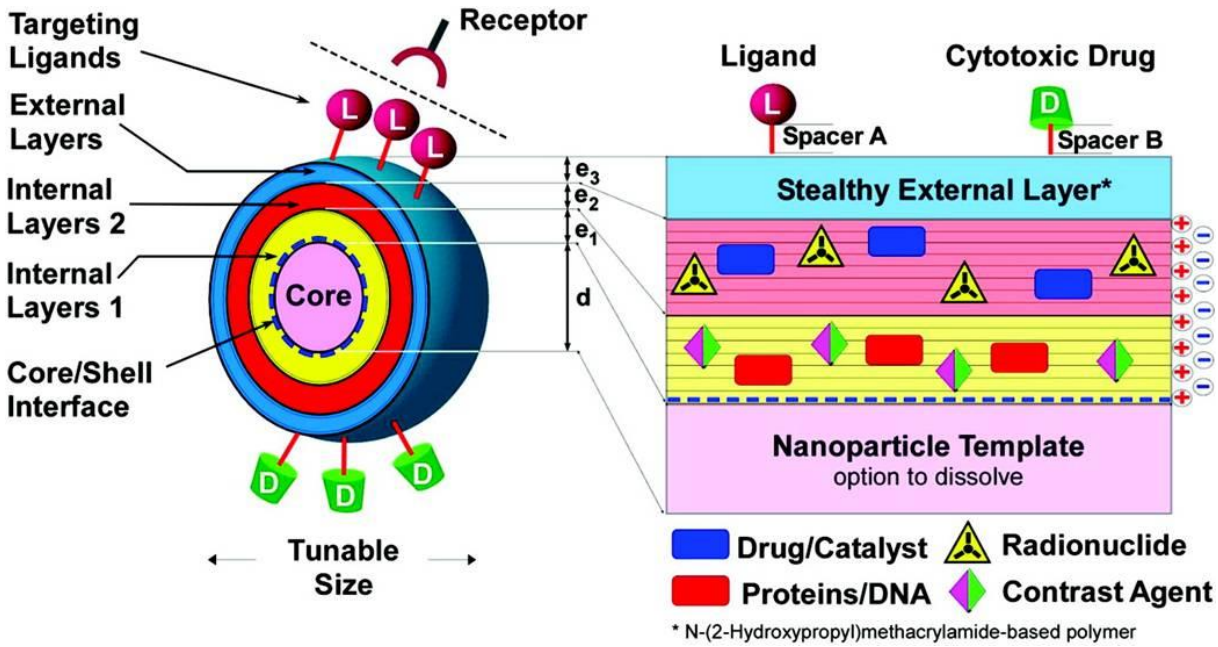


Figure 2.1: Cartoon of a multifunctional polymeric nanoparticle (Taken from Schneider et al. 2009).

The key nanocarriers that have been used in the marketed nanomedicine products or are under clinical trials to date are liposomes, polymers, dendrimers, and metal nanoparticles, and their key features are summarized below, with examples given in Table 2.2:

- Liposomes are spherical vesicles composed of amphiphilic natural or synthetic phospholipids and cholesterol, which self-assemble into bilayers to encapsulate an aqueous interior. They are one of the oldest and most widely recognized nanocarriers and can serve as a platform for delivery of both hydrophilic and hydrophobic therapeutic agents[14] (Torchilin, 2005) and encapsulation of metal nanoparticles (Mikhaylov et al., 2011). Doxil (liposomal doxorubicin) and Abelcet (liposomal Ampotericin B) were the first liposomal drugs approved in 1995 (Petros and DeSimone, 2010). Liposomes vary greatly in size from 25 nm to

[14] Therapeutic agents can mean drug, cell, DNA, siRNA, etc. for treating diseases.

5000 nm (Spuch and Navarro, 2011) and can be classified in terms of composition and mechanism of intracellular delivery into five types: conventional liposomes, pH-sensitive liposomes, cationic liposomes, immunoliposomes, and long-circulating or PEGylated liposomes (Kim et al., 2010). An advanced search conducted on 8 November 2015 of the clinicaltrials.gov website with the search term 'liposomes' and excluding trials of unknown status and setting the range of 'first received dates' from 1 January 2000 to 1 November 2015 returned 1088 listed trials, of which 217 trials were open studies. Open studies are defined as 'studies that are currently recruiting participants, will be recruiting participants in the future, or involve drugs that are available for expanded access'.

- Dendrimers are synthetic polymers in which the atoms are arranged in many branches and sub-branches radiating from a central core. Dendrimers can be categorized based on the number of the branches termed as generations (e.g., G1, G2, G3), as shown schematically in Figure 2.2.

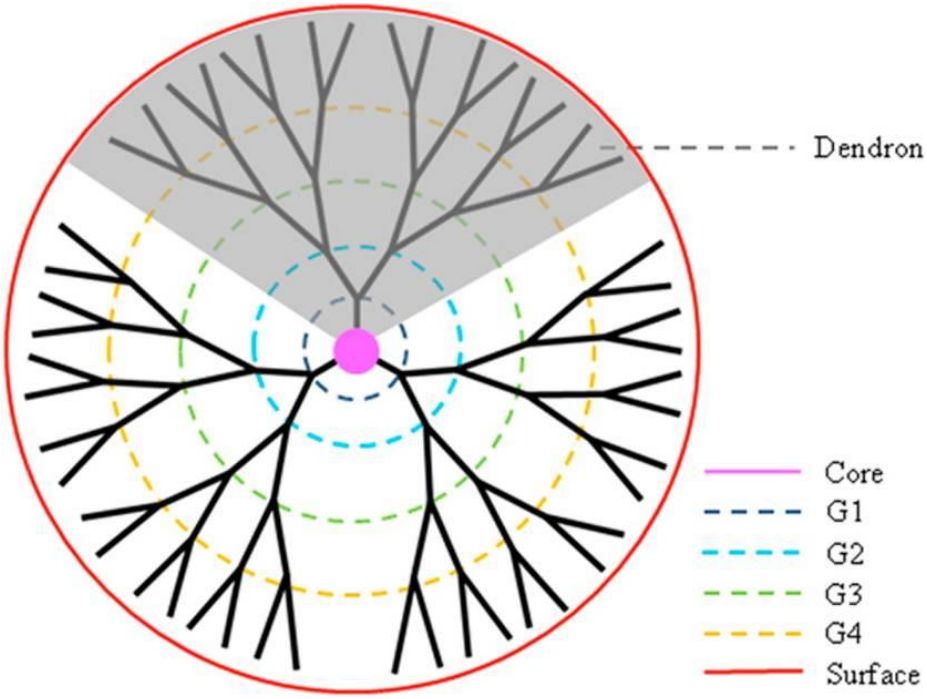


Figure 2.2: Schematic of a dendrimer showing various generations as dotted lines (Taken from Lin-ping Wu, 2015).

Dendrimers have been identified as ideal nano-scale drug delivery systems due their capacity to have multiple functionalities (therapeutic, imaging, and targeting). It has been reported that the synthesis of dendrimers is so versatile that hundreds of compositionally different dendrimers and thousands of differentiated chemical surface modifications are possible (Zolnik and Sadrieh, 2009). Due to their polycationic surface, dendrimers can themselves act as therapeutics agents. Despite their versatile nature and immense possibilities as therapeutic agents, lack of a safety profile has prevented them from being a huge success, and only two dendrimer-based therapeutics have reached the clinical stage. Vivagel® is the only dendrimer-based therapeutic that has completed a Phase III clinical trial for treatment of bacterial vaginosis (Starpharma, 2012).

- Micelles are nano-sized, spherical colloidal particles with a hydrophobic interior (core) and a hydrophilic exterior (shell or corona), which can generally self-assemble into three different types of shapes (lamellar, cylindrical, or spherical) as shown in Figure 2.3 (Zhulina and Borisov, 2012). Drugs or contrast agents may be entrapped within the hydrophobic core or linked covalently to the surface of micelles (Bawarski et al., 2008). Pluronic® block copolymers are recognized pharmaceutical excipients (Kabanov et al., 2002) and are the most widely investigated type of micelle (Wong et al., 2012). It has been shown that polymers of polylactic acid (PLA) and copolymers of polylactic-co-glycolic acid (PLGA) coated with Polysorbate 80 or Poloxamer 188 improve CNS penetration (reviewed in Patel et al., 2012). The company Nanocarrier has four oncological drugs with different pharmaceutical ingredients (e.g., paclitaxel, cisplatin, oxaliplatin) loaded into micelles currently in clinical trials (NanoCarrier, 2013). An advanced search conducted on 4 December 2015 of clinicaltrials.gov website with the search term ‘micelles’, excluding trials of unknown status and setting the range of ‘first received dates’ from 1 January 2000 to 1 November 2015 returned 12 listed trials.

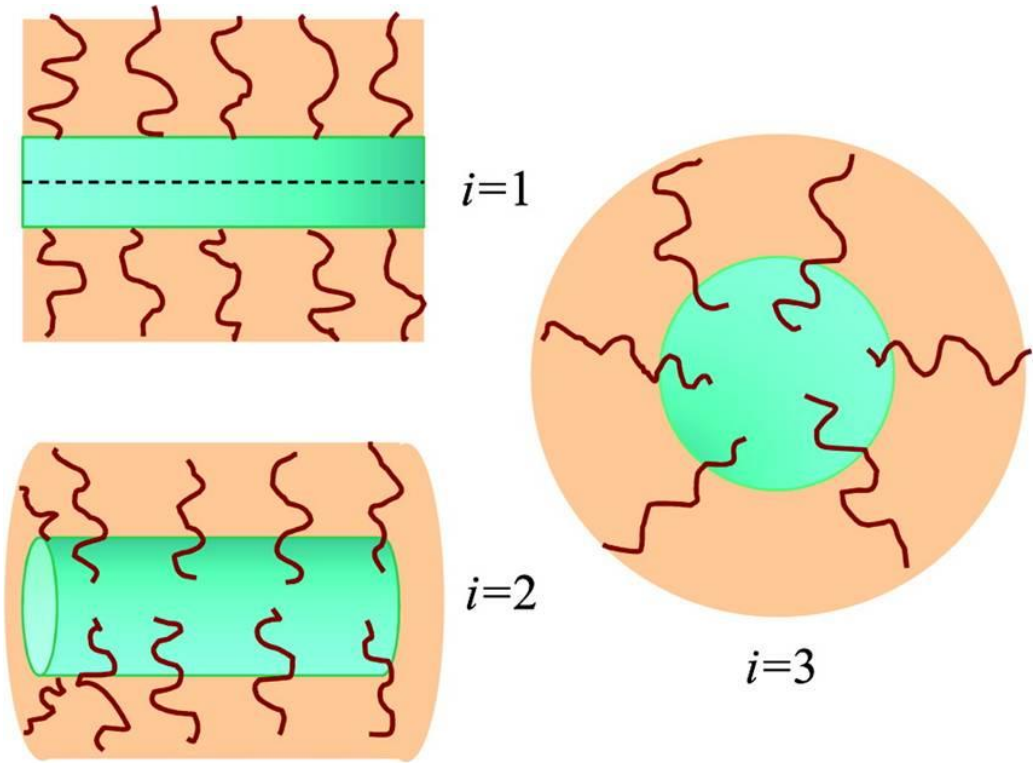


Figure 2.3: Illustration of the three morphologies of block copolymer micelles: i = 1, lamellar; i = 2, cylindrical; i = 3, spherical (Taken from Zhulina and Borisov, 2012).

- Some of the inorganic nanoparticles reviewed widely in the nanomedicine literature and showing promising applications are silica, nanodiamonds, gold nanoparticles, iron oxide nanoparticles, quantum dots, and manganese oxide nanoparticles. Health-care applications of these (except Au-NP) in the delivery of therapeutically active components are mostly in the proof-of-concept stage. A promising proof-of-concept study is the use of nano diamond conjugated to Gadolinium (III) – Gd(III) ND as an *in-vivo* imaging agent. This molecular Gd (III) complex had a relaxivity value nearly 20 times the relaxivity values of clinical Gd (III) contrast agents, Gd-DTPA, and Gd-DOTA and results in a 10-fold increase in MRI contrast enhancement (Manus et al., 2010).

Iron oxide nanoparticles have been approved for treatment of iron deficiency anaemia in adult patients with chronic kidney disease (USFDA, 2011b; EMA, 2012; Scott et al., 2013). Phase I clinical trials of Aurimune® (PEGylated colloidal-gold-bound TNF for treatment of advanced solid tumours were completed in 2009 (clinicaltrials.gov). Nanospectra Biosciences is at the investigational stage of using its patented product Auroshell® (gold-coated silica nanoparticles) for thermal ablation of refractory head and neck cancer (Nanospectra, 2012). The company is conducting clinical trials under USFDA's Investigational Device Exemption (IDE). Silica nanoparticles also show promise as imaging agents (NPG, 2010) and have the potential to be used as therapeutics. They can be synthesized as core-shell particles doped with metal nanoparticles or dyes or as mesoporous silica particles capable of carrying drugs in their pores. Based on the doping moieties, the imaging modality can be fluorescence or magnetic resonance imaging (MRI).

2.1.2 Current landscape: nanotechnology-enabled devices

Many nanotechnology-based *in vitro* diagnostic devices are being designed, tested, and marketed based on bioconjugated Au-NP, Ag-NP, Pt-NP, silicon nanowires, CNT, etc. One example worth mentioning is a diagnostic device capable of measuring disease biomarkers in exhaled breath. A Framework Programme (FP-7) project of the EU has resulted in the development of an artificial olfactory sensor.[15] This device is in completed trials for diagnosis of breast and colon cancer and gastric

[15] See http://lnbd.technion.ac.il/research/snail-trail-printing/ Details in projects: DIAGCAN and LCAOS

lesions and multiple sclerosis.[16] The sensors are made of either silicon nanowires or single-walled carbon nanotubes (SWCNT) or metallic nanoparticles such as Au-NP or Pt-NP or a combination of these. Similarly, nanostructures are being exploited to design molecular beacons (nanoMBs),[17] which may be made of nanomaterials, such as Au-NP, carbon nanotubes (CNT), graphene, Si-NP, and quantum dots.[18] In the case of medical devices, for both diagnostic and active implantable devices, applications of nanotechnology have shown substantial benefits. Nano-enabled *in vitro* diagnostic devices can help in early diagnosis of disease given their enhanced specificity and sensitivity. Furthermore they can produce results within a short time (Chin et al., 2011) and can be minimally invasive (Peng et al., 2009). Nanotechnology is enhancing the ability of diagnostic devices to detect multiple markers with minute amounts of samples and with increased specificity (Valentini et al., 2013). *In vivo* imaging agents on the market include SPIONs for imaging of liver cancer.

ENMs present in these devices, even when present in a composite form or embedded into the matrix, might find their way into the environment eventually and result in exposure, as has been the case with e-waste and battery waste.

Box 2.1 provides some examples of nanotechnology-enabled *in vitro* and *in vivo* diagnostic devices at the proof-of-concept stage or in advanced stages of development.

[16] https://clinicaltrials.gov/ (Identifier: NCT01206023, NCT01292369, NCT01420588

[17] Molecular beacons (MBs) are stem-loop hairpin-structured oligonucleotides with a fluorescent quencher at one end and a fluorescent dye (also called reporter or fluorophore) at the opposite end.

[18] For example, Verigene®, by Nanosphere, is an FDA-approved diagnostic device made up of Au-NP in the size range 13–20 nm and functionalized with specific biomolecules based on the application. Available at: http://www.nanosphere.us/page/gold-nanoparticle-technology. Other possibilities of use of Au-NP for sensing are detailed in SAHA, K., AGASTI, S. S., KIM, C., LI, X. & ROTELLO, V. M. 2012. Gold Nanoparticles in Chemical and Biological Sensing. *Chemical Reviews,* 112**,** 2739-2779.

Box 2.1: Examples of nanotechnology-enabled devices in development

To diagnose recurrence of prostate cancer: The assay involves two probes that function together to detect a targeted biomarker and then amplify its presence. It has a magnetic micro particle plate functionalised with target-specific recognition agents (in this case monoclonal anti- prostate specific antigen (PSA) antibodies) mixed with PSA target proteins. The second component consists of Au-NP probes, about 30 nm, functionalised with tosyl terminated oligonucleotide barcode DNA and conjugated with anti-PSA (goat) polyclonal antibodies. The optical signature is read on a flat-bed scanner where Ag^+ ions help in signal amplification. This assay has been successfully demonstrated for detecting prostate cancer after prostatectomy, and has proven to be 300 times more sensitive than other commercially available assays. It can help to provide substantial lead time in the diagnosis of prostate cancer (Rosi and Mirkin, 2005; Royal Society of Chemistry, 2009; Thaxton et al., 2009).

To estimate HIV viral load in the blood: A lateral flow assay strip developed with complementary oligonucleotides conjugated to 60 nm Au-NP to detect amplified HIV RNA sequences in the blood of patients to confirm whether the antiretrovirals have been effective in reducing the viral load. Estimated cost of the device is $0.80 a strip; 20 µL of blood sample is required; and it takes 20 minutes to perform the test (Rohrman et al., 2012).

***In vivo* imaging agents:** Although nanoparticle-based imaging agents are not yet in clinical use, a few applications have shown significant results at the preclinical stage. For example, DNA-GdIII@Au-NP (sizes: 13, 15, and 30 nm Au-NP) had a higher uptake in NIH/3T3 (fibroblast cell line), and HeLa cells (Song et al., 2009) and neural stem cells(Nicholls et al., 2016), had higher relaxivity when compared to commercial Gd chelates (DOTA- Gd) and acted as a multimodal imaging probes for MR, CT and fluorescence (Song et al., 2009). Also, cross-linked dextran nanoparticles in the size range 5–30 nm (with or without iron oxide core), labelled with radioisotopes such as ^{18}F and ^{89}Zr, have been used to image macrophages *in vivo* with the use of existing imaging modalities such as positron emission tomography (PET) or PET combined with fluorescence imaging (Nahrendorf et al., 2010; Keliher et al., 2011). These tools can help in quantifying the response to therapeutic treatment for cancer, cardiovascular imaging, etc.

Nanosensors to diagnose disease from breath of patients: Au-NP of 5 nm coated with different types of organic molecules with carbon chains C_4–C_{18} long, such as decanethiol and hexanethiol, are drop-casted (deposited) onto circular interdigitated (IDE) electrodes. The array consists of a few such electrodes housed in a chamber. The change in resistance in the presence of disease-specific biomarkers helps in diagnosis of diseases. This type of nanosensor is currently in its R&D phase or in clinical trials for non-invasive diagnosis of lung cancer, breast cancer, colon cancer, and gastric lesions (Peng et al., 2009).

Table 2.2: Some nanotechnology-enabled medical applications (on the market and in development). Adapted from Mahapatra et al. (2013).

Shaded rows are new additions to Mahapatra et al. (2013).

Details	Nanocomponent (size)	Drug or Device	Reference
Alkylated polyethylenimine (PEI) nanoparticles (NPs) incorporated in composite resin dental restorative materials to reduce bacterial infections and dental caries	PEI NPs	Device	(HMO, 2006)
Obturators lined with Silicon Incorporated With Quaternary Ammonium Polyethylenimine (PEI) NPs for managing post surgery infection in head and neck cancer	PEI NPs	Device	(Anat S., 2009)
Liposomal formulation of two anti-Leishmaniasis drugs for treatment of Leishmaniasis	Liposome	Drug	(TUMS, 2010)
Liposome formulation of combination anticancer drugs: • Cytarabine and daunorubicin for acute myeloid leukemia • Irinotecan and Floxuridine for colorectal cancer	Liposome	Drug	(Celator Pharmaceuticals)
Chemotherapeutic drug (paclitaxel) associated albumin nanoparticles with the aim to be used in various cancers	Albumin NPs (130 nm)	Drug	(GBG, 2011)
Chemotherapeutic drug (Rapamycin) bound to albumin nanoparticles (Nab-rapamycin, ABI-009) for Nonmuscle Invasive Bladder Cancer	Albumin nanoparticles	Drug	(Aadi LLC, 2013)
Chemotherapeutic drugs doxorubicin associated with polyethylene glycol (PEG) liposomes	PEGylated liposomes	Drug	(Ulrich B., 2009)
p53 cDNA encapsulated by a positively charged liposome with targeting ligand anti-transferrin receptor (TfR) single-chain antibody fragment (scFv) for Glioblastoma	Liposome	Gene therapy	(Larson et al., 2013; SynerGene

Details	Nanocomponent (size)	Drug or Device	Reference
			Therapeutics Inc., 2014)
Single stranded DNA 24 base oligonucleotide (PNT100) encapsulated in liposomes and targeted to hybridize to BCL2 gene for treatment of advanced solid tumor	Liposome (130 nm) (PNT2258)	Drug	(ProNAi Therapeutics Inc., 2010; Rodrigueza et al., 2014; Tolcher et al., 2014)
• PEGylated interferons + drug for treatment of Hepatitis C • methoxy PEGylated erythropoietin receptor activators for anaemic patients with chronic kidney disease or myeloma • Monoclonal antibody directed against TNF-α with a PEG tail for treatment of rheumatoid arthritis and Crohn's disease	PEGylated proteins	Drug	Summarised in (Barnes and Moots, 2007; Duncan and Gaspar, 2011)
Thermosensitive Liposome in combination with Doxorubicin and radiofrequency ablation or hyperthermia or high intensity ultrasound for treatment of breast cancer, colorectal liver and bone metastases	Thermosensitive Liposome	Drug	(NIHCC, 2004; Celsion, 2011; 2012)
siRNA targeted towards the serine/threonine-polo like protein kinase (PLK1), a key regulator of mitosis in mammalian cells, in stable nucleic acid lipid nanoparticles (SNALP) for liver cancer	SNALP: synthetic cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine PEG-cDMA, and 1,2-dilinoleyloxy-3-(N,N-dimethyl) aminopropane	Drug	(Steegmaier et al., 2007; Judge et al., 2009; Arbutus Biopharma Corporation, 2010)
Chemotherapeutic drug paclitaxel in polymeric micelles for	PEG and poly(D,L-lactic acid)	Drug	(Kim et al.,

Details	Nanocomponent (size)	Drug or Device	Reference
treatment of breast cancer, lung cancer, advanced ovarian cancer	polymeric micelle		2010; Oerlemans et al., 2010)
Anticancer drugs paclitaxel, cisplatin and oxaliplatin in polymeric micelles	Polymeric micelle	Drug	(NanoCarrier, 2013)
Polymeric micelle with covalently attached ligands specific to viral targets for treatment of herpes, flu, HIV / AIDS, etc.	Polymeric micelle	Drug	(NanoViricides Inc.)
Chemotherapeutic drug camptothecin (CPT) attached to cyclodextrin-polyethylene glycol (CD-PEG) co-polymer (CRLX101)	cyclodextrin-polyethylene glycol (CD-PEG) co-polymer (30-40 nm)	Drug	(Cerulean Pharma Inc.; 2011; Young et al., 2011)
Chemotherapeutic drug doxorubicin associated with PEGlyated liposomes and the monoclonal antibody cetuximab as a targeting ligand for Epidermal Growth Factor Receptor for treatment of solid tumors	Liposome (80-100 nm)	Drug	(Mamot et al., 2005; Mamot et al., 2012)
Autoimmune antinuclear antibody conjugated to liposomal nanoparticles containing Actinomycin D for the treatment of Ewing's Sarcoma	Liposome (120 nm)	Drug	(NanoSMART Pharmaceuticals Inc.; Smith and Smith, 2010)
Chemotherapeutic drug docetaxel in block co-polymer nanoparticles attached to targeting ligands (BIND 014) for treatment of KRAS Positive or Squamous Cell Non-Small Cell Lung Cancer, Metastatic Castration-Resistant Prostate Cancer	Block copolymers of either poly (D, L- lactide)(PLA) and poly(ethylene glycol) (PEG) or poly (D,L-lactide-co –glycolide) (PLGA) and poly(ethylene glycol) (PEG)	Drug	(http://clinicaltrials.gov/; Http://clinicaltrials.gov/)
Curcumin nanoparticles as a therapeutic agent for improving cognition for schizophrenic patients	Colloidal curcumin nanoparticles (190 nm)	Drug	(Sasaki et al., 2011; Davis C. Michael, 2014)

Details	Nanocomponent (size)	Drug or Device	Reference
Radioactive Yttrium-90 conjugated with monoclonal antibody directed against CD40 antigen of B cells for treatment of relapsed or refractory, low-grade, follicular or B-cell Non Hodgkin's Lymphoma (nuclear medicine or biotech medicine)	--	Drug	(Duncan and Gaspar, 2011)
Circulating Tumour cells Test/Assay for Diagnosis of metastatic breast, colorectal or prostate cancer : Ferro-magnetic NPs labeled with monoclonal antibodies corresponding to specific antigen expressed in cancer cells	Magnetic Nanoparticles	Device	(Veridex LLC)
Infectious disease tests, cardiac tests, etc. using gold NPs functionalized with specific biomolecules like oligonucleotides, antibodies	Au-NP(13-20 nm)	Device	(Nanosphere Inc.)
Fifth generation PAMAM dendrimers used for immunoassays as confirmation test for the occurrence of myocardial ischemia	Dendrimers	Device	(Siemens Healthcare Diagnostics Inc.; Azzazy and Christenson, 2002)
Mannosylated polyethyleimine (PEI) polymers containing plasmid DNA as therapeutic vaccine for HIV/AIDS	PEI polymers	Device (the delivery patch)	(Lisziewicz et al., 2012; Lőrincz et al., 2012)
A fourth generation L-Lysine dendrimers with napththalene disulfonic acid surface groups in a gel base for treatment of bacterial vaginosis, coating of condoms for Sexually Transmitted Diseases, etc. (the surface groups on the dendrimers impart high surface	Lysine dendrimer	Drug	(Tyssen et al., 2010) (Starpharma, 2012)

Details	Nanocomponent (size)	Drug or Device	Reference
hydrophobicity and negative charge density)			
PEGylated colloidal gold bound TNF for treatment of advanced solid tumors	Au-NP(~27 nm)	Drug	(Cytimmune Sciences Inc)
Gold coated silica nanoparticles for thermal ablation of refractory head and neck cancer	Au-Si NP (150 nm)	Device	(Nanospectra, 2012)
Silica nanoparticles with Cy 5.5 dye and targeting peptides (cyclic arginine–glycine–aspartic acid [cRGDY] peptides) functionalised with ^{124}I (Iodine) and coated with PEG for imaging for treatment of Head and Neck Melanoma, Prostate and Cervical/Uterine Cancer Patients	Silica nanoparticles (7 nm)	Device	(http://clinicaltrials.gov/; Benezra et al., 2011)
Superparamagnetic iron oxide nanoparticles as contrast agents for delineating the bowel, gliobostoma multiforme, lymph nodes in prostate cancer	Iron oxide NPs*	Drug	(Amag Pharmaceuticals Inc.; Neuwelt E., 2008; NCI, 2011a)
Iron oxide nanoparticles coated with polyglucose sorbitol carboxymethyl ether for treatment of iron deficiency anaemia in Chronic Kidney Disease	Iron oxide NPs (30 nm with coating)	Drug	(Amag Pharmaceuticals Inc.; Drugs@FDA)
SPIONs (superparamagnetic iron oxide NPs) for tracking of inflammatory (mononuclear) cells	Iron oxide NPs*	Drug	(Richards J. M., 2010)
SPIONS with aminosilane coating for treatment of Multiforme Gliobostoma (an aggressive brain cancer) in combination with application of external magnetic field	~ 15 nm Iron oxide NPs	Device	(MagForce AG)
Iron nanoparticles injected into the prostate of prostate cancer patients	Iron nanoparticles	-	(https://clinicaltrials.gov/)

Details	Nanocomponent (size)	Drug or Device	Reference
Silver nanoparticles associated with wound dressings	Nanocrystalline Silver	Device	(Smith&Nephew)
Nanosilver fluoride (Silver nanoparticles, chitosan and fluoride) for preventing the growth of bacteria *(S. mutans)* in dental plaques	Silver nanoparticles	Drug	(de Luna Freire, 2013; dos Santos Jr et al., 2014)
Nano silver hand gel	Nanosilver	Drug	(https://clinicaltrials.gov/)
Nano silver impregnated activated carbon wound dressing	Nanosilver	Drug and device combination	(https://clinicaltrials.gov/)
Nano silver coated latex central venous catheters to reduce chances of infections	Nanosilver	Device	(Antonelli, 2006)
Hafnium oxide NPs for treating soft tissue carcinoma of extremity and head and neck cancer	Hafnium oxide NPs	Device	(Nanobiotix; 2011; 2013)
*Though the exact sizes are not known here, superparamagnetic and ultrasuperparamagnetic iron oxide nanoparticles are mainly made of ɣ Fe_2O_3 and Fe_3O_4 and have core diameter <25 nm (Kim et al., 2012b) and 5–12 nm (Bumb et al., 2010) respectively. These magnetic particles are coated with silica, dextran, etc. for specific applications.			

We live in reference to past experience and not to future events however inevitable.
H G Wells

Health-care applications and environmental risks

2.1.3 The context of existing pharmaceuticals[19] and environmental risks

The primary focus of drug delivery research in nanomedicine has been to design delivery agents that have the ability to cross various biological barriers in the body and deliver therapeutic agents to the target site with the aim to increase therapeutic efficacy. The therapeutic agents may be conventional small-molecule drugs, which have found limited clinical use due to their systemic toxic effects or poor solubility. To anticipate likely exposure scenarios and environmental effects, it is necessary to envision – although it is difficult to do so – what can possibly happen based on current science. This necessitates a review of the existing scientific literature on conventional pharmaceuticals in the environment. Concerns about the effects of pharmaceutical products (PPs) in the environment have been expressed (Daughton and Ternes, 1999; Boxall, 2004) and this is now an active area of research.[20] About 600 pharmaceutically active compounds (PhACs) (Küster and Adler, 2014) from various therapeutic classes have been detected at concentrations in the range of nanograms per litre or per gram to micrograms per litre or milligrams per kilogram in

[19] The terms therapeutic agent, active pharmaceutical ingredient (API), pharmaceutical products (PPs), drug, and pharmaceutical active compounds (PhACs) have been used interchangeably. For the purpose of this thesis, they all mean medicines for treatment of human diseases.

[20] A Web of Science search conducted on 5 December 2015 (for the time span of 2013-15) with the following parameters returned 5053 results: **TOPIC:** ((pharmaceutical* OR API* OR drug* OR PPCP* OR PhAC*)) ***AND*** **TOPIC:** ((soil OR effluent* OR waste water* OR landfill* OR aquatic* OR river* OR stream* OR surface water* OR freshwater* OR groundwater*)) ***AND*** **TOPIC:** (environment*) Refined by: **RESEARCH AREAS**: (TOXICOLOGY OR ENVIRONMENTAL SCIENCES, ECOLOGY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR WATER RESOURCES OR MARINE FRESHWATER BIOLOGY) ***AND*** **DOCUMENT TYPES**: (ARTICLE OR REVIEW OR ABSTRACT). (I chose the time span 2013–2015 because values from articles published between 2009 and 2012 were already included in the paper published in Jan. 2013)

different environment compartments, including sewage effluents (Bueno et al., 2012), surface water (González Alonso et al., 2010; López-Roldán et al., 2010), receiving coastal waters (Fang et al., 2012a), estuaries (Yang et al., 2011), sediments and soils (Vazquez-Roig et al., 2010), and landfill leachate (Eggen et al., 2010) and at lower concentrations and frequencies in groundwater and drinking water sources (Fram and Belitz, 2011; Wang et al., 2011a). Concentrations of PPs in effluent water from pharmaceutical manufacturing facilities were found to frequently exceed 1 mg L^{-1} in studies published between 2005 and 2014 as reviewed by Larsson (2014). In the case of freshwater, in many instances (see Table A2 in Annexe to Chapter 2), concentrations of PPs exceeded the current PECsw threshold limit of 0.01 µg L^{-1} suggested by the EMA, and 102 PPs have also been found in aquatic biota (Ramirez et al., 2009; Lajeunesse et al., 2011; Sanchez et al., 2011). The most widely detected PPs in the environment belong to the therapeutic classes of antibiotics, non-steroidal anti-inflammatory drugs, blood lipid lowering agents, sex hormones, CNS disorder drugs, and β-blockers (reviewed and summarized in (Santos et al., 2010)). Pharmaceuticals are metabolized and excreted out of the body either unchanged or in a conjugated form (e.g. glucoronide, sulphates, and glycinate conjugates) and hence the main sources for human pharmaceuticals and their metabolites in the environment have been identified as effluents of waste water treatment plants (STPs) from communities (Vieno, 2007), hospitals (Verlicchi et al., 2012a), and pharmaceutical manufacturing facilities (Sanchez et al., 2011). Approximately 28% of the world's population in 2008 was not connected to sewage systems (WHO/UNICEF, 2010) and approximately 9% of the waste water in EU countries is not treated or the waste water treatment systems do not have secondary treatment

steps (EEA, 2010), sewage systems are leaky (Wolf et al., 2012), or contamination of storm water from waste water exists (Sauvé et al., 2012), thereby giving rise to the possibility of further environmental contamination. It has been established that the fate, removal, and partitioning of pharmaceutical compounds are dependent on the design of the STP (Owen and Jobling, 2012), e.g., removal efficiency for ibuprofen was below 25% for a STP having only a primary treatment process compared with a removal efficiency of 90% in a STP having secondary treatment (Fang et al., 2012a). Furthermore, a few drugs have been shown to have negative removal percentages in STPs, and it has been suggested that these negative removal percentages might be due to errors in analytical instruments, sampling variations, etc., but they also give credence to the hypothesis that conjugated metabolites may undergo bio-transformation in the environment to form the parent drug (removal efficiencies in STPs has been reviewed by (Verlicchi et al., 2012b)). Pharmaceutical products can also undergo abiotic transformations in environmental matrices including photo-transformation and hydrolysis and can be deactivated to ecologically benign molecules or form harmful transformation products. For instance, photo-transformation of diazepam (a widely prescribed antidepressant) and its metabolites was recently studied (West and Rowland, 2012) and the investigators concluded that diazepam would be transformed under some conditions present in the environment. However, the photoproducts that were identified had chemical structures similar to identified endocrine disruptors. Another antidepressant, Oxazepam, was found to be persistent for decades in lake waters and sediments in a study conducted in Sweden, which estimated historical loading from the 1970s. This study also indicated the importance of local weather conditions in transformation of PPs (Klaminder et al.,

2015). The pressures of modern society and consequent competitiveness and negative social relationships can influence psychological health (Janssens et al., 2014) and will likely increase the consumption of psychoactive drugs and hence environmental exposure. A few examples of the occurrence of pharmaceuticals and their metabolites in different environmental compartments are presented in Table A2 (Annexe, Chapter 2). Spatial, temporal, and geographic variations [e.g., (Daneshvar et al., 2010; Madureira et al., 2010; Bueno et al., 2012)] have been shown to occur in the concentrations and type of PPs detected. Fluctuations in the concentrations of PPs have also been shown in effluents and in receiving water bodies during special episodes, e.g., disease outbreaks (Daneshvar et al., 2012; Leknes et al., 2012). In addition to monitoring campaigns, models such as SimpleTreat, LowFlow 2000-WQX, and PhATE have been used to predict environmental concentrations in various compartments (Cunningham et al., 2012; Kugathas et al., 2012). Photolytic and oxidative transformation of drugs has been reviewed in Fatta-Kassinos et al. (2011).

Pharmaceutical products such as ibuprofen, acetaminophen, ciproflaxin, and ketoprofen have high removal percentages in STPs that have secondary treatment steps. However, some PPs (e.g. fenofibrate and anthracyclines from blood lipid regulators and anticancer therapeutics, respectively) that are removed from the aqueous phase are adsorbed onto sludge or other solids (Mahnik et al., 2007; Jelic et al., 2011). The fluoroquinolone antibiotics – ofloxacin, ciprofloxacin, and norfloxacin – and the bactericides triclosan and triclocarban were present in quantities ranging from 1000 ng g^{-1} to 11,000 ng g^{-1} (dry weight) in dewatered municipal sludge (Gottschall et al., 2012). Some other PPs found in sludge at concentrations higher than 100 ng g^{-1} (dry weight) include antibiotics (azithromycin, 4-epitetracycline,

carbamazepine, and diphenhydramine) and the antidepressants Fluoxetine and Citalopram (Gottschall et al., 2012). This may be due to their hydrophobicity (K_{ow} and K_{oc}), leading to binding interactions with particles in soil, and thereby contributing to a new exposure pathway when this nutrient-rich sludge is used as manure.

Pharmaceuticals are designed to affect biological receptors and hence it should not come as a surprise that they have stimulatory or inhibitory or dual effects on non-target organisms upon exposure to different concentrations, especially when the targets and biochemical pathways are similar. A well-known example of this is the ER-receptor agonist and antagonist behaviour associated with naturally occurring and synthetic hormones (e.g., ethinylestradiol, the active ingredient in oral contraceptives), which can result in endocrine disruption (Jobling and Owen, 2013). Sometimes non-target organisms, e.g. algae and cyanobacteria, which have non-related biochemical and metabolic pathways, can also be affected by exposure to pharmaceuticals (Perron and Juneau, 2011). Organisms might show limited toxicity in acute toxicity tests with higher toxicity in chronic tests for particular chemicals (Zhang et al., 2012b). Organisms might respond differently to exposure to a single contaminant than to a mixture of contaminants, and effects might not be the same across multiple generations (Dietrich et al., 2010). It has been observed that exposure to pharmaceutical products affects behaviour of organisms (Brodin et al., 2014) and their growth and results in physical malformations (reviewed in Larsson, 2014), feminization of males (e.g., Peters et al., 2007), changes in photosynthetic activity (Perron and Juneau, 2011), and bacterial metabolic processes (Underwood et al., 2011). To date, very few ecotoxicity studies on pharmaceuticals have been conducted at environmentally relevant concentrations and hence there is

inconclusive evidence to understand the true implications of their presence in the environment. A review of ecotoxicological studies of key pharmaceuticals is provided by Santos et al. (2010). A key concern related to nanomedicines is that their dual carrier and targeting functions may make PPs more bioavailable in the environment.

Early ecotoxicity studies reported toxicity effects at higher exposure concentrations and focused on growth inhibitory and reproductive effects. Recently, the emphasis has shifted towards assessing impacts at low concentrations and assessing the increased number of physiological biomarkers such as studying the production of reactive oxygen species (ROS) and transcription of genes. For example, a decrease in nitrate reduction potential of groundwater bacterial communities was observed at an exposure concentration of 5 nM sulfamethoxazole (Underwood et al., 2011) and changes in behaviour of marine amphipods by exposure to fluoxetine (antidepressant, a selective serotonin reuptake inhibitor) at concentrations of 10 ng L^{-1} was reported (Guler and Ford, 2010). A long-term study in an experimental lake to assess the population level sustainability of the fathead minnow upon exposure to low levels (5–6 ng L^{-1}) of synthetic oestrogens (Kidd et al., 2007) has shown that the population can collapse owing to feminization of males. 17α-ethinyl estradiol can increase stress in fish and can impact shoaling behaviour even at concentrations of 5 ng L^{-1} (exposure duration 14 days). Higher concentrations (25–100 ng L^{-1}) and longer exposures (14–21 days) were shown to impact fertility in both male and female fish and spawning behaviour by affecting the transcription of genes related to male sex differentiation (Peters et al., 2007; Salierno and Kane, 2009; Reyhanian Caspillo et al., 2014; Volkova et al., 2015). Various publications have suggested the need for assessing mixture toxicity (Pomati et al., 2008; Vannini et al., 2011;

Madureira et al., 2012; Backhaus, 2014) because of the additive, cooperative and antagonistic effects of different class and compounds of pharmaceuticals.

Many knowledge gaps have been identified in the literature, which makes the task of conducting a plausible environment risk assessment for pharmaceuticals particularly challenging. These gaps in knowledge create large uncertainties and hence lead to inconclusive results. Furthermore, analytical challenges, e.g., non-extractable residues, interference from other contaminants in complex mixtures of sewage and hospital waste water, and the trace level of these compounds complicate the matter. The repeatedly mentioned knowledge gaps identified in the literature are summarized below. Limited knowledge exists on:

- occurrence, fate, and activity of metabolites and their transformation products in the environment, mode of action of pharmaceuticals, metabolites and excretion rates;
- long-term exposure to low levels of pharmaceuticals, ecosystem level impact, mixture toxicity;
- exposure and effects data on soil organisms and marine species, effects data on ionic and polar compounds; and
- bioconcentration factors and bioaccumulation.

Intensive research in the field of environmental occurrence, fate, and consequences of drugs and transformation products took off in the 2000s, following the first findings regarding the occurrence of pharmaceuticals and their metabolites in the late 1970s in sewage effluents in the US; however, the impacts of pharmaceuticals on ecosystems are yet to be established with certainty. The only population-level impact

attributed with certainty to pharmaceuticals is the >95% decline in the population of vultures in the Indian subcontinent due to extensive use of diclofenac in veterinary medicines (Oaks et al., 2004). This case study is also widely cited as an example of unexpected routes of exposure and bioaccumulation in the published literature on the environmental impacts of pharmaceuticals. Many national and international collective and cross-sectoral efforts over the past few years (e.g., ERApharm 2007[21] (ERAPharm), KNAPPE 2008[22] (KNAPPE, 2008), and MistraPharma of Sweden) have been funded to study pharmaceuticals in the environment. Publicly accessible websites such as Pharmaceuticals in the environment (https://pharmaceuticals-in-the-environment.org/), Information for Assessing Risks (http://www.chbr.noaa.gov/peiar/), and the Swedish medicine information portal (www.fass.se) provide information on medicines in the environment. More recently, key gaps in knowledge to help streamline research and efforts in this field have been identified (Boxall et al., 2012). Additionally, different approaches to prioritization schemes for environment risk assessment for pharmaceuticals have been suggested, e.g. fish plasma model, logP ranking, hazard-based ranking, and quantitative structure–activity relationship (QSAR) approach, and these ranking schemes have been conducted for a substantial number of pharmaceuticals (Cooper et al., 2008; Ginebreda et al., 2010; Roos et al., 2012). In Jan. 2012, the European Commission put forward a proposal to amend the Water Framework Directive to include three pharmaceuticals (diclofenac, 17α-ethinyl estradiol, and 17β estradiol) in the list of priority substances in Annexe X of the Directive (EU, 2012b). The positive

[21] Environmental Risk Assessment of Pharmaceuticals (ERApharm): A EUFP-6 program (Duration: October 2004 to September 2007).
[22] Pharmaceutical Products in Environmental Waters (KNAPPE): A EUFP-6 program (Duration: February 2007 to July 2008).

outcomes of the above-mentioned initiatives are that regulatory steps are being taken; however, it also exemplifies the time lag between knowing that a problem exists, proving its environmental impacts, and developing or amending the relevant regulatory guidelines.

2.2 Engineered nanomaterials (ENMs) and environmental risks

2.2.1 Possible sources, fate, and effects of ENMs[23] in the environment

Worldwide annual production of ten NMs – TiO_2, ZnO, FeO_x, AlO_x, SiO_2, CeO_2, Ag, quantum dots (QDs), CNT, and fullerenes – was projected to be 0.6–5500 tonnes (median values), the maximum being that of SiO_2 and the minimum (0.6 t), that of fullerenes and QDs (Piccinno et al., 2012). The continued fascination with nanotechnology and other advanced technologies as drivers of innovation and economy will result in the development of a large number of new and complex materials and, inevitably, in their release into the environment (Kiser et al., 2009; Lee et al., 2012). The possible entry routes of ENMs into the environment include intentional (e.g., remediation) and accidental releases, including emissions from manufacturing facilities, abrasion, and weathering of products containing ENMs. The specific entry route into a particular environmental compartment will depend on the life cycle of the product and the disposal method used; for example, washing nano-functionalized textiles releases the ENMs into the sewerage system, which are finally transported to natural waters (Blaser et al., 2008). To the best of my knowledge, no actual field-level environmental monitoring of ENMs has been reported in the

[23] Engineered nanomaterials (ENMs) refer to all engineered or manufactured nanomaterials.

literature, although environmental concentrations of some ENMs – silver, zinc oxide, titanium dioxide, fullerenes, ceria, and CNT – based on models have been estimated and reported.

As is the case with pharmaceuticals, ENMs also give rise to transformation products under various environmental conditions. The type of transformation products that will form depends on the nanoscale properties of the ENMs and on the conditions of the environmental matrices, e.g., magnetic iron nanoparticles aggregate at near-neutral pH due to their magnetic properties but at higher pH they are more dispersed (Hong et al., 2009). The key transformation mechanisms can be aggregation (homo- and hetero- aggregation) or agglomeration, dissolution, oxidation/reduction, and adsorption (Lowry et al., 2012).

Under simulated situations it has been found that natural organic matter (NOM) such as humic substances (Cumberland and Lead, 2009) and extracellular polymeric substances (Khan et al., 2011; Sheng and Liu, 2011) influence the fate and behaviour of ENMs. Studies have shown that NOM in the environment influences the stability of ENMs (Fabrega et al., 2009a; Fabrega et al., 2009b) and hence their bioavailability and toxicity (Li et al., 2010b; reduction in toxicity shown by Gao et al., 2012; Zhang et al., 2012a) although less effect of NOM on polymer-coated nanoparticles has been observed (Hitchman et al., 2013). It has also been demonstrated that Ag-NP in soil rich in organic matter become more bioavailable after ageing (Coutris et al., 2012). In addition to NOM, physicochemical properties such as pH, ionic strength, salinity, and mineral content or hardness of the aqueous environmental compartment have also been shown to influence the behaviour, fate, and toxicity of ENMs. For instance, it was shown that *E. coli* survived at pH 10 even

at very high concentrations of iron oxide nanoparticles whereas *S. cerevisiae* (a eukaryote) did not (Schwegmann et al., 2010). Hardness of water, at near-neutral pH, can result in formation of aggregates of ENMs and facilitate biouptake by filter feeders (Lee et al., 2011) or settling down and enhancement of availability to pelagic organisms or earthworms. High total organic carbon (TOC) and low ionic strength, conditions typical in freshwaters, can stabilize ENMs and make them persistent and available for filter feeders, fish and algae, whereas low TOC and high ionic strength such as in sea water can aid in rapid aggregation and settling of ENMs (Keller et al., 2010). For further studies on possible fate, behaviour and effects of ENMs in the environment, the reader is referred to articles by Handy et al. (2008), Ju-Nam and Lead (2008), Klaine et al. (2008), Fabrega et al. (2011).

The key factors influencing ENM toxicity are composition, size, surface properties (both for the ENM and their transformed products), sensitivity of the species, and presence of other contaminants. For example, cationic branched polymer-coated (PEI) Ag-NP (10 nm) were shown to be more toxic than citrate- and PVP-coated Ag-NP to a Gram-positive bacterium, *Bacillus sp.* (El Badawy et al., 2010). Similarly, positively charged Au-NP of 2 nm was reported to lyse *Bacillus subtilis,* but had no effect on *E. coli*, a Gram-negative species (Hayden et al., 2012). Bioaccumulation and trophic transfer of ENMs can also occur (Ferry et al., 2009; Croteau et al., 2011). Many investigators have shown biofilms to be an effective sink for ENMs (Ferry et al., 2009; Morrow et al., 2010; Stojak et al., 2011) and have demonstrated the ability of aquatic organisms like filter feeders to uptake and biotransform suspended and dispersed ENMs present in the aquatic matrix (Hull et al., 2011; Montes et al., 2012). Furthermore, exposure of organisms to ENMs would be dependent on the presence

of other environmental contaminants, mode of action of the chemical, and differences in the physiology of exposed species. Phenanthrene adsorbed onto n-C60 was shown to be more bioavailable to algae and daphnids but more toxic to algae (Baun et al., 2008), whereas n-C60 fullerenes were shown to sequester the synthetic hormone 17-α ethinylestradiol (EE2), thereby reducing its bioavailability (Park et al., 2011). Similarly, it was demonstrated that mixed iron oxide ENMs in an organic-matter-rich environment with low salinity and near-neutral pH could adsorb the antibiotic chlorotetracycline (Zhang et al., 2011a). Interactions between hydrophobic ENMs and PPs can sequester PPs from the environment and thus reduce or increase their bioavailability in a given time frame.

2.2.2 Possible sources, fate, and effects in the environment of nanomedicines

Nanomedicine: mode of action and possible environmental implications

Depending upon the desired effect, a molecule, while useful as a therapeutic agent in the target species, might prove deleterious to non-target species primarily because of the evolutionary conservation of genes and metabolic pathways across species, the zebra fish and humans or the mouse and humans, for example (Liao and Zhang, 2006; Howe et al., 2013). Sometimes, even organisms with dissimilar physiological systems are affected (e.g., endocrine disruptors can affect organisms like algae and cyanobacteria that are without endocrine systems (Perron and Juneau, 2011)).

The mode of action of nanomedicines can have unintended environmental consequences. For example, hollow mesoporous silica nanoparticles (HMSNPs) of variable pore sizes (3.2 nm, 6.4 nm, and 12.6 nm) reduced cellular ATP levels in a

drug-resistant human breast cancer cell line MCF7 at concentrations of 20 μg mL^{-1}. Such nanoparticles can be utilized to enhance cellular retention of drugs for multi-drug-resistant cancer where drug efflux needs to be reduced. HMSNPs showed slight reduction in cellular ATP levels, and this effect might be useful in lowering cellular energy levels in a minimally harmful way (Gao et al., 2011). However, if HMSNPs loaded with anticancer drugs find their way into the environment, they may contribute to additive adverse effects on non-target organisms. Mesoporous silica has been approved by the USFDA for use in brachytherapy and drug delivery from implants (Dufort et al., 2012), and a silica nanoparticle is in clinical trials as an imaging modality (Benezra et al., 2011) (Refer to Table 2.2).

A study by Comfort et al. (2011) explored the effects of 10 nm Ag-NP, Au-NP, and SPIONs on the epidermal growth factor (EGF) signal transduction pathway in a model cell line. Au-NP and SPIONs were found to be biocompatible, i.e., no cell death was observed and production of ROS was minimal at the higher exposure concentration of 25 μg mL^{-1}. Although the authors expressed their reservations about extrapolating the *in vitro* results to humans (this is true of most *in vitro* and small-animal models and has been widely discussed in the safety assessment literature in medicine), it was shown that the ability of the proteins involved in the signal transduction pathway to carry out their functions was negatively impacted by all the three NPs studied: SPIONs, in particular, altered the EGF-dependent gene transcription. Although the biocompatibility, ROS-scavenging capacity, and inhibition of the EGF signal transduction pathway of Au-NP might prove to be advantageous with regard to treating inflammatory disease conditions and cancer, the same

properties might have negative or unknown ecological consequences (Comfort et al., 2011).

If such applications with such unique modes of action finally make it to clinical use, the high burdens of cancer and other diseases would mean that larger quantities of these materials may reach the environment and may persist there, thereby increasing the chances of non-target organisms being exposed to these materials.

There is insufficient knowledge regarding possible amounts and entry routes of nanomedicine products in the environment; however, it should not deter one from making estimates of likely routes of entry, based on the knowledge of environmental release and transport of pharmaceuticals. Figure 2.4 is a conceptual model of likely release and exposure pathways of nanomedicines and a key research issue is to quantify the concentrations and fluxes within this conceptual model. This is attempted in Chapter 4 where probabilistic mass modelling provides some quantification and fluxes from Au NP used in nanotechnology-enabled medical products.

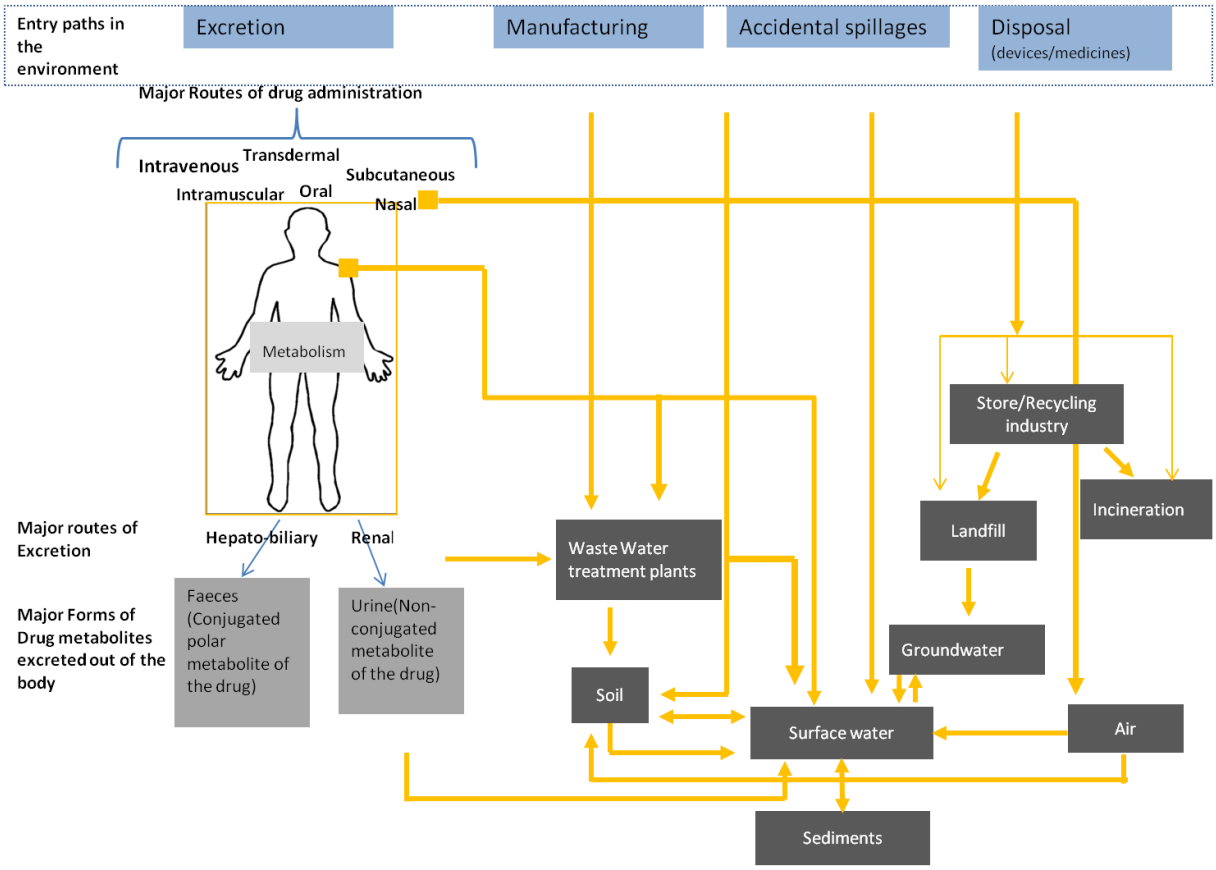


Figure 2.4: A conceptual schematic showing likely sources and transport of nanomedicines in the environment.

Nanomedicines and transformed products may be released into water through excretory routes, washing off from skin, from manufacturing facilities, spillages, and disposal of products. Nanomedicines can be released into the atmosphere from nasal inhalers. Incineration of composite medical products and abrasion and weathering in landfills may also lead to release into the atmosphere.

There are different entry routes for various ENMs into the environment. In the case of therapeutic applications, the obvious route is via the urinary and the hepato-biliary paths of excretion into domestic sewage and then subsequently to STPs and to receiving water bodies and land (with the caveat mentioned earlier that a large percentage of waste water even in the EU goes untreated). Other possible routes are release into the air from inhalers; poor disposal of unused medicines from hospitals, R&D laboratories, and clinical research facilities by casual workers and

poorly trained staff; release during manufacturing, transport, and accidental spills; and release from incinerators. Due to their high specific surface areas, ENMs might get adsorbed onto waste solids in the combustion chamber of an incinerator or be present in the off-gas (Walser et al., 2012b). In the case of medical devices, their improper disposal, especially that of disposable *in-vitro* diagnostic products, is likely to release ENMs into the environment. Although we know quantitatively very little at the moment, a priori some pathways are likely to be of major importance, including 1) waste water and storm water to waste water and sludge and then to freshwater and soil, 2) treated flue gas from incineration to the atmosphere and then to water and soil, and 3) landfill to groundwater and soil and then to surface water (Figure 2.4).

2.2.3 Fate and behaviour

Polymer coating on ENMs will affect their fate and behaviour in STPs. Silica oxide NP (~ 56 nm) coated with Tween 20 were shown to remain in the sludge, whereas uncoated silica oxide NP did not flocculate and remained in the effluent (Jarvie et al., 2009). Biofilms can act as potential 'sinks' for ENMs either in the secondary treatment stage of a sewage treatment plant or in freshwater ecosystems. Sometimes, PEG coating on an ENM can integrate itself with the protein component of the biofilm and change the roughness coefficient of the biofilm but shield the toxic effects of the core particle (Morrow et al., 2010). Size can also have an influence by changing the morphological properties of a biofilm. Stojak et al. reported an increase in roughness coefficient and a significant decrease in plankton biomass in a mature biofilm of *L. pneumophila* after 2 days of exposure to citrate capped Au-NP of 4 nm and 18 nm size (Stojak et al., 2011). However, no change was observed in the

biofilm exposed to 50 nm gold NP. Furthermore, it was observed that the 4 nm and 18 nm AuNP got adsorbed onto exopolysaccharides of the bacterial cell wall and also got entrapped in the bacterial cell (Stojak et al., 2011).

Polymers may additionally be utilized as carbon sources or energy sources by organisms. It was recently demonstrated that PEG-coated ENMs could be degraded by bacteria from an urban stream. However, the degradation rate and aggregation depended on the available chain end groups of the two different conformations of polymer (polyethylene oxide) coated ENMs studied (Kirschling et al., 2011). Polymer-coated ENMs (PEG b-ε-caprolactone) were found to adsorb onto cellulosic surface irreversibly and the adsorption mechanism was found to be size dependent.[24] The investigators hypothesised that adsorption could be due to interdigitation and entanglement of the ENMs with D-glucose chains of cellulose (Zhang and Akbulut, 2011). However, the adsorption was found to be partially reversible in the case of sand and the adsorption rate constant was found to be inversely proportional to particle size (sizes used in the experiment were 90–305 nm) (Zhang et al., 2013). In a later study by the same group, it was shown that the mobility in sand of polymer-encapsulated anticancer drugs was affected by the surface charge on the polymer and the presence of salts of calcium in the sand (Chen et al., 2015).

2.2.4 Biotransformation and excretion

Ingested and injected PPs are amenable to biotransformation in the body due to the action of various enzymes and are excreted primarily with urine and/or faeces (Taft,

[24] The mean values of Z-average sizes of four different batches of PNDDS were as follows: Mean Particle sizes: Mean value of Z-averages: 46± 1 nm 81±2 nm, 159±1 nm, 197±4 nm, 238±7 nm, and 271±2 nm.

2009). Studies have been done to find out the clearance mechanisms of nanomaterials with prospective use in medicine. Biodistribution studies have been conducted by different investigators and it has been found that the clearance pathway is dependent on size, shape, surface coating, and charge of the particle as well as on the route of administration. Lipka et al. (2010) showed that a 10 kDa PEG-coated 5 nm Au-NP followed the hepato-biliary route, whereas another study (Balasubramanian et al., 2010) showed that uncoated 20 nm Au-NP was recovered primarily from urine. A recent study showed that hepato-biliary clearance was inversely related to negatively charged Au-NP of different sizes (1.4, 2.8, 5, 18, 80, and 200 nm). The investigators concluded that small, negatively charged Au-NP were excreted via the hepato-biliary excretion pathway because of dynamic protein binding and exchange, which are major mechanisms determining Au-NP accumulation in various organs and tissues' (Hirn et al., 2011). By extension, there might be differences in biodistribution profiles of encapsulated and free drugs. A study showed that urinary excretion of the unaltered drug when encapsulated in poly-epsilon-caprolactone (a widely researched polymer for medical applications) nanocarriers was about 15% higher than that of the non-encapsulated drug (Ferranti et al., 2001), hence would result in more discharge to the environment unless the dosages are altered. When the biological fate of a model PEG-protein conjugate was studied, it was found that a major amount (46.5% cumulative average) of the administered dose of PEG was excreted in urine up to 7 days after the dose. The same study also reported that intact PEGylated model protein was excreted in the first few days post administration (Elliott et al., 2012). Figure 2.5 shows a concept of biodistribution of nanoparticle in various organs (Aggarwal et al., 2009); depending

on the type of coating, ENMs might be distributed to the brain, liver, and kidneys. The liver and the kidneys are the predominant excretory pathways of consumed drugs. Table A1 (Annexe) to the chapter details some studies on biodistribution of Au-NP of various sizes and coatings in animal models.

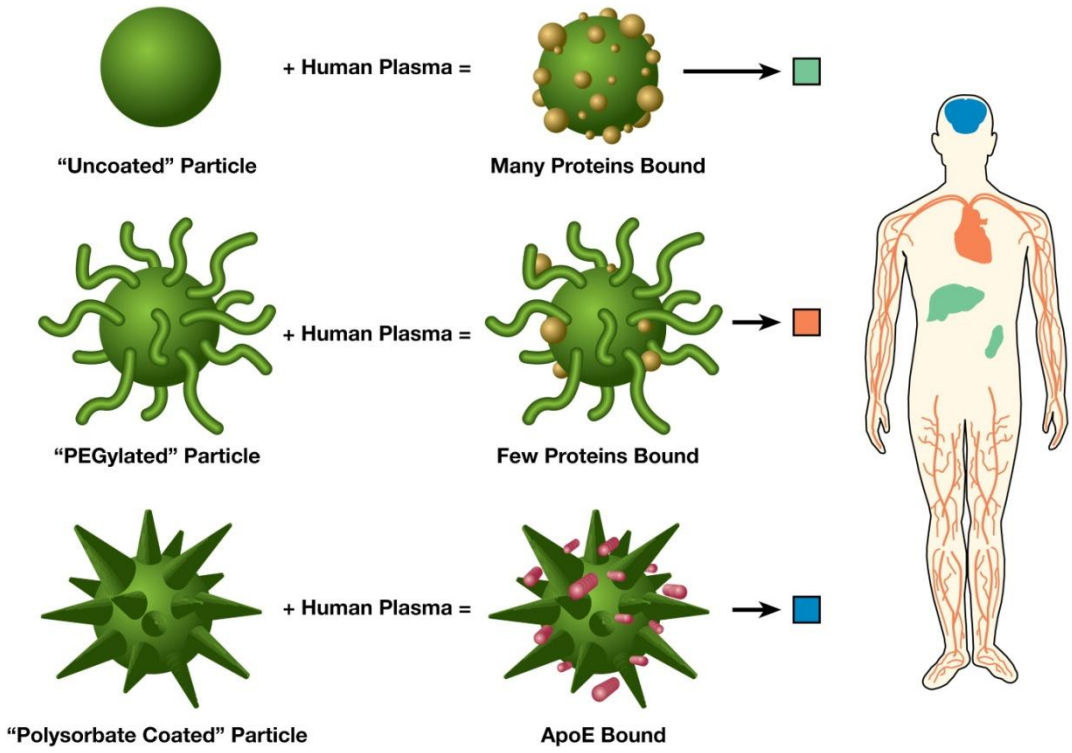


Figure 2.5: A theoretical concept of the distribution of nanoparticles in the body based on the absence or presence of a polymer coating (Taken from Aggarwal et al., 2009).

In many cases, nanoformulations help to reduce systemic toxicity, especially of anticancer drugs. For example, nab-paclitaxel, a nanomedicine available in the market, is a formulation of paclitaxel (empirical formula: $C_{47}H_51NO_{14}$, a plant alkaloid) bound to human albumin NP with a mean particle size 130 nm has been shown to have better therapeutic efficacy than conventional paclitaxel (Taxol®) for breast

cancer. The dosage of this new formulation is 260 mg m^{-2} of body surface area every 3 weeks compared to Taxol's prescribed dosage, which ranges from 135 mg m^{-2} to 175 mg m^{-2} of body surface area every 3 weeks, showing the possibility of higher doses that can be achieved through nanoformulation. Traditional chemotherapeutics are highly hydrophobic drugs, and hence are generally assumed to be adsorbed onto the sludge of a STP (Mahnik et al., 2007) and then mainly either incinerated or spread onto agricultural soils (in Switzerland and the UK, respectively). The possibility of administering increased dosages and changing excretion profiles by using the new nanoformulations will potentially increase the environmental concentrations of these highly cytotoxic PPs. The above examples indicate the likely problem areas; however, I acknowledge the fact that more targeted medicines, customized for small populations (personalized medicines), and the possibility of reduction in premedication amounts might result in a more favourable benefit–risk balance when all aspects are taken into consideration.

2.2.5 Biouptake and effects

Monodispersed, stable, and targeted ENMs, such as monodispersed iron oxide NP (Nam et al., 2003; Ho et al., 2011), are important in medical applications in order to fully exploit their novel properties, increase shelf life, and to influence physiological responses with increased effectiveness. These same design requirements may dictate the fate and risk of ENMs in the environment by not only arresting the growth and reproduction of organisms exposed to the ENMs but also by interfering with metabolic processes and hence in turn impacting key ecosystem services. However,

to a certain extent, organisms might be able to tolerate exposure to nanomedicines, although this aspect is poorly quantified.

Nanoparticles for use in medicine are typically coated with organic polymers (the 'stealth' properties) to escape the body's mononuclear phagocytotic system or to target specific cells. Only a few ecotoxicity studies have been conducted on polymers used in medical applications, and of the few that I am aware of, most have been done on dendrimers.

Dendrimer toxicity to various model organisms (*Daphnia magna*, *Vibrio fischeri*, *Pseudomonas subcapitata*, and *Thamnocephalus platyurus)* has been shown to increase with increase in the generation of cationic dendrimers. Table A4 in the annexe to this chapter gives a summary of selected ecotoxicity studies which can be linked with ENMs used in medical applications. Although a fair number of ecotoxicity studies have been done with ENMs, those done for model ENMs used in medical applications are few and far between, except, of course, for Ag-NP. The environmental sources, fate, and effects of Ag-NP have been widely reported in scientific literature (Fabrega et al., 2011; Yu et al., 2013; SCENIHR, 2014) and therefore Table A3 does not cover ecotoxicity studies of Ag-NP.

Nanoecotoxicity studies done on various types of Au-NP – different sizes, shapes, uncapped, polymer-conjugated. – have shown Au-NP to have the potential to cause sublethal effects. A study explored the effects and mode of action (toxicity) of gylcodendrimer-coated Au-NP on the green algae *Chlamydomonas reinhardtii* and showed that algal cells aggregated due to the interaction of the glycodendrimer coating with the cell wall components of the algae. The aggregation resulted in

inhibition of cell division and reduction in photosynthetic activity (Perreault et al., 2012a). Selected ecotoxicity studies of Au-NP are presented in an annexe to Chapter 4. It has been demonstrated that citrate-capped Au-NP of 15 nm have the capacity to induce mutagenic effects and hence potential intergenerational transfer, overexpression of oxidative stress proteins, and reduction in lifespan and fertility in *Drosophilia melanogaster* (Pompa et al., 2011; Vecchio et al., 2012). Robbens et al.(2010) did a comprehensive toxicity study on two polymeric nanocarriers particularly promising for medical applications – a cationic PEI and a pH-sensitive polymer PDMAEMA [poly(2-(dimethylamino) ethyl methacrylate] – and their polymer–DNA complexes, i.e., PEI:DNA and PDMAEMA:DNA (Robbens et al., 2010). Both polymers are ideal for delivering membrane-impermeable molecules such as siRNA, DNA, and oligonucleotide. As shown in Table 2.2, a PEI-polymer-based immunotherapeutic is in Phase II clinical trial for treatment of HIV/AIDS. For tadpole larva both PEI (EC_{90} = 1 μg mL^{-1}) and PEI:DNA showed teratogenic effects (PEI: DNA, LC_{50} = 1 μg mL^{-1} and EC_{50} = 0.1 μg mL^{-1} at 96 h exposure). PEI showed significantly higher toxicity (EC_{10} = 40.8 μg mL^{-1}) than PDMAEMA (EC_{10} = 78.0 μg mL^{-1}) for the algae *Pseudokirchneriella subcapitata* and all polymer–DNA complexes were less toxic than the free polymers (EC_{10} increased by a factor of 1.5) (Robbens et al., 2010). However, this study can be criticized for using high concentrations of the polymer and those that are not environmentally relevant.

QDs can be used as live cell imaging agents and their utility for *in vitro* diagnostic purposes is expected to increase even though their applicability in drug delivery is limited due to their inherent toxicity. However, currently Cd-free QDs are being researched for *in vivo* applications (Zimmer et al., 2006; Li et al., 2009). Cationic

PEI-coated CdSe/ZnS QDs upregulated the genes related to nitrogen fixation and the authors hypothesised that it might be because of the strong interaction of the QDs with the negatively charged bacterial cell wall (Yang et al., 2012). Another laboratory-scale experimental food chain study showed that bare or uncoated CdSe QDs can potentially be biomagnified: QDs inhibited digestion in the ciliated protozoa *Tetrahymena thermophilia* and the Cd concentration was found to be approximately 5 times higher than the concentration in bacteria, indicating that this QD would be available to the higher trophic levels. The QDs were found to be intact inside both bacteria and protozoa (Werlin et al., 2011).

2.3 Regulatory framework for medicines and medical devices

2.3.1 Regulations for pharmaceuticals for human use

Extensive studies for assessing toxicity are conducted after identification of a promising new entity that has therapeutic potential. A battery of tests and assays are performed to understand whether there are risks of human carcinogenicity, genotoxicity, reproductive and development toxicity, immunotoxicity, etc. Pharmacodynamics and pharmacokinetics studies are conducted using small-animal models to assess the distribution of the drug, the mode of action and physiological effects, metabolism, and excretion. Data from these studies are required to be submitted to the relevant medical regulatory agency before enrolling human subjects to establish the safety and efficacy (Phase I to Phase III clinical trials) of the new drug. The preclinical and the clinical trial data form the basis of the marketing authorisation application (MAA) in the EU and member states. Applications for

therapeutics for cancer, neurodegenerative diseases, HIV/AIDS and immune dysfunctions, and viral diseases are submitted to the centralized medical regulatory agency in the EU, namely the European Medicines Agency (EMA). A few other therapeutics which go through the centralised procedure include officially designated 'orphan' [25] medicines, biotechnology-based therapeutics, and products of tissue engineering. Marketing surveillance ('pharmacovigilance') of the medicine post authorisation is another regulatory step, which helps to monitor the therapeutic agent's safety. Figure 2.6 is a simplified depiction of the medicine innovation pathway, key checkpoints with regard to involvement of the regulatory agency, and the underlying guidelines on ethics and safety during innovation. The decision for approving a medicine is based on careful evaluation of benefits and risks from a particular therapeutic for the target group of patients.

[25] To qualify for **orphan designation**, a medicine must meet one of these criteria (as defined by the EMA):
(1) it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people in the EU at the time of submission of the designation application and (2) it is intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic condition and without incentives it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development.

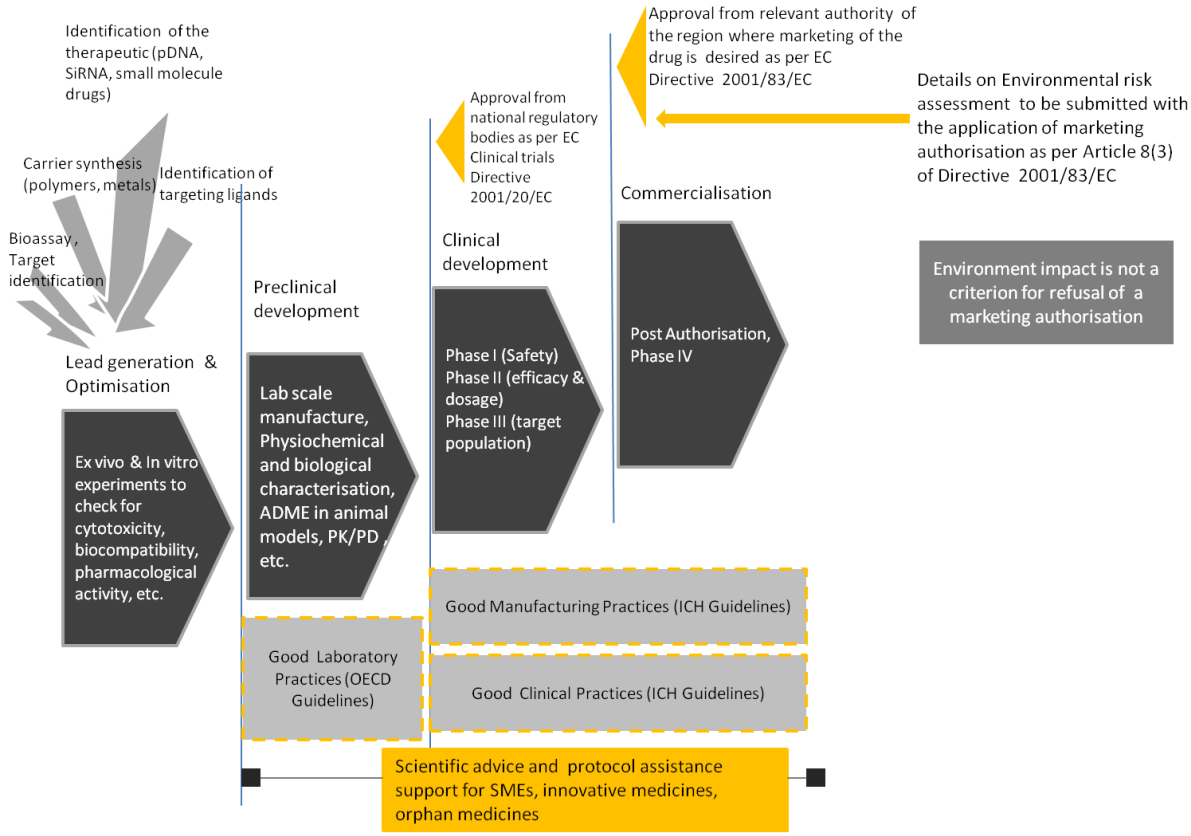


Figure 2.6: General stages of nanomedicine development and the key points of interaction between regulatory agencies and nanomedicine developers.

Good Laboratory Practices, Good Manufacturing Practices, and Good Clinical Practices are the quality and ethical guidelines followed by pharmaceutical companies and researchers and monitored by regulators. Because of the rapid advancement in technology and science and the need for innovations to be an economic driver, regulatory agencies are now present from earlier stages of product development than before.

2.3.2 Medical device legislation

The regulatory context with regard to medical devices in the EU is substantially different from that of medicines for human use. The regulatory pathway for medical devices and that for medicines have been distinct and clearly demarcated. The directives related to medical devices are implemented at the EU member-state level with no overarching body at the EU level. There are three different regulations to capture all the different types of devices used in the medical industry: the Medical Device Directive, Active Implantable Medical Device Directive, and In Vitro Diagnostic

Directive. Combination products, i.e., those that combine a medical device and a medicine, spurred by nanotechnology, have blurred the distinction between the two distinct regulatory pathways, and a need for revisions in the current legal framework has been voiced in the public consultation process, a part of the undergoing process of revision (2008 onwards) of the medical devices directives. Also, a few member-state regulators (e.g. the UK and Sweden) have taken the required steps towards addressing the issue.

Medical devices are classified according to their perceived level of risk: Class I, representing the lowest level of expected or perceived risk, and Class III, representing the highest level of risk. The degree of risk assigned then determines the level and type of evidence required for award of the CE (Conformité Européenne) mark. Clinical data required for awarding the CE mark for Class III medical devices are not mandatory to prove safety; literature analysis showing clinical investigations and experience related to similar devices and appropriate justification can be used while applying for an approval (Kramer et al., 2012). Tests to identify human toxicological risks from materials used in medical device components, (e.g., polymers) need to be performed. However, no environmental risk assessment of medical devices is required. Unfortunately, the medical devices directives do not cover the entire life cycle of the product and disposal of the devices follow national regulatory guidelines on waste management. There are possibilities of producing similar environmental and occupational health problems as electronic waste (Robinson, 2009) when cost-effective *in vitro* diagnostics using nanotechnology and nanoscience are mass produced and used.

2.3.3 Current regulatory context (human medicines) related to environmental safeguards

The EMA's Guideline on Environmental Risk Assessment (ERA) of pharmaceuticals (EMA, 2006a) follows a tiered assessment approach comprising Phase I and Phase II (Tier A and Tier B). Figure 2.7 gives a concise schematic explanation of the approach. An ERA needs to be provided with every new MAA for a pharmaceutical; however, granting of market authorisation is independent of the environmental impact. In the US, under the National Environmental Policy Act (NEPA), the FDA promulgated the inclusion of environment assessment (EA) for pharmaceuticals and biologics (gene therapies, vectored vaccines, and recombinant viral or microbial products)[26] with new drug application (NDA), investigational new drug application (INDA), abbreviated new drug application (ANDA), and biologics licence application (BLA) (USFDA, 1998). Failure to submit an EA (unless sufficient evidence indicates to the FDA that an EA is not required) can result in withholding of the application for approval or refusal from FDA to file the application. Rather than going into too much depth, it would be sufficient to mention here that this guideline to industry follows a tiered risk-assessment approach similar to that given in the EMA guideline, barring the threshold limit of $\log k_{ow}$, which is 3.5, and the FDA-mandated chronic toxicity tests in Tier III. The EMA requires that ERAs be submitted with applications for approval for generics as well as biosimilars (EMA, 2015).

[26] http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm401869.htm

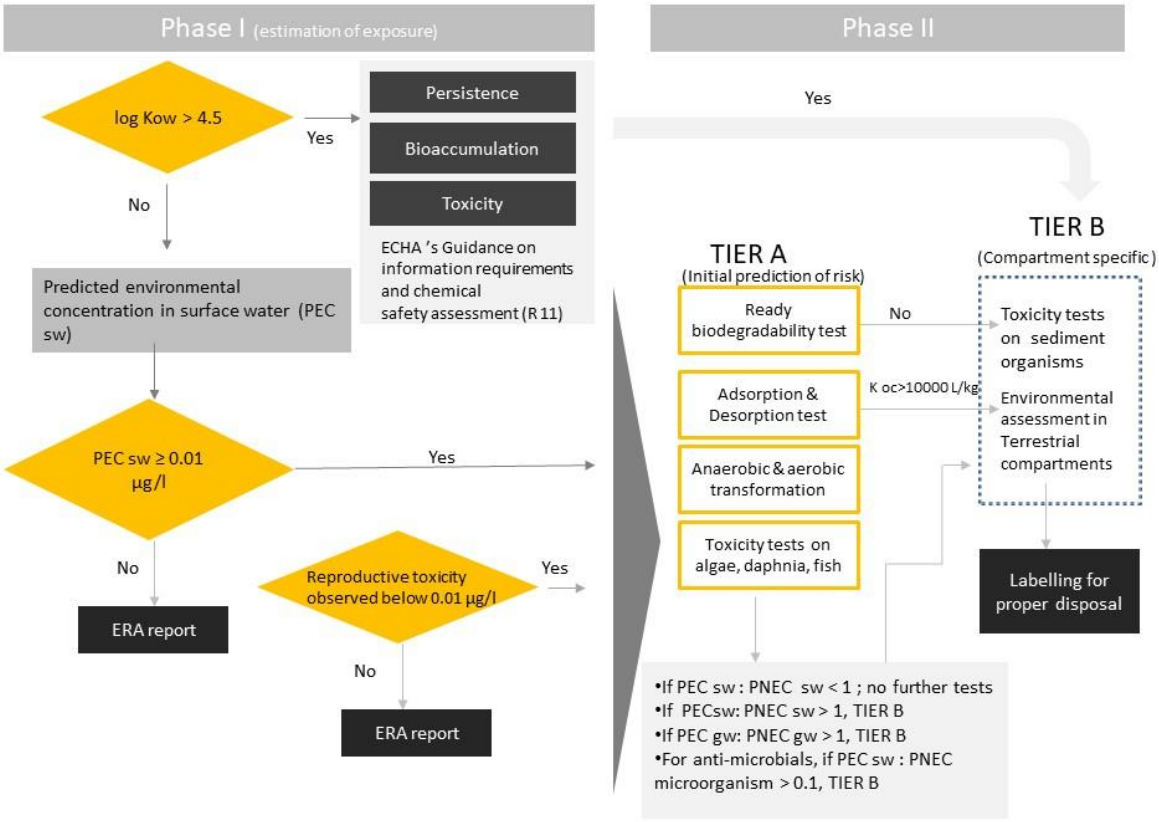


Figure 2.7: Key requirements in the tiered environmental risk assessment process for medicines for human use.

For anti-microbials, if the PNEC:PECsw is less than 0.1, extended environmental fate and effect studies become mandatory, which include soil and sediment compartments and terrestrial organisms. PNEC: predicted no effect concentration; PEC: predicted environmental concentration; Koc: adsorption coefficient; Kow: octanol–water partition coefficient; PEC sw: PEC surface water; PEC gw: PEC groundwater.

There are two initial pre-screening steps – (a) if the predicted environmental concentration of the pharmaceutical exceeds the threshold value of 0.01µg/L (0.01 ppb), then it triggers the need for conducting a few acute ecotoxicity tests on regulatory species to calculate the predicted no effect concentration (PNEC); (b) if the octanol-water partition coefficient (log K_{ow}) is greater than 4.5, persistence, bioaccumulation, and toxicity (PBT) assessment needs to be conducted by following the ECHA's guidance on chemical safety assessment. Firstly, the questions arise,

how is the PEC calculated for nanomedicines? Apart from concerns which are similar to all ENMs, should it to be based on the drug, the nanocarrier or on the nanocarrier-drug conjugate? How would the PEC be derived for more complex nanomedicines? As with all ENMs, nanomedicines may present unique concerns and the applicability of such ERAs has not been fully demonstrated.

Secondly, it is well established that log K_{ow} has deficiencies as a surrogate for determining the mobility and partitioning of PPs or for application to ENMs (Petersen et al., 2010). For example, the antidepressant carbamazapine was found in fish from effluent-dominated streams although the drug has a log K_{ow} of 2.67. Similarly, Ciprofloxacin, an antibiotic, adsorbs well onto sludge or sediments (Huang et al., 2002; Giger et al., 2003) despite a log K_{ow} of –1.74 (cited in Stuer-Lauridsen et al., 2000) and was found to be persistent (Walters et al., 2010). Similarly, ibuprofen, an acidic drug, was found to pass through soil (Eggen et al., 2010). Also, it has been widely debated that log K_{ow} for acidic and basic drugs is misleading, because the coefficient is dependent on solution pH, ionic strength, NOM, redox conditions and other factors. In the case of ENMs, the inadequacy of the test protocol to determine log K_{ow} has been discussed (Petersen et al., 2010).

Another study on different generations of dendrimers showed that dendrimers with a terminal NH_2 group exerted cytotoxic effects, although logK_{ow} of the polymer was negative for G1–G5 PAMAM dendrimers and G6-NH_2 and G8-NH_2 dendrimers partitioned at the octanol–water interface (Giri et al., 2009). The negative log K_{ow} indicates that under the current ERA guidelines, it will not be necessary to conduct a Tier 1 risk assessment. Similarly, PEG has a negative log K_{ow} and the coefficient

does not change much with the chain length; furthermore, PEG is not easily biodegradable.

Although the action limit of 0.01 μg L^{-1} is very low, it is based on acute rather than chronic toxicity tests, and it has been widely known both for pharmaceuticals and ENMs that chronic and sublethal toxicity end points are important in assessing the environmental risks of a product and that the link between chronic and acute toxicity is not well established for ENMs. Furthermore, the test protocols suggested in the ERA guidelines for human pharmaceuticals for conducting the studies related to fate and effects studies are based on the OECD test guidelines for chemicals. The recommended study types include adsorption–desorption studies using a batch equilibrium method, a ready biodegradability test, aerobic and anaerobic transformation in aquatic tests, algae growth inhibition, and a *Daphnia* reproduction test. The drawbacks of, and the need to adapt, the current OECD tests and protocols, originally meant for chemicals, to ENMs have been widely discussed and reviewed (Malkiewicz et al., 2011; Handy et al., 2012). Key issues are the influence of the test conditions of the medium on ENMs (Naha et al., 2009; Römer et al., 2011; Tejamaya et al., 2012), the need to include benthic and filter-feeding organisms as test species, the necessity of investigating chronic effects and finding novel toxicity end points, the need for extensive *in-situ* physicochemical characterization, and the limited applicability of the persistence and bioaccumulation tests. The applicability of testing to nanomedicines will include the same issues and perhaps other specific ones including the role of the nanocarrier in increased uptake. However, work is under way at OECD, and it is the remit of the Working Party on Manufactured

Nanomaterials (WPMN) to advise on test protocols and methods suitable for ENMs.[27] Similarly, programmes funded under the Seventh Framework Programme (FP-7) of the EU, such as *NanoTest* (to find out alternative testing strategies for ENMs used in medical diagnostics), *Smart-Nano* (measurement, detection, and quantification of ENMs in complex matrices), *ITS-Nano*, and *Nano-ecotoxicity*, are all working towards improving the fate, transformation, risk assessment, and categorization for ENMs.

2.4 Nanomedicine and responses by regulatory agencies: the EU and the US

Regulators in both the EU and the US have conducted workshops and set up special task forces to be abreast of nanotechnological advances in medicines. In 2006, the USFDA formed the Nanotechnology Task Force to assess its capacity to evaluate product categories under its remit that were declared to be based on nanotechnology. Two public meetings were held, one in October 2006 and another in September 2008. The report by the task force was published in July 2007. Since then, the FDA has published four draft industry guidelines.[28] Across the Atlantic, the EMA published a reflection paper on nanotechnology in medicine in 2006 (EMA, 2006c) and then constituted an ad hoc expert group on nanomedicine in 2009. The following year, the agency held an international scientific workshop on nanomedicines, which included a presentation on methodological issues in ERA for nanomedicine (EMA, 2010). The agency has been active in various nanomedicine

[27] http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2009)20/rev&doclanguage=en

[28] Guidance for Industry: Safety of Nanomaterials in Cosmetic Products", Draft Guidance for Industry, Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology and 'Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives, and, on 5 August 2015, a guidance document related to the use of nanotechnology in food for animals.

and nanomedicine-related (for example, polymer therapeutics) conferences by engaging with the academic communities and has published reflection papers on:[29]

1. the development of block-copolymer-micelle medicinal products,
2. data requirements for intravenous liposomal products developed with reference to an innovator liposomal product,
3. surface coatings: general issues related to parenteral administration of coated nanomedicine products,
4. data requirements for intravenous iron-based nano colloidal products developed with reference to an innovator medicinal product.

The EMA acts as a nodal agency for the EU for providing centralised MAAs for therapeutics belonging to only designated therapeutic categories (for other categories, the applicant needs to prove that the medicine is significantly novel to go through the EMA). The agency is also responsible for authorising medicines designated as orphan drugs, advanced therapy drugs, biotechnology-based drugs, and drugs meant for paediatric use. In all other cases, an applicant has to apply to the respective national regulatory agency of the EU member state for approval.

The agency's Committee for Medicinal Products for Human Use has constituted the *Innovative Task Force*, which has competencies from the areas of quality, safety, efficacy, pharmacovigilance, good practices compliance, regulatory and legal affairs, and scientific advice and is mandated[30] to provide an initial discussion forum or views on emerging technologies, therapies, and borderline cases, meant for product developers as well as for the various teams and committees within the EMA.

[29] http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp
[30] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004912.pdf

Nanomedicine is under the remit of this task force. However, as nanotechnology is an enabling tool, nanomedicines encompass many and diverse fields and hence should be horizontally integrated with the Advanced Therapy Medical Regulation (1394/2007/EC) and the Orphan Drug Regulation (Chowdhury, 2010; Dorbeck-Jung and Chowdhury, 2011). Integration is also an issue with the USFDA, with its divergent centres such as CDER (Center for Drug Evaluation and Research), CDRH (Center for Devices and Radiological Health), and CBER (Center for Biologics Evaluation and Research) (Bawa, 2011).

The growing trend towards harmonisation and standardization in the medical field is evident in the creation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Medical Device Regulators Forum (IMDRF) [31] to bring uniformity in national regulations concerning medical devices (countries participating in the IMDRF are the US, member-countries of the EU, Japan, Australia, and Canada). The major difference between the Council and the Forum is that the former is legally binding on the participating members whereas the latter is not (Altenstetter, 2011). Moreover, although 'nano' has recently figured on the IMDRF agenda,[32] a quick search with the term 'nano' on the ICH website returned no results. As of now, no new regulation has been passed regarding nanomedicine, and both the regulators have taken the stance of approving medicines and medical devices using nanotechnology on a case-by-case basis. The two regulators also hold frequent informal discussions (personal communication with EMA officials) and have encouraged interaction with developers

[31] Erstwhile Global Harmonisation Task Force (GHTF).

[32] A presentation available on the internet by Dr. Artur Menzel, for the IMDRF meeting held on 20 March 2013, mentions nanomaterials in medical devices. Available at: http://www.imdrf.org/docs/imdrf/final/meetings/imdrf-meet-130319-france-presentation-mechanism-action-use.pdf#search=%22nano%22

from the early stages of research in the form of scientific advice (which is chargeable) from the EMA, and parallel advice can be sought from both the agencies for breakthrough therapies.

To provide an impetus to nanomedicine and to fulfil the aim of maintaining competitive advantage and sustained growth, the European Commission has formed an industry-led technology platform on nanomedicine, namely ETP - Nanomedicine, or the European Technology Platform (in the US, the National Cancer Institute / the National Institutes of Health are leading the application of nanotechnology to medicine, e.g., the cancer nanotechnology plan[33]). Hence, there is no denying the fact that regulatory agencies in the EU and the US and the governments have tried to engage with nanotechnology in medicine. However many issues remain to be addressed more comprehensively, such as physicochemical characterisation of nanomedicines both *in vitro* and *in vivo*, safety assessment, manufacturing, designing appropriate bio-distribution experiments for the whole construct, and environment policies (Zolnik and Sadrieh, 2009; McNeil, 2011; Tyner and Sadrieh, 2011).

So far I have presented the research and development trends related to designing nanomaterials for medical purposes, the poorly understood risks from pharmaceuticals in the environment, the regulatory framework for assessing environmental risks from medicines and the non-existent environmental risk guidance for medical devices, in addition to the many known and unknowable unknowns in the case of nanomedicine in the environment. Given these circumstances, governance for environmental protection and societal benefit cannot be solely dependent on

[33] Available at: http://ncl.cancer.gov/about_cnplan.asp#cnplan

regulatory command and control approaches but should be oriented towards self-regulation or governance of research. Moreover, regulators might not have the requisite capacities or the mandate to address the broader issues around moral, ethical, equity and justice dimensions of nanomedicine innovation (see Marchant et al., 2009). Therefore, strategies for innovation should be designed in such a way that broader societal implications are taken into account from the innovation stage. Creating an adaptive and integrative risk governance framework in institutions meant to control, manage and minimise risks can help to manage risks arising nonetheless, when products get embedded in society (Klinke and Renn, 2012). Dialogue with public and amongst experts brought together from various disciplines and from institutions, such as universities, industry, regulatory bodies, NGOs, and policy makers provides an important foundation of strategies to govern research and its products (UK House of Lords, 2000; Irwin, 2006; Jones, 2008; Stirling, 2008).

Before detailing (Section 2.8) the 'in vogue' proposal on governance of innovation of new and emerging technologies, I discuss in Sections 2.6 and 2.7, the definition of innovation, the meaning of innovation in the health care field, and the imperative for governance of innovation.

2.5 Unpacking 'innovation'

There are many definitions of innovations applicable to different contexts; hence innovation can be defined from different perspectives. In the context of business organisation, innovation broadly can be defined as something new which brings about a change in products, processes, services to gain competitive advantage and

differentiation in the market place (See analysis of the existing definitions of innovation by Baregheh et al. (2009) where the authors pooled definitions from published literature of various disciplines like economics, innovation and entrepreneurship, business and management, and science and engineering).

According to Noah Webster's first edition of American dictionary of the English language: Innovation (n.) is defined as "*change made by introduction of something new*".

The above basic definition of innovation is applicable to the pharmaceutical and medical device industry; however, the term is defined more broadly.

Innovation can be of many types. Freeman and Perez's typology of innovation (Dosi et al., 1988) consists of four different modes:

1. Incremental innovation
2. Radical innovation
3. Changes in technology systems – has the ability to impact widely different aspects of the economy, for example, biotechnology
4. Innovation that changes the techno-economic paradigm, such as nanotechnology and genomics

Innovative products can only fulfil their role when they are associated with human agency and social and institutional structures (Garud and Rappa, 1994) and hence there is co-evolution or co-development of innovation, society, and institutions. Nanotechnology products in the health care sector can bring about changes in the techno-economic paradigm (for example, development of remote blood glucose monitoring introduces issues of patient data and privacy, creates the need for robust

ICT systems, and results in obsolescence of existing health care infrastructures and service modalities and design of new ways of manufacturing and marketing) and hence it necessitates that before the technologies are embedded 'in the world', questions on wider societal and future implications are considered.

2.6 Innovation in the pharmaceutical and medical device sector

Innovations in biological sciences are at best incremental changes, where various concepts and theories have been proven, drawing upon various disciplines like immunology, cell biology, over the years and methods and tools developed to quantify and report these discoveries and the associated social interactions between scientists (for example, refer to Melinda Fagan's historical account of blood stem cells discovery and applications) in alignment with Latour and Woolgar's findings that science is always in the making (Latour and Woolgar, 1979; Latour, 1987; Fagan, 2010). There has not been significant changes in the pharmaceutical innovation process over the years (Tait, 2007), and the development pathway is generally sequential in nature or, 'stage-gated' (Cooper, 1990). See Figure 2.6 in Section 2.3 for an idea of the innovation model for pharmaceuticals.

An 'innovative' drug *per se* is not defined in the regulatory context of the US and the EU. The EMA in its website (heading "Innovation Task Force"[34] gives a scroll note regarding innovative medicines and states that: "[an innovative medicine is] *a medicine that contains an active substance or combination of active substances that has not been authorised before*" and there are no other definitions found in related

[34] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp

legislations or rules and guidance documents for both the US and the EU.[35] However, as mentioned before, 'new' is used in the regulatory definitions rather than 'innovative' in case of pharmaceuticals. The novelty and newness of a therapeutic can be due to various properties, e.g., chemical structure, new target, improved pharmacodynamics and pharmacokinetics, improved delivery through re-formulations and innovation in synthesis, or new mechanism of actions (Ferner et al., 2010).

In the regulatory context of the US there are ambiguities with respect to terms and their definitions, e.g., new chemical entity (NCE), New Molecular Entity (NME), active ingredient and moiety, drug, and drug substance. However, this study does not delve into definitional issues. Furthermore, in the case of pharmaceuticals, regulations and research and development have been found to influence each other and hence are dynamically adaptive (refer to Carpenter's (2010) historical account of the USFDA for further details).

To promote innovation in the pharmaceutical sector, both the USFDA and the EMA have procedures and processes in place to give derogations to novel drugs whilst also fulfilling their goal of safeguarding public health. Also, legislations and regulations exist which confer certain advantages to novel drugs, such as market exclusivity, data protection and in the EU, centralised access to European market (28 Member States of EEA and Iceland, Lichtenstein, and Norway). Although I am not mapping the nuances in the definitions, and their convergences and divergences, in order to give an idea of what innovation might mean in the pharmaceutical sector to set up the background for Chapter 6 of this thesis, I present here briefly, what novel (new) drugs can mean. I chose the recent definitions given for NCEs and NMEs (in

[35] Innovative drug is defined in the Canadian drug regulatory framework, which I have not discussed here.

the EU, the term used is new active substance, i.e., NAS) as per existing Guidelines. For 'new' drugs which meet unmet clinical needs, drugs which demonstrate better safety and efficacy than existing drugs or drugs which have the potential to treat life-threatening conditions, USFDA reduces the approval time of the drug, and has various designation categories: 1) fast track, 2) priority review, and 3) breakthrough drug category. Additionally, scientific and regulatory assistance is provided by these agencies to drug developers researching and developing new drugs.

2.6.1 Innovative therapeutics and devices

New Chemical Entity (NCE) is defined as "a drug[36] that contains no active moiety[37] that has been approved by the USFDA in any other application submitted under section 505(b) of the Food, Drug and Cosmetics Act (21 CFR 314.108)." The USFDA clarifies on its website the difference between NCE and NME and that the latter is meant more for review purpose. It says:[38]

"*Certain drugs are classified as new molecular entities ("NMEs") for* ***purposes of FDA review.*** *Many of these products contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a*

[36] The USFDA clarifies in its Guidance to Industry issued in 2014 that 'drug' means 'drug substance' and not a 'drug product'. For details regarding the differing usage of substance and product the following can be referred to: USFDA. 2014. *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products: Draft Guidance for Industry* [Online]. United States Food and Drug Administration. Available: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf [Accessed 15 December 2015].

[37] **Active moiety** means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.108

[38] Title New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products. Available at: http://www.fda.gov/ Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm20025676.htm

combination product; these products frequently provide important new therapies for patients. Some drugs are characterized as NMEs for ***administrative purposes,*** *but nonetheless contain active moieties that are closely related to active moieties in products that have previously been approved by FDA.....FDA's classification of a drug as an "NME" for review purposes is distinct from FDA's determination of whether a drug product is a "new chemical entity" or "NCE" within the meaning of the Federal Food, Drug, and Cosmetic Act*." (emphasis mine)

Similarly, in the EU, new active substance (NAS) is defined as a substance not previously authorised in the Union. I give the detailed definition in the annexe to this chapter.

It is sufficient to mention that the substance might have been earlier approved but if some change in it confers it to be safer or more efficacious, it is treated as new. As explained in Sections 2.1 and 2.2, nanoformulations can increase safety and efficacy of available medicines or shelved medicines.

Successful medical device development is an iterative process which includes many feedbacks loops in each step of its development pathway – validation in the laboratory, prototyping, validation in an operational environment, improvements and re-validation and testing, optimization, and finalisation and marketing. The general schema of a medical device innovation pathway, with indicative steps and iterations is shown in Figure 2.8 (USFDA, 2011a).

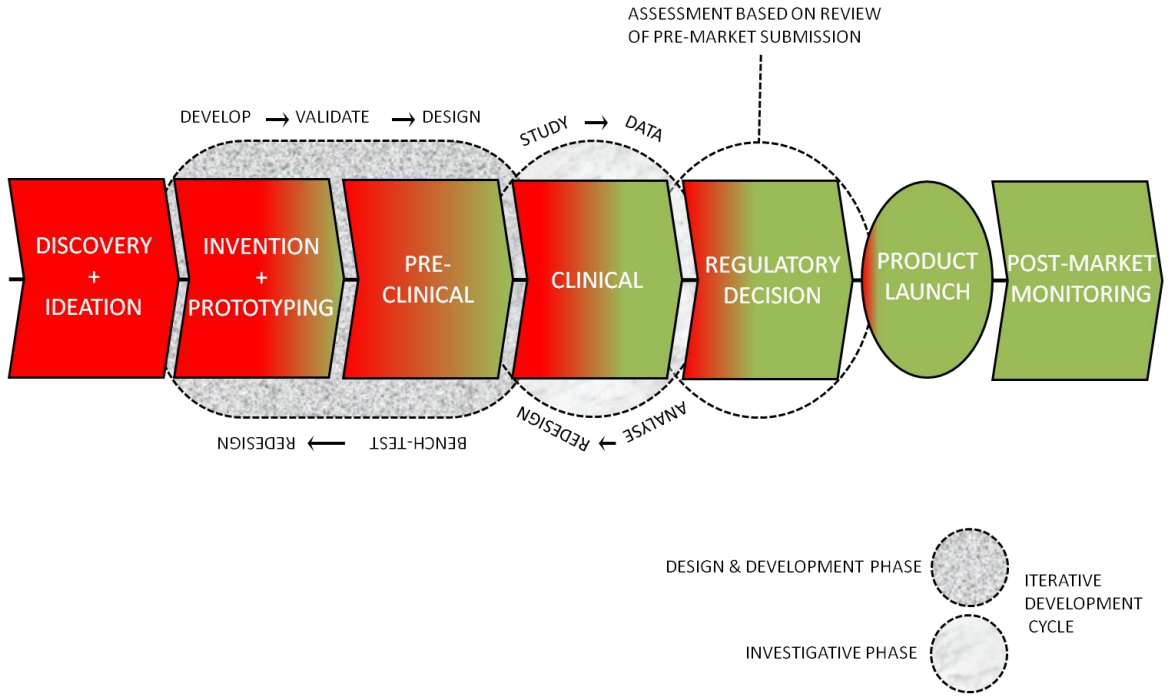


Figure 2.8: Schematic of medical device innovation pathway (Taken from USFDA 2011).

The regulatory review of medical devices in the US is more suited towards incremental developments in the medical devices. Similar to the EU, the USFDA assigns classes for devices and is based on perceived risk – Class I, very low risk; Class II, high risk; Class III, highest risk. The class is generally assigned based on intended use, indications for use and risk to patients and/or the user. There are two distinct regulatory pathways - if a class I or Class II device is not an exempted device (most Class I devices are exempted from a pre-market notification process (510k)) but if the applicant could prove it to be substantially equivalent to an existing medical device, then the applicant submits a pre-market notification. In the case of Class III medical device (very few Class III can follow the 510k route), the applicant submits a pre-market authorisation (PMA) request with data on safety and efficacy of the device collected from non-clinical tests and clinical trials. However, to initiate clinical trials,

an investigational device exemption should be submitted to the USFDA. If the device is classified to be very risky, only then is FDA approval necessary, otherwise, the dossier containing clearance from an Institutional Review Board, informed consent from all patients; labelling stating that the device is for investigational use only; and other associated documents is submitted to the FDA.

With regard to innovative or combination products containing a medical device, the USFDA has an expedited review process (USFDA, 2013), and it uses the criteria given in section 515(d)(5) of the Federal Food, Drug, and Cosmetic Act. A device is considered to be innovative if the product:

"is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and meets at least one of the following:

- The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology.
- No approved alternative treatment or means of diagnosis exists.
- The device offers significant, clinically meaningful advantages over existing approved alternatives.
- The availability of the device is in the best interest of patients".

Previously, under the Protocol Development Program, advice was provided by the regulator to applicants on scientific data collection methods for innovative devices; however, it was sparingly used. In 2011, to facilitate innovation and commercialisation of pioneering innovative medical devices (most likely due to the transformative possibilities promised by new and emerging technologies and scientific breakthroughs), the Center of Devices and Radiological Health (CDRH) at

the USFDA initiated the “Innovation Pathway Initiative” with the aim to provide regulatory expediency and scientific assistance to these devices. It has set up criteria (similar to the above criteria) to identify devices that can be included in the Pathway and had the proposition to discuss regulatory implications with device developer at the initial stages of product development (pre-IDE stage). Medical Device Innovation Consortium (MDIC), a public private partnership, was set up in 2011, to respond to regulatory challenges posed by innovative devices.[39] The European context is different in terms of authorisation of medical devices, as the authorisation of medical devices is under the jurisdiction of the respective national medical authorities and evaluation of devices is performed by independent, commercial entities known as ‘notified bodies’ which are recognised by the EU member states (details in Section 2.4.2). There is no specific thrust with regard to supporting innovative devices in the EU.

2.6.2 Model of pharmaceutical innovation

The growth of the pharmaceutical industry is dependent on innovation, though the amount of growth is influenced by many factors (Demirel and Mazzucato, 2012). Pharmaceutical firms spend billions of dollars per year on research, the largest companies spending around $8–10 billion per year (e.g., Novartis spent ca. $10 billion dollars (around 17% of net sales) on R&D in 2014 (Novartis, 2015); Roche spent similar amounts in 2014 (Roche, 2015). Over the years, the research and development in the pharmaceutical sector has moved from strictly internal industry-led R&D to ‘open innovation’ (Chesbrough and Appleyard, 2007) where knowledge

[39]See http://mdic.org/about-us/

and information is exchanged and strict firm-led stage-gated model has changed to a more dynamic and complex interactional model between various actors. However, government funding still remains important for the initial phases of innovation (Mazzucuto, 2011; Toole, 2012). Collaborations between industries, universities and government are now pervasive in the pharmaceutical sector (see e.g.,Hunter and Stephens, 2010; Schuhmacher et al., 2013). The nanomedicine field is getting considerable investment support from 'big pharma' (e.g., Pfizer and AstraZeneca promised investment of ca. 200 million USD to Bind Therapeutics for development and commercialisation for every potential drug that can be developed using BIND Therapeutics' Medicinal Nanoengineering® platform and then tiered royalties in the event of future sales of medicines) and the governments (e.g. NIH's funding to NNI, EU's FP7 and Horizon 2020). Support for innovations in this area is also evident from regulators, who are keen to help researchers identify protocols for assays, standards of assessment and engage early on with the developers. In such a scenario, how RI can be conceptualised is examined in Chapter 6.

The Innovative Medicines Initiative[40] launched in 2008, is a public private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It has funding from both the European Union's Framework Programs and from the EFPIA to facilitate development of medicines. Though IMI do not explicitly mention 'nano' in their website, the potential of nanotechnology in the health-care has already been discussed in earlier sections and the idea that nanotechnology is an enabling technology indicates that all these initiatives can act as test case for RI.

[40]Details available at: http://www.imi.europa.eu/content/mission

2.7 The need to move from governing of risks to governing of innovation

"Jobs, growth and investment will only return to Europe if we create the right regulatory environment and promote a climate of entrepreneurship and job creation. We must not stifle innovation and competitiveness with too prescriptive and too detailed regulations." (Jean-Claude Juncker, President of the European Commission, Speech on July 15, 2014)

"Modern technology has introduced actions of such novel scale, objects and consequences that the framework of former ethics can no longer contain them." (Jonas, 1985 , p 34)

2.7.1 Science, Technology, Innovation: Importance and Implications

Innovation is considered to be the cornerstone for economic growth and global competitiveness and is extolled for making the life of humans easier. In fact, so much importance has been given to the virtues of science and technology that it had been suggested that even income inequality and poverty would be removed by the beginning of this millennium (Snow, 1959). However, the products and processes of innovation do not always contribute towards increased welfare of people and the environment but can lead to negative consequences either because they are used with a wrong intention or their everyday use resulted in long term changes in the environment or caused accidents which had ramifications for many years. We are aware of major innovations in products and process in this century and the associated consequences and I do not need to exemplify here in detail, but a few would suffice to act as a quick reminder. Nuclear energy and the disasters at Chernobyl and the Three Mile Island, the atomic bombs; automobiles and urban air pollution; the industrial revolution and compromised worker welfare; refrigerants and

the depletion of ozone layer, pesticides (e.g., DDT) and associated ecological consequences; and asbestos the wonder material which is linked to respiratory diseases and cancer—all have shown the impacts of a technologically driven age. Ulrich Beck, Anthony Giddens and others (Winner, 1980; Beck, 1992; Giddens, 1999; Beck, 2009) advocate that contemporary society is organised around risks and safety concerns created by modernisation and that we live in a world of 'manufactured risks'; risks which are increasingly difficult to anticipate and manage, because of rapid development of technology, widespread usage, and our dependency and idea of dominating and manipulating nature.

Furthermore, epistemic (lack of knowledge of fundamental phenomena) and aleatory (complexity, variability and unpredictability of natural systems) uncertainties (Paté-Cornell, 1996), and ambiguities − both interpretative and normative − make risk characterisation from incumbent technologies and conventional chemicals a challenge. Since science is restricted / bounded by the current state of knowledge, it creates the need for continuous and unceasing research to protect human health and the environment from undesirable implications from technology and associated products. Also, scientists and researchers tend to produce conflicting results and many times do not agree with each other. For an example, see the account of the cholesterol level controversy by Garrety (1997). In the case of nanomaterial risk assessment, the waters are murkier, for example, even if the tests are conducted on nominally the same type of nanomaterials the results might be different and such differences may arise due to batch-to-batch variability in nanomaterials, differences in exposure conditions (e.g., pH, ionic strength, redox conditions, light), lack of

available tools and methods to characterise nanomaterials *in vivo*, and/or poor or limited mechanistic knowledge about nanomaterials' fate inside an organism.

There is a time lag of decades from knowing of a problem, to proving a particular effect and enacting change in regulations (EEA, 2013; Jobling and Owen, 2013) and hence regulators always tend to play catch up. The time lag in change of regulations can be due to many issues, as elaborated by Moses (2007):

1. The need for special rules and regulations to control the risks of new technologies;
2. Technological changes creating uncertainties in the application of existing legal frameworks
3. The possibility of existing rules to either over include or under include all the associated consequences due to new technologies; and
4. The potential for technology to make existing rules and regulations obsolete.

Furthermore, some other issues are lobbying by industries against rule changes in regulations (Stenzel and Frenzel, 2008; HAI/CEO, 2012), for example, 35 chemical firms aired their discontent with the ECHA's decision to regulate silicon dioxide under REACH (ChemicalWatch, 2015) and the time and costs involved in change of regulations (in July 2013 public consultation[41] started in EU for amendments to REACH annexes for nanomaterials and the results are yet to be published, this is as of December 2015).

[41] http://ec.europa.eu/environment/consultations/nanomaterials_2013_en.htm

2.7.2 Risk governance and emerging technologies

New and emerging technologies, like nanotechnologies, create challenges to existing regulatory scenarios (e.g., a new regulatory pathway is required for theranostics – which combine aspects of diagnostics and therapeutics with regulatory implications from both domains)(Gaspar, 2010). In a study involving telephonic surveys of various stakeholders in the EU and US, it was found that industry and regulators agreed that traditional risk assessment cannot be done based on the current knowledge regarding exposure and hazard known for nanoparticles (Helland et al., 2006) and materials should be judged on a case by case basis. The need for adaptation of the existing risk assessment procedures and protocols for nanomaterials was also reflected by SCENIHR (2007) and the European Food Safety Authority (2011) and ECHA (2014). Despite investment in the EHS area for nanomaterials, the uncertainties remain, e.g., identifying a suitable dose-metric (Oberdorster et al., 2005; Simkó et al., 2014) for risk assessment. I have elaborated in Section 2.4.3 the challenges of assessing log K_{ow} for nanomaterials, which is important for environmental risk assessment of medicines and I will present viewpoints from experts regarding their ideas on risks from nanomedicines and adequacy of risk assessments frameworks for nanomaterials in Chapter 5. There has not been any change yet in regulations (except EU Cosmetic Regulation 1223/2009) and the product-based case-by-case approach remains.

As mentioned earlier, ERA in general and ERA of pharmaceuticals in particular, are dogged by uncertainties and gaps in knowledge despite much research in this area. Gaps are known to exist in knowledge and in data related to pharmaceuticals, including their metabolic products and excretion rate, their behaviour and fate in the

environment, the efficiencies of STPs in removing these chemicals, chronic toxicity data and bioaccumulation. In the domain of nano-ecotoxicology, the key gaps include environmental concentrations, behaviour and fate in the environment, dynamic changes in physical and chemical properties both *in vitro* and *in vivo*, applicability of exposure assays, dose metrics for exposure assessment, biouptake and toxicity mechanisms, and relationships between chronic and acute toxicity. Some of the above gaps may also constitute 'unknown unknowns' because we do not fully understand the interrelationship between novel properties and potentially novel effects. In this 'post-normal science' situation in nanomedicine where uncertainties and stakes are high (Ravetz and International Society for Ecological Economics, 2013) an exploratory study is needed to understand whether nanomedicine might create newer forms of environmental hazards and risks. There is no doubt that the 21st century is the era of multifunctional, complex, and 'smart' systems (Subramanian et al., 2010); however, the environmental implications of such active and targeted systems need to be considered while they are yet at an early stage so as to reap sustained benefits from this emerging field without unintended and undesirable environmental consequences.

Due to uncertainties – unknown unknowns, indeterminacy, complexity, ambiguity – and time constraints to produce evidence-based research, it is widely accepted that discursive models of policy making are superior (Haas, 2004, Stirling, 2008). Moreover, as Latour argues, science and societies are 'co-produced' (Latour, 1993, p.134). Hence it is important that we find ways and means whereby 'spaces' can be created for deliberations which include anticipation of future trajectories of innovation and possible implications and reflection on the purposes and motivations of research

for new products and technologies in order to avoid negative developments and to enable creation of alternate and productive paths of development.

2.8 Responsible innovation – beginnings

> Perhaps it is always hard to see the bigger impact while you are in the vortex of a change. Failing to understand the consequences of our inventions while we are in the rapture of discovery and innovation seems to be a common fault of scientists and technologists; we have long been driven by the overarching desire to know that is the nature of science's quest.....Bill Joy, WIRED, 2000

'Responsible innovation' (RI) or 'responsible research and innovation' (RRI) has gained momentum in policy discussions across the developed world, but more especially in European policy circles with regard to governance of new and emerging technologies. In the last 2−3 years (2013−2015), the concept has been discussed in journal articles, blog posts, newspapers, book chapters, and in various contexts, like privacy and ICT (Grimpe et al., 2014). It has been critiqued (van Oudheusden, 2014), fine tuned or adapted (Stahl, 2013), and also compared and contrasted with existing criteria for research funding (e.g. National Science Foundation's need for proposals to address broader societal impacts) (Davis and Laas, 2014) and one can say that the concept of RI is both a product and a process. In 2013, it was adopted by the European Commission[42] and the UK's EPSRC and Innovate UK (erstwhile Technology Strategy Board). The concept was applied as a test case with respect to funding of proposals by UK Research Councils (Owen and Goldberg, 2010). The embryonic concept was put into practice by using the concept of a risk register which made scientists introspect on possible implications of the ideas being developed in

[42] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

their proposals *ex ante*. In the UK, the abandonment of the SPICE project,[43] funded by the EPSRC, due to public criticism, showed the importance of timely and earlier engagement with wider societal actors (Macnaghten and Owen, 2011). The EPSRC framed its funding call on nanotechnology for health care in 2009 after conducting public consultation in 2008; the consultation resulted in many intriguing insights regarding public reluctance towards "theranostics" (an area which is considered to be very exciting in the nanomedicine community) where people felt they would lose control to monitor their disease (Jones, 2008). The Netherlands Organisation for Scientific Research (NWO) funded projects from 2009 which either imbibe or explore and further develop the concept of RI. The projects funded by NWO involve deployment of existing technologies which range from implementing renewable energy projects, water filters in developing countries, enrolling people in clinical trials, and access to new drugs to designing smart cities (Kiran, 2012).

As mentioned in Chapter 1, several workshops on responsible innovation have taken place, for example a Franco-British workshop on Responsible Innovation in 2011 in London[44], RI conference held in the Hague every year (4th conference held in 2015), a workshop in Brussels conducted by DG-Research (EC, 2011b) and similar workshops in the US. The videos of some of these conferences are available on You Tube (https://www.youtube.com/watch?v=lCO0UcUP6mU) and other media and hence widely available to the public. These workshops have discussed how best to envision and articulate RI.

[43] SPICE: Stratospheric Particle Injection for Climate Engineering.
[44] http://www.ambafrance-uk.org/Franco-British-workshop-on,18791

On 13 December 2015, the search phrase “responsible innovation” (quotations used in the search) in Google gave 102,000 results which shows a rapid increase in its popularity in comparison to early 2011, when I started research in order to know more about the term (advanced search in Google for the custom date range: 1 January 2011 to 31 December 2011, returned about 1,890 results). In 2013, the Virtual Institute of Responsible Innovation [45] was established at Arizona State University, funded by the US National Science Foundation. In 2014, the peer-reviewed Journal with the title “*Journal of Responsible Innovation”* was launched (Guston et al., 2014). The Institute has academics from the UK, the Netherlands, Germany, Denmark, Norway, Brazil and Canada. However, the concept of RI or RRI is not entirely new and has its foundations in the discourses on the ‘co-production’ of science and society (Jasanoff, 2004), social construction of technology (Pinch and Bijker, 1984), science policy and innovation studies, risk governance, and ethical, legal and social (ELSA) studies and borrows from the concepts of technology assessment in all its forms, e.g., Constructive (Schot and Rip, 1997), Participatory (Durant, 1999), Real Time (Guston and Sarewitz, 2002), and other concepts, such as upstream public engagement (Wilsdon and Willis, 2004), anticipatory governance (Karinen and Guston, 2010b) and mid-stream modulation (Fisher and Mahajan, 2006).

The first uses of the term RI, I found, is in Thomas Hellström’s article published in 2003 (Hellström, 2003) wherein he proposes a general framework whereby technological risks are identified and risk reduction measures designed and implemented by sharing information (e.g., establishing clearing houses), and he cites

[45] Details at: https://cns.asu.edu/viri

David Guston's idea on creation of RI Centres at Universities.[46] Guston focussed on such a need because of the immense thrust towards commercialisation of inventions in US Universities due to the Bayh–Dole Act, 1980, which allowed government funded inventions at universities and businesses to be patented and also allowed for exclusive contracts and licensing for development and commercialisation of the inventions. Before discussing further about RI, I will briefly present the background which likely led to calls for governance of nanotechnology—the focus of this thesis.

The US was the flag bearer in starting a distinct and focussed program on nanotechnology in the year 2000 by establishing the national nanotechnology initiative with sign off from the then President, Bill Clinton. This led to many initiatives all across the world to start state-funded nanotechnology focussed programs (Roco, 2005; Bajwa et al., 2012; WPN, 2013). Deliberations related to its development directions and priorities gained prominence due to the scenarios of harm and risk portrayed by an NGO – the ETC group[47] − and Munich Re's[48] report on liabilities of nanotechnology firms. The ETC group appealed for a moratorium on nanotechnology and Greenpeace commissioned Imperial College, London to assess the field of nanotechnology and Artificial Intelligence. The dystopian vision of the future articulated by writers including Eric Drexler[49] was another source of concern. Prince Charles of the UK, made a public expression of anxiety regarding nanotechnology which was not much different from concerns raised by Bill Joy[50] regarding new and emerging technologies, but did not sit well with the populace whose concerns also reflected the recent regulatory failure regarding GMOs in the

[46] See Footnote in page 372 in HELLSTRÖM, T. 2003. Systemic innovation and risk: technology assessment and the challenge of responsible innovation. *Technology in Society,* 25**,** 369-384.
[47] http://www.etcgroup.org/content/no-small-matter
[48] http://www.anet.co.il/anetfiles/files/241M.pdf
[49] Eric Drexler's book 'Engines of Creation' was published in 1986.
[50] Bill Joys' essay "Why the future doesn't need us "in WIRED in 2000.

EU. Discussions on risks abounded in the media from 2002 onwards (Gaskell et al., 2005). As a response, the concept of responsible development of nanotechnology came into focus (Winner, 2003; RS/RAE, 2004) and became the dominant narrative of research in the emerging science and technology field of nanotechnology. The term responsible development was used in the US "21st Century Nanotechnology Research and Development Act" (Public Law 108-153)[51] which was passed in December 2003. Responsible development of nanotechnology as defined by the Committee set up to review the National Nanotechnology Initiative is, "*Responsible development of nanotechnology can be characterised as the balancing of efforts to maximise the technologies positive contributions and minimize its negative consequences. It implies a commitment to develop and use technology to help meet the most pressing human and societal needs, while making every reasonable effort to anticipate and mitigate adverse implications and unintended consequences*." (Committee to Review the National Nanotechnology Initiative, 2006). However, the way the concept was put forward reflected the implicit conflict between potential benefits of innovation and possible negative impacts from innovation. It also indicates that it is accepted unconditionally that there will be negative impacts of innovation.

Responsible development of nanotechnology is pursued as a specific policy in countries, such as Australia, Argentina, Norway, Germany and China (WPN, 2013). Many other initiatives started along similar lines, including, for example, the Responsible NanoCode (UK), DEFRA's Voluntary Reporting Scheme for Engineered Nanoscale Materials, the USEPA's Nanoscale Materials Stewardship Program, and

[51] http://www.gpo.gov/fdsys/pkg/PLAW-108publ153/html/PLAW-108publ153.htm

the EC's code of conduct for Responsible Nanoscience & Nanotechnologies research (EC, 2009). Industry also took lead, for example, BASF's Voluntary Code of Conduct on Nanotechnology", as well as their role in forming the 'Dialogforum Nano. [52] Another industry and environment partnership was by DuPont-Environmental Defense Fund - Nano Risk Framework to Aid in Responsible Development of Nanotechnology (Ramachandran et al., 2011). However, these were primarily focussed on mainstream nanotechnology applications and no such approach exists for nanotechnology enabled medical applications. Also, results of the voluntary reporting initiatives were not very encouraging due to low number of respondents (Widmer et al., 2010). Moreover, the responsible development dialogue which was started in 2004 lost its momentum (Fisher and Rip, 2013). The various codes of conducts and formulations on responsible development of nanotechnology involved discussions on wider health and environmental risks, ethical aspects, workplace health and safety, stakeholder involvement, and transparency, but they were generally individual initiatives and were often disconnected. Responsible innovation acts as a means to knit a concept for governance of research and innovation from the different threads of risks and safety, anticipatory governance of science and technology, science and society and ethics.

2.9 Responsible innovation (RI) or responsible research and innovation (RRI): Meaning and definitions

The conceptualisation of responsible innovation includes the need for wider participation in the decision making process and not only of expert committees consisting of researchers from the ethical, legal and social fields to anticipate the

[52] http://www.basf.com/group/corporate/en/sustainability/dialogue/in-dialogue-with-politics/nanotechnology/stakeholder-engagement

applications of inventions and the implications of innovations. Also, the idea is to move away from the narrow framing with regard to risks and impacts related to a technological innovation and towards the intent behind the research and innovation – the purpose, the motivations and the need. RI seeks to propagate moral virtue in the 'enactors'[53] and thus would require robust inter-disciplinary and trans-disciplinary collaboration between scientists, engineers, social scientists and applied ethicists (Grunwald, 2011).

Hans Jonas argued that the concept of responsibility is a new term and was not central in the philosophical discussions on ethics or older moral systems and he goes on to say that "Care for the future of mankind is the overruling duty of collective human action in the age of technical civilization that has become 'almighty'....." (Jonas, 1985, p.136). Whereas, Vincent presents different conceptions of responsibility oriented more towards attributing penalty – Capacity, Causal, Role, Outcome, Virtue and Liability. She argues "that 'responsibility' can be used in so many different ways.....the word represents a 'syndrome' of concepts – i.e. to multiple concepts that share a common word – rather than a single, unitary, or generic concept" (Vincent, 2011a, p.18). However, RI works in the sphere of positive conceptions of responsibility like care and responsiveness, rather than the consequentialist and negative framing of responsibility, in terms of liability and of accountability. It argues for normative and substantive motivations of research[54]

[53] Enactors are scientists, industrialists, government agencies, technology developers and promoters (p.52) of RIP, A. & TE KULVE, H. 2008. Constructive technology assessment and socio-technical scenarios. *In:* FISHER, E., SELIN, C. & WETMORE, J. M. (eds.) *The Yearbook of Nanotechnology in Society, Volume 1: Presenting Futures.* Springer.

[54] I draw from Stirling (2008) explanation of normative, substantive and instrumental motivations. Normative imperatives mean developing a strategy for research just because it is the 'right thing to do, without reference to the ends in question'. A research can be substantively motivated if it 'generally leads to better ends and instrumental motivations for research is when research is done to fulfil a particular goal. STIRLING, A. 2008.

rather than instrumental motivations[55] and seeks towards integrating the moral dimension of responsibility (Ladd, 1982). Pavie (2014) extends responsible innovation to 'Innovation-Care' as a necessity and bases his concept on the deontological ethics of Emmanuel Kant.

There have been many ways in which responsible innovation has been framed (a widely accepted definition of RI is yet to crystallize and it may never be required if its core meaning and intent are understood and internalised at various socio-political levels) but, as I will note later, the key dimensions of RI have not changed drastically in the various academic conceptualisations of RI. I present below a few of the most widely referred to ones:

Renè von Schomberg defines RRI as:

"*a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society*)."(von Schomberg, 2013, p.63)

von Schomberg's definition includes the concepts of open and transparent deliberation with various actors, responsiveness to ideas suggested and emerging from the participatory process, and ethical acceptability and sustainability of the products from innovation. Whereas, Davis and Laas (2014) proposed a variation of von Schomberg's definition of RI by putting forth their arguments against limiting

"Opening Up" and "Closing Down": Power, Participation, and Pluralism in the Social Appraisal of Technology. *Science, Technology & Human Values,* 33**,** 262-294.

[55] Based on Stirling's (2008) explanations, innovations in the pharmaceutical sector can be said to be driven by instrumental and substantive goals.

innovation to marketable products and instead focussing on scientific and technological or knowledge advances, making societal desirability the super-set within which ethics and sustainability are included (for a more detailed discussion refer to Davis and Laas (2014)):

"*Responsible Research and Innovation (RRI) is a transparent, interactive process by which researchers, innovators, and other societal actors become mutually responsive to each other with a view to embedding scientific and technological advances in society in societally desirable ways (including, but not limited to, ways that are sustainable and ethically acceptable).”* (p.971)

The Lund Declaration [56] in 2009 emphasised the role of research in addressing societal needs and subsequent changes happened in EU research policy. Research and innovation is considered as a means to create economic prosperity, effectively address societal challenges,[57] and strengthen the EU's position in the world and these positions and ideologies can be evidenced in the Horizon 2020 policy and program documents. The EC also adopted RI as integral to funding research. To quote from the EC website "RRI is furthermore a 'cross-cutting issue' in Horizon 2020, which will be promoted throughout Horizon 2020 objectives". The EC definition states:

"*RRI refers to ways of proceeding in Research and Innovation that allow those who initiate and are involved in the processes of research and innovation at an early stage (A) to obtain relevant knowledge on the consequences of the outcomes of their*

[56] https://www.vr.se/download/18.249c421a1504ad6d28144942/1444391884365/Lund_Declaration_2009.pdf

[57] The societal challenges identified for funding in the Horizon 2020 program are: Health, demographic change and wellbeing; Food security, sustainable agriculture and forestry, marine and maritime and inland water research, and the Bioeconomy; Secure, clean and efficient energy; Smart, green and integrated transport; Climate action, environment, resource efficiency and raw materials; Europe in a changing world−inclusive, innovative and reflective societies; Secure societies−protecting freedom and security of Europe and its citizens.

actions and on the range of options open to them and (B) to effectively evaluate both outcomes and options in terms of moral values (including, but not limited to wellbeing, justice, equality, privacy, autonomy, safety, security, sustainability, accountability, democracy and efficiency) and (C) to use these considerations (under A and B) as functional requirements for design and development of new research, products and services" (EC, 2013d, p.56).

The EC definition of RRI emphasises the importance of gaining knowledge of downstream 'hard' and 'soft' impacts[58] of research and innovation and designing and developing research, products and services considering these impacts.



Figure 2.9: Wordle of RRI text from the European Commission website.

Note: The word 'environment' does not appear in the wordle, indicative of its lack of prevalence in the original text. Taken from: https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

[58] See discussion by Swierstra (2015) on hard and soft impacts of technology. He defines hard impacts as impacts which can be quantified (such as health, safety) and clear accountability established for any negative impacts. Soft impacts of technology, according to him, are those which are "qualitative, ambiguous and/or indeterminate" and harms are not clearly attributable to anyone in particular. (p.7) SWIERSTRA, T. 2015. Identifying the normative challenges posed by technology's 'soft' impacts. *2015***,** 16.

Bernd Stahl (2013) proposes the definition of RI as:

"*a higher level responsibility or meta-responsibility that aims to shape, maintain, develop, coordinate and align existing and novel research and innovation-related processes, actors and responsibilities with a view to ensuring desirable and acceptable research outcomes."* (p.5)

The EPSRC clarifies its desire that the researchers it funds should follow the key principles of RI which EPSRC outlines as: Anticipate, Reflect, Engage, Act, and uses the acronym AREA (as a mnemonic tool). It has not defined RI *per se*, however, the Council does explain what it means and that researchers are free to interpret the term according to their own research program areas. However, the EPSRC has appealed to the researchers it funds to demonstrate that they are aware and are committed to responsible innovation. The EPRSC suggested: "*RI is a process that seeks to promote creativity and opportunities for science and innovation that are socially desirable and undertaken in the public interest."*[59]

The Technology Strategy Board (named as Innovate UK from September 2014, hereafter referred to as TSB in this thesis), UK released a responsible innovation framework for commercialisation of research findings to be referred by project applications in synthetic biology (TSB, 2012).

The definition put forward by Owen et al. (2013a) is:

"RI is a collective commitment of care for the future through responsive stewardship of science and innovation in the present." (p.36)

[59] EPSRC: Framework for Responsible Innovation. Available at: https://www.epsrc.ac.uk/research/framework/

The Responsible Innovation Framework as proposed by Owen et al. (2013a, p. 38) has the following four dimensions:

1. **Anticipatory**: considering *ex ante* the various trajectories that the innovation can take, the associated economic, societal and environmental implications.
2. **Reflective**: (1st and 2nd order), thinking through the overall intent, goals, reasons behind the proposed research and innovation; exploring the uncertainties and knowledge gaps, the dilemmas and trade-offs.
3. **Deliberation**: collective thinking and discussion by stakeholders and broader society regarding the 'future' innovation.
4. **Responsive**: taking actions as per the knowledge and insights gained from the anticipatory, reflective and deliberative exercises; these actions should be adaptive and dynamic in nature.

These definitions have not discussed how innovation processes can be improved or what innovation is, but have elaborated on how innovations can be responsive to societal aspirations. Similarly, whether society can be considered as a singular, homogenous entity with similar aspirations of all human beings can be argued. How or will a pluralistic society with different aspirations come together to collectively steer research and innovation are questions worth exploring, which indicates that the concept of RI is highly context dependent, which the proponents have noted. To quote Owen et al.(2013b, p.43) *"…..beneath the general framework researchers, innovators and those who fund them should have flexibility in the details of how its dimensions are taken forward…….that suit its context of application best and that they themselves value"*. In Chapter 6, I will touch upon how these conditions are

broadly adhered to and practiced by pharmaceutical companies (for example, detailing on responsiveness is a mandatory criterion if a firm wishes to use the AccountAbility Standards (AA1000AS) and Global Reporting Initiative's (GRI) reporting guidelines for reporting its triple bottom line, i.e., economic, environmental, and social performance) and recommend some improvements that can be effected. However, it is worth mentioning here that all the proposed RI definitions, although not identical or agreed upon have some common underpinning principles or characteristics, namely:

- Involvement of different stakeholders
- Care for the future (and hence future generations and therefore can be integrated in the concept of sustainable development)
- Thinking through the implications both positive and negative, ideating on possible alternatives, considering the purpose and motivation behind the research and innovation and judging it with the lens of ethics and values
- Aligning research and innovation to societal needs
- Being responsive and taking actions in light of issues that emerge out of the foresight, reflective and engagement exercises**.**

The concept of RI has entered the policy arena where many other related concepts already existed. If we examine the range of available concepts related to governance of innovation, such as sustainable innovation and green chemistry, and prevention and management of risks, various frameworks to report and monitor company's performance on social and environmental aspects, voluntary codes of

conduct for fair business practices, and guidelines and standards of industry practice, we find a complicated web where there are similarities of intention, and overlapping and criss-crossing of ideas. Some of these concepts relate to nanotechnology, such as, the EC-Code of Conduct on Responsible Research and Development of Nanotechnology, and some relate to the voluntary practices existing in the chemical arena: 'responsible care', green chemistry. RI is therefore a meta- or uber- concept which brings together and unites various activities from divergent fields of sustainability, ethics, and stakeholder engagement, and the various actors engaged in research and innovation and actors engaged in governance and regulation of innovations allowing implementation of an overarching framework. I will argue in Chapter 6 how these existing concepts can be used in addition to some new aspects to operationalise RI.

To recapitulate, my questions focused on developments in nanotechnology-enabled medical applications, and I explore the possible future implications, especially the environmental implications, of nanomedicine. Many nanomedicines are yet at the proof-of-concept stage, and I decided to check whether the existing governance frameworks dealing with risks are fit for nanomedicine. Also, I discuss the broader concept of governing innovation rather than governing risk.

The above intentions, namely keeping abreast of developments in nanomedicine, exploring future implications, assessing the existing regulatory frameworks, and discussing the governance of innovation, crystallised into the following objectives:

- To critically review the existing literature on pharmaceuticals and nanomaterials in the environment, to review the current scenario of regulation in medicine and medical devices, and to ascertain the developments in nanomedicine.

- To estimate prospective environmental concentrations of nanomedicine and, based on the predicted releases, perform a risk assessment.
- To ascertain stakeholder views on the potential environmental risks of nanomedicine and the adequacy of current risk governance frameworks to manage these risks.
- To explore the construction of the concept of RI by experts in the nanomedicine innovation chain.

Suitable methodological approaches and methods to fulfil the objectives are described in the next chapter.

Chapter 3: Methodology

The purpose of this chapter is: first, to outline the overall research approach; second, to describe the process of collecting secondary and empirical data; third, to describe the methodological approach to analyse the empirical data; and, fourth, to inform my positionality which is likely to influence the interpretation of the study data.

3.1 Overall Research Approach

The central purpose of this thesis is to explore anticipatorily the possibility of future environmental risks from nanomedicine and to add insights to the evolving framework of Responsible Innovation in order to make it applicable for nanomedicine. I use numerical data from literature to mathematically estimate prospective environmental concentrations (from nanomedical uses) to support environmental risk assessment of gold nanoparticles used in nanomedicine, and supplement this with narratives from expert interviews regarding their perceptions on (potential) environmental implications of nanomedicine and their thoughts on the adequacy of current regulatory frameworks for assessing environmental risk from nanomedicine. I also use textual data from the interviews to understand perceptions of interviewees and to make recommendations and proposals on how RI can be conceptualised (operationalised) for the nanomedicine sector. The majority of data for the qualitative part comes from a series of 62 in-depth interviews with various experts conducted over a period of 2 years and 4 months. Additionally, I analysed peer-reviewed literature from the sciences and the humanities, policy documents, and grey literature

such as company web pages, blog posts, news, and newsletters of professional networks, give context to the study as well as to draw conclusions.

The thesis is an exploratory 'embedded' case study using mixed methods approach. By embedded case study, I mean that the thesis overall assesses the nanomedicine sector as a case study for operationalisation of RI, and embedded within that, gold nanoparticles from medical applications was used as a case to explore possible future environmental implications from nanomedicine and to report on the data gaps and uncertainties for modelling and predicting potential impacts.

The study applies a mixture of methods, methodologies and paradigms (Creswell and Clark, 2007, p.5) to be able to address the evolving research objectives and the central purpose of the research. The reason for adding the quantitative component was to help address different objectives for the sake of 'completeness' and for 'improving the usefulness of findings' to the 'practitioners' (Bryman, 2006, p. 106) and to appeal to the broader audience of the nanomedicine innovation sector.

3.1.1 Case Study Research

The study was conceived as both a descriptive and an exploratory case study to explore the possibility of environmental implications arising as a consequence (unintentional side effect) of the widespread use of nanomedicine and to add insights to the evolving framework of RI. The approach is descriptive because a reference model developed by Gottschalk and Nowack [60] was used that guided data collection

[60] More details regarding the reference model in Chapter 4. The model developed by Gottschalk and Nowack (2009) is a probabilistic mass flow model. GOTTSCHALK, F., SONDERER, T., SCHOLZ, R. W. & NOWACK, B.

(Scholz and Tietje, 2002, p.12) to facilitate the prediction of environmental concentrations of nanomedicine and to perform a probabilistic risk assessment. It is exploratory because this research can be considered as a 'pilot study' to guide future research based on filling knowledge gaps and uncertainties identified through the research, strategies, directions and investments in research. Also, Scholz and Tietje (2002) categorise the type of research that is done in this study as 'groundbreaking' research because the initial and final state is not known, and the barriers that need to be crossed in order to reach the final state are unknown (Scholz and Tietje, 2002, p. 26). They argue that ground breaking case study methodology is suitable for environmental sustainability projects because of the multiple disciplines and complex problems (Scholz and Tietje, 2002, p.27). The unit of analysis here is the nanomedicine research and innovation sector.

As mentioned in Chapter 1, to explore the environmental impacts of nanomedicine, Au-NP was taken as a case study because of its potential for an exponential increase in use in the health care sector. Moreover, in terms of environmental risks, studies on potential flows and concentrations of Au-NP in anthropogenic and ecological systems are non-existent. Overall there is limited environmental hazard data and no exposure data, making risk assessment highly problematic. Hence, it was timely to model their environmental flows and concentrations to help frame the risk analysis (Owen and Handy, 2007; Pastoor et al., 2014), as has been done also for other nanomaterials (Gottschalk et al., 2009; Keller et al., 2013; Keller and Lazareva, 2014; Sun et al., 2014).

2009. Modeled Environmental Concentrations of Engineered Nanomaterials (TiO2, ZnO, Ag, CNT, Fullerenes) for Different Regions. *Environmental Science & Technology,* 43**,** 9216-9222.

Qualitative research is generally flexible and is not prescriptive and the methodology should be responsive to the evolving nature of the project. *"The purpose of qualitative interview is not to discover how many, and what kinds of, people share a certain characteristic....it is categories and assumptions not those who hold them, that matter. In other words, qualitative research does not survey the terrain, it mines it."* (McCracken, 1988, p.17).

Both qualitative research and case study research have been criticised because of their so called 'shortcomings' – no fixed methodology, various definitions, flexible, subjective – and many discussions have happened in the sociological literature. Here, I am inspired by McCracken's take on quantitative verses qualitative research:

"The quantitative researcher uses a lens that brings a narrow strip of the field of vision in to very precise focus. The qualitative researcher uses a lens that permits a much less precise vision of a much broader strip." (McCracken, 1988, p.16)

I use quantitative research to focus on the single dimension of anticipating environmental risks from nanomedicine but then use qualitative research to broaden the vision (albeit maybe a less precise vision) to suggest how to direct research and governance in nanomedicine in the "real life context" (Yin, 2009, p.18) so that the goals of safeguarding society and the environment is achieved whilst also allowing innovation to flourish. Moreover, this mixed methods case study research strategy gels well with interdisciplinary research.

One of the long-time defenders of case study research is Bent Flyvbvjerg. Box 3.1 provides the five popular misunderstandings about case study research as summarised by him (Flyvbjerg, 2006) and argues the importance of context

dependent knowledge and the subsequent expertise that gets built from it. Although case studies have been criticised for their lack of generalisability, and qualitative research's aim is also not one of generalisability, I have the aspiration that the findings of my case study can be generalised and that they are influential for other studies, e.g., operationalising responsible innovation in finance, and online retail.

Box. 3.1 Five misunderstandings about Case Study research (Flyvbjerg, 2006)

1. In general, theoretical (context-independent) knowledge is more valuable than concrete, practical (context-dependent) knowledge.

2. One cannot generalize on the basis of an individual case; therefore, the case study cannot contribute to scientific development.

3. The case study is most useful for generating hypotheses; that is, in the first stage of a total research process, while other methods are more suitable for hypotheses testing and theory building.

4. The case study contains a bias toward verification, that is, a tendency to confirm the researcher's preconceived notions.

5. It is often difficult to summarize and develop general propositions and theories on the basis of specific case studies.

3.1.2 Research scope

Within the three broad aspects of nanomedicine – drug delivery/therapeutics, diagnostics, and regenerative medicine – I have focussed on the first two. Regenerative medicine was not included in the ambit of my study because it has more cross linkages with biotechnology and tissue and cell engineering. However, the idea to exclude regenerative medicine came later in the design of the PhD research. The reasons to exclude regenerative medicine were manifold, but the main one was to prevent the scope from becoming unmanageable. Furthermore,

regenerative medicine involves different sciences (more molecular and cell biology and biotechnology based science, hence falling under the remit of BBSRC and MRC in funding, and less chemistry and physics and material sciences —the mandate of EPSRC). The leaning towards EPSRC was because of the ease of participant recruitment for interviews and because of the leadership position the Council took in embedding RI principles into its research funding strategy for emerging technologies. The EPSRC had conducted a series of public dialogues on nanomedicine in 2008 (Bhattachary et al., 2008) and devised its research call in 2009 on nanotechnology for health care accordingly (Jones, 2008). Additionally, the Council designed the call in a stage-gated framework, whereby after the initial three years of funding by EPSRC, the projects having potential needed to collaborate with industry to continue to the second phase which was to be funded primarily by TSB, thus, in principle, driving the translation from the lab to clinic or commercialisation.

In the case of the quantitative study, the geographical boundary is the UK and the US. The reasons for selecting the US as the spatial boundary for the mathematical model to estimate environmental concentrations of nanomedicines are: 1) the US has consistently the highest R&D expenditures, including industrial R&D, for the pharmaceutical sector in the world; 2) It is the world's largest market for pharmaceuticals (EC, 2013a); 3) he environmental variability can be extrapolated to other countries and; 4) a pragmatic point, the move of the lead supervisor to the US led to the inclusion of US in the geographical boundary.

The choice of UK was obvious: the majority of the data for the qualitative research was gathered from interviews conducted with experts residing in the UK. Furthermore, in the UK, pharmaceutical R&D was 28% of the total business R&D of

around £17.5 billion in 2011 and 64% of all total R&D undertaken in the country (NAO, 2013). Moreover, the UK generally has high industrial R&D spends; in 2013 it topped industrial R&D spend in the EU (EFPIA, 2013). It is the fifth largest pharmaceutical market in the EU (EFPIA, 2013). In the medical device sector, around 3,300 companies have a presence in the UK with a combined annual turnover of £17 billion (HM Government, 2013).

The temporal aspect of conducting the study and the geographical coordinates can be considered as limitations, however, the strength of case study research is that it can help to feed back into a preliminary framework like RI or can act as a test case to understand how the framework can be operationalised. Nanomedicine can be thought of as a 'post-normal' science (Funtowicz and Ravetz, 1991) so a variety of viewpoints need to be captured and included, which can inform decision making and help formulate better policies.

3.2 Overall method to gather secondary data for the research

My aim was to gather an empirical base sufficiently broad to be able to weave the various concepts and findings of the individual research objectives and make the generalisations intriguing and applicable to different industrial sectors, different firm sizes – SMEs and larger firms, small laboratories to multidisciplinary research and development (R&D) centres, and different types of organisations – national funding agencies, bilaterals and multilaterals. I wanted to move from the lens of application of nanotechnology for medical purpose to the 'ensemble' of nanomedicine-society-economy-environment.

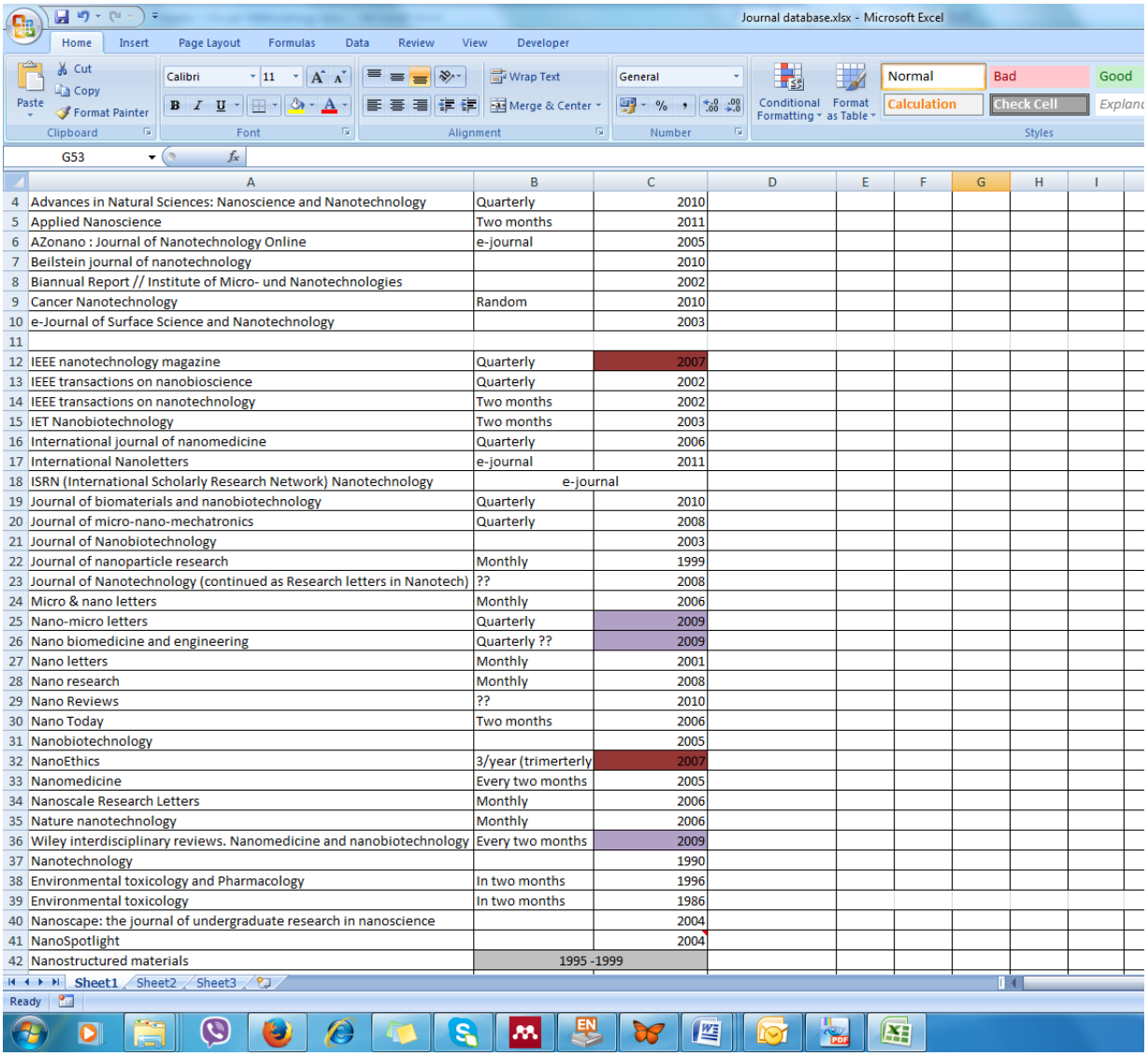
3.2.1 Developing theoretical sensitivity

In the initial phases, I identified journals related to 'nanotechnology' and scoped each of these publications to gauge their coverage of nanomedicines. I kept a track of the issues that I read. Figure 3.1 is a snapshot of the journal list created in order to keep myself abreast of the recent developments in nanomedicine. I also registered with Zetoc Alert (a search service for research publications globally) to receive email bulletins on recently published articles, and signed up for pharmaceutical newsletters, for example Nanowerk, FiercePharmaMarketing, FierceDrugDelivery, and Evaluate Pharma. I also got access to the subscription database of 'Citeline' and 'Adis R&D Insight' during winter 2012-13, which enabled research on Objective 2 of the thesis.

I attended two conferences related to nanomedicine – *4th European Conference for Clinical Nanomedicine* (May 2011, Basel, Switzerland) and *9th International Symposium on Polymer Therapeutics From Lab to Clinical Practice* (May 2012, Valencia, Spain) - which helped me to gather the trends in nanomedicine and one training programme - *Nanomedicine: what is it and how can it help the patient?* (22 March 2011, Glasgow, UK). I also attended the inaugural meeting and launch of the British Society of Nanomedicine, in Liverpool on 15 and 16 October, 2012 and the *6th International Conference on the Environmental Effects of Nanoparticles and Nanomaterials* (September 2011), in London which helped me to strengthen my conceptual knowledge and gave me a good foundation for the issues and challenges facing the EHS community. The NanoKTN[61] online membership was very helpful to keep abreast of UK nanomedicine developments. The team at NanoKTN uploaded

[61] NanoKTN: Nanotechnology Knowledge Transfer Network. This is UK's knowledge-based networks for micro and nanotechnologies.

the presentations of events organised by them on the web which are freely available to its members.



Journal database.xlsx - Microsoft Excel

	A	B	C
4	Advances in Natural Sciences: Nanoscience and Nanotechnology	Quarterly	2010
5	Applied Nanoscience	Two months	2011
6	AZonano : Journal of Nanotechnology Online	e-journal	2005
7	Beilstein journal of nanotechnology		2010
8	Biannual Report // Institute of Micro- und Nanotechnologies		2002
9	Cancer Nanotechnology	Random	2010
10	e-Journal of Surface Science and Nanotechnology		2003
11			
12	IEEE nanotechnology magazine	Quarterly	2007
13	IEEE transactions on nanobioscience	Quarterly	2002
14	IEEE transactions on nanotechnology	Two months	2002
15	IET Nanobiotechnology	Two months	2003
16	International journal of nanomedicine	Quarterly	2006
17	International Nanoletters	e-journal	2011
18	ISRN (International Scholarly Research Network) Nanotechnology	e-journal	
19	Journal of biomaterials and nanobiotechnology	Quarterly	2010
20	Journal of micro-nano-mechatronics	Quarterly	2008
21	Journal of Nanobiotechnology		2003
22	Journal of nanoparticle research	Monthly	1999
23	Journal of Nanotechnology (continued as Research letters in Nanotech)	??	2008
24	Micro & nano letters	Monthly	2006
25	Nano-micro letters	Quarterly	2009
26	Nano biomedicine and engineering	Quarterly ??	2009
27	Nano letters	Monthly	2001
28	Nano research	Monthly	2008
29	Nano Reviews	??	2010
30	Nano Today	Two months	2006
31	Nanobiotechnology		2005
32	NanoEthics	3/year (trimerterly	2007
33	Nanomedicine	Every two months	2005
34	Nanoscale Research Letters	Monthly	2006
35	Nature nanotechnology	Monthly	2006
36	Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology	Every two months	2009
37	Nanotechnology		1990
38	Environmental toxicology and Pharmacology	In two months	1996
39	Environmental toxicology	In two months	1986
40	Nanoscape: the journal of undergraduate research in nanoscience		2004
41	NanoSpotlight		2004
42	Nanostructured materials	1995 -1999	

Figure 3.1: A screenshot of the journals used for the review of nanomedicine literature.

I adopted a similar methodology for the scientific fields of environment and nanomaterials and pharmaceuticals to keep me updated with recent research in environmental concentration, fate and behaviour of nanomaterials and

pharmaceuticals. This research work and networking activities helped me identify the experts in the fields related to my research study for interviewing.

The approach to the qualitative part of the literature review was more intuitive rather than structured in the initial five months of starting the research. Nanotechnology and ethics was in the domain of the journal: Nanoethics and a variety of bibliometric related studies and some qualitative studies were published in the Journal of Nanoparticle Research; from these two journals I was updated about the discussions in nanotechnology advances, risks and governance issues. My introduction to the field of Science, Technology and Society (STS) was through the article on anticipatory governance by Karinen and Guston (2010a), and gradually I made myself aware of the key concepts in this field and came to know the leading researchers in the EU and the US. Furthermore, I attended the workshop "*A New Mandate? Research Policy in the 21st Century*" on 24 March 2011 in London and I was selected to attend the inaugural Winter School arranged by the Center for Nanotechnology in Society at Arizona State University in the Anticipatory Governance of Emerging Technologies, held in, 2013, which helped me to understand the dominant and emerging thoughts from the STS and science policy communities. Towards the end of 2013, I started following twitter updates; blogs from the social scientists involved in emerging science and technologies and registered to various email lists of EU projects related to RI.

3.2.2 Approach to collect data for the quantitative study

Details of the methodological approach and secondary data collection methods for the quantitative study are described in Chapter 4 and the annexe to it. Briefly, geographical regions of the UK and the US (excluding dependent areas) were the units of analysis for the study, to prospectively estimate the environmental concentration of Au-NP from select medical applications and to conduct a preliminary risk assessment. Since no measured environmental concentration data is available for Au-NP, probabilistic material flow analysis has been used (Gottschalk et al., 2010a) to track the flow and fate of Au-NP during use and disposal as a first step to establish the possible future baseline in a worst case Au-NP release scenario. This approach attempts to address the uncertainty and variability in the data by creating probability distributions for all input data as has been described before (Gottschalk et al., 2010a; Gottschalk et al., 2010b). Where there is limited toxicity data and where experimental procedures and methodologies have variability, use of probabilistic/stochastic methods to establish and quantify environmental risks can help to increase the robustness of the risk quotients. Thus, probabilistic species sensitivity distribution (pSSD) was used to quantify ecotoxicological risks, and comparing the modeled PEC to the predicted no adverse effect concentration (PNEC) based on toxicity data for the corresponding environmental compartment (Gottschalk and Nowack, 2013) forms the basis of my approach to derive risk levels for the ecosystem.

An extensive literature search (conducted between Dec 2012 and April 2014) was carried out to identify relevant peer-reviewed scientific publications of Au-NP or gold colloids in the medical field to extract administration doses, distribution, excretion,

environmental fate and behaviour, and environmental toxicity data. To gather data for environmental and technical compartments, in addition to reports by various Government Departments and Agencies, I consulted relevant experts in the field and the grey literature. Further details on the methodology are in Chapter 4.

3.3 Collection of Empirical Data

3.3.1 Details of Questionnaire

I used a questionnaire (which was shared in advance with the interviewees) to guide the interview and followed a semi-structured style of interviewing because it allows enough flexibility to follow a conversational mode whereby the questions can be answered without the need to follow a strict order. The initial questionnaire of each stakeholder group was long and had around 20 questions, derived from issues identified in my literature review (part of which is published in Mahapatra et al. (2013)). The questions were related to projects being done by the upstream[62] experts; their perceptions on nanomedicine patents, the stage-gating approach to funding adopted by EPSRC, and the challenges and opportunities regarding translation of nanomedicine from laboratory to clinic; their views on the EC's definition of nanomaterials, labelling of nanomedicines, funding scenario, and other similar questions. Furthermore, the questionnaire was customised to each

[62] I refer to Powell's (2007) description of scientists' 'location'. She describes upstream scientists as scientists "who design and develop new (and usually synthetic) materials". They are typically engineers, chemists, physicists, and materials scientists. According to her, downstream scientists usually have little to do with creating new materials and technologies. They are toxicologists, epidemiologists, and other public health scientists who study the health and environmental effects of materials that have found their way into the environment or human bodies, or environmental chemists and engineers who monitor where these materials are and how they are transformed in the environment. (p. 175). Though I have adopted these two terms to convey the predominant research background of the scientist, I do not endorse them. POWELL, M. C. 2007. New risk or old risk, high risk or no risk? How scientists' standpoints shape their nanotechnology risk frames. *Health, Risk & Society,* 9**,** 173-190.

interviewee's expertise. For example, for the UK RCs, some of the questions which I asked were questions on their funding strategies with regard to nanotechnology, their considerations regarding environmental hazards and risks in funding projects related to nanomedicine, the definition of 'nano' in the selection criteria of the projects, and their opinions regarding the adequacy of regulatory frameworks. Some common questions remained the same across a stakeholder group. The questionnaires for each stakeholder groups were reviewed by my PhD supervisors and advisors to the project. Some questions on patenting and translation I found were a challenge to get answers to; [63] moreover, the issues regarding product approval and patenting and translation were not relevant to the expertise of 'downstream' scientists and hence were later dropped from the questionnaire. Similarly, some questions evolved over time, for example, one question evolved from RI in medicine to a non-context specific question on RI.

The interviews with various stakeholders were distributed and interspersed over the timeline. With each interview, I learnt about the interviewee's level of comfort with the questions belonging to a particular stakeholder group. I asked questions based on the level of comfort, knowledge and expertise of the interviewee which I assessed while interviewing. Hence, I followed a more 'adaptable method' (Mach et al., 2005) of interviewing. Also, I gradually developed more focus in the research questions and realised that the less questions I ask the more clarity I will have. Hence, I prepared an abridged questionnaire with common questions to act as a checklist for me (see annexe to this chapter for the set of questions which formed this abridged questionnaire) which were important to be asked to all the interviewees to fulfil the

[63] I found it very hard to get answers to the question which was constructed to explore challenges with regard to product approval and patenting in the existing regulatory framework.

research objectives. This helped to steer the conversation (even though the full length questionnaire was with the interviewee and me) while maintaining a flexible style of interviewing. Along with the individually customised questionnaire which was emailed to the expert in advance, I provided additional documents if I felt that a term might not be known by an expert. For example, I provided a document detailing Technology Readiness Levels (TRLs) and also provided EMA's Environment Risk Assessment Guideline for pharmaceuticals for human use.

After a few initial interviews, with each stakeholder group, I started giving examples for specific questions. For example, rather than directly asking whether nano-enabled medical products would give rise to environmental hazards and risks, I framed the question by giving examples of some nanomedicines in clinical trials.

The PhD research design and associated details were submitted to, and approved by, the University of Birmingham's ethical review process.

3.3.2 Details of Interviews

62 in-depth interviews with various experts with different disciplinary backgrounds involved in aspects of nanomedicine (development, commercialisation, funding, risk governance, innovation policy) were conducted based on a pre-set questionnaire. Among those interviewed, 20 were from the nanomedicine research community of which five were academics who had established or were part of spin-off companies or used to work in the health care sector. The other experts interviewed belonged to the field of human toxicology, ecotoxicology, or were representatives of policy making bodies in the UK, Research Councils (RCs), and regulatory bodies. Clinicians and

patients are a notable exception to the choice of stakeholders. Although nanomedicines have been approved and are currently in use in the UK, in my experience general patient facing clinicians are not aware of the developments in nanomedicine. Clinicians are generally more concerned with effectiveness of a particular medicine. Moreover, in the UK, because of the public health care system, different governance structures are in place when compared to the US. The National Institute for Health and Care Excellence (NICE) approves the medicines to be used in hospitals and hospitals procure medicines based on their annual budget. Generally, non–research based clinicians are not involved in the process of selecting medicines. Also, the aim was to keep a manageable sample size keeping in mind time constraints. Most of the interviews conducted were with well established experts in the UK; however, five interviews were with leading academics located in mainland Europe.

Figure 3.2 gives a distribution of interviewees' research foci. Representatives of RCs were either Heads of Departments or Programme Managers of nanotechnology related funding in health care or the environment. The industry representatives were a mixed group; they were CEOs, Technology Managers, Directors or Heads of Departments. Similarly, the representatives from the Regulatory bodies were also from various seniority levels, they ranged from Heads of Departments or Thematic Areas to Managers, Senior Scientific Officers or likewise. Of the 38 academics I interviewed, 27 were Professors and the remaining were Lecturers or Senior Lecturers (well known in their communities), and in the case of nanomedicine-focused scientists they were Principal Investigators (PIs) of grants from the EPSRC.

Therefore, I classify all the interviewees as eminent experts (except one interviewee who was at the initial stages of her/his career).

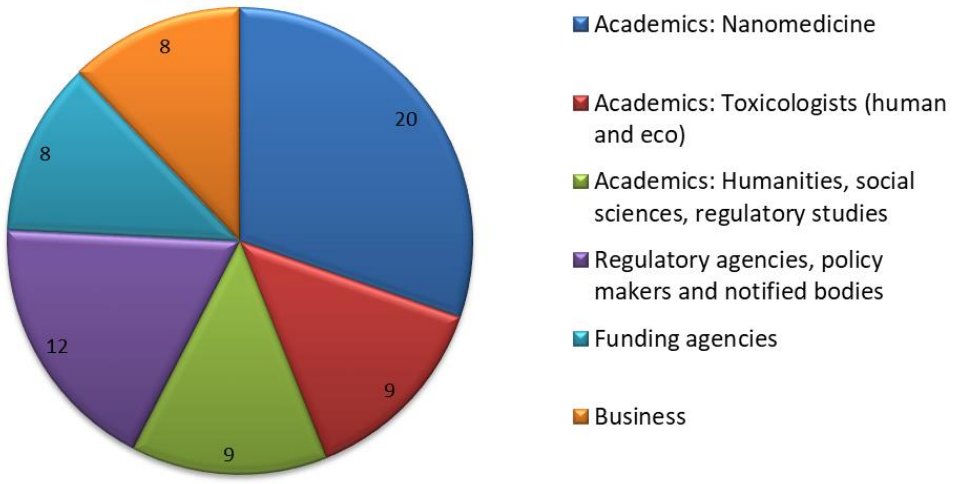


Figure 3.2: Number of academic experts interviewed and their broad research areas and number and details of other stakeholders (Total: 66 interviewees).

3.3.3 Selection of Interviewees

The knowledge gained from reading peer-reviewed literature, funding agency websites, newsletters, blogs, and networking at conferences helped to identify key experts in academia, industry and regulatory areas who could be approached for interviewing on nanomedicine. To begin the academic interviews, the scientists contacted were Principal Investigators (PIs) of the EPSRC nanotechnology grand challenge healthcare call. [64] Other than EPSRC funded PIs, more scientists researching in nanomedicine [65] were identified from the published literature (last

[64] The Research Councils UK had identified (2007−2008) nanoscience and nanotechnology as one of the priority themes of research and within which they funded three areas related to the challenges facing 21st century society: Nanotechnology for Healthcare; Nanotechnology for the Environment and Nanotechnology for Energy.

[65] The Journals covering the nanomedicine literature was vast since nanomedicine is multidisciplinary in nature with physics, chemistry, biology, materials science, electronic engineering, biotechnology, etc. and hence published papers were found in various Journals. However, some journals such as Journal of nanotechnology, nanomedicine and biology, Advance drug delivery reviews, and Nanomedicine were found to be very useful.

authors or corresponding authors or well established / leading scientists in their domains – suggestions regarding nanomedicine scientists from the initial interviewees helped confirm these selections), information available online with regard to various conferences, and the speakers advertised or the members of the advisory board of the conferences. Cross-referencing searches were also done to find relevant literature to help conceptualise how the proposed framework for RI could be made useful to the health care industry.[66] Scientists researching on human and eco-toxicological aspects of nanomaterials were identified from the literature (and whom I considered were relevant to my research) and then were contacted via email with the request for interview after discussion with supervisors. Similarly, scientists researching on science, technology and society studies and on the topic of RI were identified through their conference presentations or from published papers and contacted to check whether they would be willing to take part in the study. The regulatory agencies that I selected to interview were the agencies involved in the pharmaceutical R&D and approval of products and manufacturing. The industry representatives were identified from the list of industries funded by the TSB under the call for proposals titled "Nanoscale Technology Enabled Healthcare: Building the Supply Chain competition for collaborative R&D funding". Some industries were identified from the NanoKTN website.

Two interview participants also helped me to recruit industry participants to the study. Of the 74 experts directly contacted (an additional 9 experts were contacted because their names were referred to by the direct contact, therefore in total 83 professionals were contacted), 59 agreed to an interview and seven of their colleagues were also

[66] Health care industry here means only pharmaceutical and medical diagnostics and device industries.

interviewed either individually or were present in the interview. Of the three academic experts whom I contacted and who didn't respond to my mails, one expert was researching on regenerative medicine (regenerative medicine was subsequently excluded from the research scope and hence I didn't follow up with this expert). The others either refused because they expressed their limited involvement in nanomedicine[67] and the remaining refused due to lack of time. The technique of interviewing consisted of three styles: face to face, over phone and Skype, and email interviews. 44 expert interviews were conducted in person in a location that suited them, 14 interviews were conducted over phone, 6 over Skype and 2 via email responses to the questions. It is acknowledged that responses to interview questions via email limit the inferences that can be drawn from it. The face-to-face interviews gave a chance to have a more open and free discussion with some exploratory questions when it was found that more information was needed to better discern the meaning.

The academics and professionals interviewed are all well recognised in their respective disciplines. The industry representatives interviewed were also actively engaged in the nanotechnology discussions. To get information about companies who were manufacturing nanomaterials for nanomedicine and contact details of the right person took time as has been experienced by other researchers (Engeman et al., 2012). Interview durations ranged from 0.5 hrs[68] to 2.5 hrs since the questionnaires included questions which related to the interviewees' experiences and

[67] Experts whom I contacted were all involved in nanotechnology in health care, however, the poorly defined and multidisciplinary nature of the field, could provide reasons for experts to refuse interviews. I considered it inappropriate to write back to the expert about their co-authored publications, about them being part of consortia in nanomedicine related projects or their conference presence.

[68] Only one interview was of 0.5 hrs. The phone connection was not good and the recording had a lot of background noise. Eventually this interview could not be transcribed fully and only key notes are kept as a record. This interview was with an expert of one of the funding agencies; a second interview was arranged with another expert from the same funding agency.

project details and interviewees were free to talk about their projects. Interviews were conducted in the period from 12 May 2011 to 12 September 2013.

To prepare myself for each interview I read details of the nanomedicine research project funded by EPSRC for which the interviewee was the PI. I also read 4−6 key publications by the expert to be abreast of their work. However, mid-way through the interviews I realised that the background knowledge was not needed and I prepared myself less for subsequent interviews with interviewees selected from the nanomedicine field. Each interview was exhausting and I realised later that the entire day had only the interview as the productive output. McCracken shares his own experience about the exhaustion and suggests it is due to the immense effort spent on the "listening process" (McCracken, 1988, p.39). However, despite the energy drain, I enjoyed the interviews because all the interviewees were open and forthcoming once into the discussion and didn't make me feel like an outsider.

The social scientists were aware of the key tenets behind RI. This could be due to both selection bias and the interconnectedness in the STS group and interviewees awareness of the discussions regarding the 'new' framework of governance of innovation which was being developed at the time the interviews were conducted. This also reflects the fact that RI was an agenda pursued by social scientists or 'downstream' scientists. However, I wanted to explore their views on the question of RI (in the nanomedicine context) in order to add to the range of views and capture their thoughts when expressed in a conversation. I asked them their views on the RI, how it was different from the existing concepts of governing science and technology and how RI could be implemented.

3.3.4 Access to Interviewees

As mentioned earlier, all except one interviewee can be classified as an eminent interviewee. I identified the experts I wanted to interview and mails were sent by my supervisors to most of them explaining my PhD topic and requesting an interview.[69] After securing 2−3 interviews I could gather additional interviews based on references made by the interviewed experts. The academics were supportive of being interviewed and it was a pleasure to receive their encouraging responses. I lost an interview conducted with a nanomedicine expert and the expert non-hesitantly gave a repeat interview. Similarly, there was a lot of background noise in another interview conducted over Skype and I was once again granted another interview. However, as would be the case, the answers I had in my handwritten notes while conducting the first interview was slightly different when I interviewed the expert the second time.

Out of the 17 industry representatives or consultants working closely with industries that I contacted, I interviewed eight of them. [70] I had met four industry representatives at conferences and meetings and secured two interviews (one of them finally declined after many email exchanges and one didn't respond to my mails). After the first four interviews, the industry was most difficult to access; however, finally I shared my background of working with industries to establish contacts and assured firmly of confidentiality and anonymity. Interviews with half of the industry representatives took place between June 2013 and September 2013, the

[69] With each stakeholder group, the first mails of introduction were sent by my supervisors.
[70] Two out of the eight industry representatives were program managers of specific themes of the NanoKTN. There were chosen because of their close relationships with industries and with the idea that they can be valid representatives of the stakeholder group – industry.

final stages of the entire duration spent on data collection. To contact the TSB funded industries, I used the reception number as given on the website or sent a mail. Generally I got a response from the receptionist; however, there were delays to actually speaking to the expert as I was informed that the person I wanted to get in touch with was busy in meetings or travelling. Finally I got responses after frequent and regular follow-ups. A couple of introductory emails to nanomedicine companies were also sent by Industry 04 (one of the industry representatives I had met early on at a meeting). Some industry representatives declined to be interviewed by citing the reason that they cannot add value to my study because they were not directly involved in nanomedicine. Table 3.1 provides an idea of the number of interviews as per stakeholder category and dates of the interviews.

Table 3.1: List of interviews conducted arranged as per stakeholder category

Discipline	Name	Date of interview
Nanomedicine Scientists	NMS01	12 May 2011
	NMEn02	12 May 2011
	NMS03	16 May 2011
	NMS04	17 May 2011* & 29 July 2011
	NMS05	08 September 2011
	NMS06	01 November 2011
	NMEn07	02 December 2011
	NMS08	17 January 2012
	NMS09	27 January 2012
	NMEn10	27 January 2012
	NMS11	14 March 2012
	NMEn 12.1+ NMS12.2	30 March 2012
	NMS15	16 July 2012
	NMS16	16 October 2012
	NMEn17	31 October 2012
	NMS19	06 November 2012
	NMS18	02 November 2012
	NMS13	14 March 2012
	NMS14	29 May 2012
Total		***19***

Toxicologists	ETOC1	15 February 2012
	HTOC1	13 August 2012
	HTOC2	15 August 2012
	ETOC3	05 September 2012
	ETOC4	08 October 2012
	HTOC3	19 October 2012
	ETOC5	23 October 2012
	HTOC4	30 October 2012
	ETOC6	05 December 2012
Total		***9***
Social scientists	SS01	11 September 2012
	SS02	09 November 2012‡ & 08 July 2013
	SS03	17 October 2012
	SS04	24 October 2012
	SS05	25 October 2012
	SS06	14 November 2012
	SS07	15 November 2012
	SS08	11 July 2013
	SS 09	02 August 2013
Total		***9***
Regulatory Agencies and Policy makers	Regulator 01	14 November 2011
	PP1.1	14 December 2011
	PP1.2	14 December 2011
	PP2.1	20 December 2011
	PP2.2	20 December 2011
	Regulator 02	27 January 2012
	Regulator 03	02 February 2012
	Regulator 04	24 August 2012
	Regulator 05	13 November 2012
Regulatory Toxicologist	PP2.3	20 December 2011
Total		***10***
Funding agencies	RC01	24 April 2012
	RC02	22 May 2012
	RC03	06 June 2012
	RC04	19 June 2012
	RC05	15 October 2012
	RC 6.1	15 July 2013
	RC 6.2	12 September 2013
Total		***7***
Industry	Industry 01	03 May 2012
	Industry 02	09 July 2012
	Industry 03	13 July 2012

	Industry 04	12 November 2012
	Industry 06	17 July 2013
	Industry 05	12 July 2013
	Industry 07	30 July 2013
	Industry 08	07 August 2013
Total		***8***

*The recorder containing the first interview with NMS 04 was lost. Hence, a repeat interview was done.
‡Due to Skype disturbances, there was lot of noise in the recoding. Hence, a repeat interview was done.
Note: When two or more interviewees were interviewed from the same organisation, the numbering is X.1, X.2, and X.3.
Abbreviations: NMS - nanomedicine scientist; NMEn - nanomedicine entrepreneur; HTOC- Human toxicologist: ETOC - Ecotoxicologist, RC - Research Council; SS - Social scientists; PP - policy makers.

3.3.5 Style of Conducting Interviews

Around 65% of interviews were conducted face-to-face. This helped to have a more open and free discussion with some exploratory questions when I found that more information was needed which could help me to better discern the meaning. The interviews began with the typical structure of a qualitative interview where the research purpose and aims were discussed once again (the introductory letter sent to the experts contained the objectives of the research) with the interviewee and their right to confidentiality and anonymity was confirmed.

When representatives from the research councils, regulatory bodies and health and safety agencies and industries were interviewed, their viewpoints might not reflect their organisation's stand /opinion because in order to follow a conversational style, sometimes, they were asked to share their personal opinion and views. However, a mixed style of interviewing was followed with both verbatim reading of questions and conversational style which allowed me to probe further meanings when possible.

Some interviews had breaks with tea/coffee and a walk through laboratories, thus allowing me to get acquainted with the EPSRC funded projects that the scientists were doing, and over these informal settings I learnt a different dimension about my research. For example, the idea that working on health issues itself is responsible research; a polite mention about contextualising the environmental risk implications of nanomedicine against conventional chemicals.

3.4 Qualitative Data Analysis Methodology and Approach

The interviews were transcribed verbatim. Out of the 62, I transcribed 34 interviews and gave the remaining interviews to professional transcribers to create distance from the text. I was gaining too much familiarity with the text because of the transcribing process which hampered my objectivity while interviewing. Since the transcribers were not aware of the many technical terms used, which was compounded by various accents of interviewees, I had to revise and fill in the gaps of each outsourced interview. I did this after I completed all interviews in September 2013.

I used qualitative content analysis since I was not trying to develop a theory or test a hypothesis. Cho and Lee (2014) argue why qualitative content analysis is best suited for novice researchers. I used both inductive and deductive approaches in content analysis. For research objective 3,[71] I used the general inductive approach which is suitable for researchers who have the philosophical stance of a critical realist due to the absence of pre-existing codes or influence from theory. For research objective

[71] Objective 3: To ascertain stakeholder views on the potential environmental risks of nanomedicine and the adequacy of current risk governance frameworks to manage these risks.

4,[72] I used both deductive and inductive approaches to data analysis, whereby I defined some specific categories beforehand – the categories were the four dimensions of RI (Owen et al., 2013b): anticipatory, reflective, inclusive or deliberative, and responsive – and is the governing theoretical framework, and let the others emerge from the data. I primarily used directed content analysis. Directed content analysis can be used when "existing theory or prior research about a phenomenon is incomplete or would benefit from further description," with the goal "to validate or extend conceptually a theoretical framework or theory" (Hsieh and Shannon, 2005, p. 1281). The coding was not done by using any of the available qualitative software. I used MS Word highlighting tool to develop my codes. I printed the transcribed interviews and while reading them underlined sentences and phrases which seemed important and made notes in the margins. After reading each transcript 5−6 times (and revisited the empirical data many times while writing the thesis), I teased out recurrent themes and concepts, and using various colours in the highlight option of MS Word, highlighted the key categories which emerged. I compared the interview data with the literature to develop the results which are presented in Chapters 5 and 6.

3.5 Positionality and Reflexivity

Before explicating about my position, I will say that I am not inventorying where I stand but am putting forth my prejudices, biases and beliefs arrived at by self-reflection and which will undoubtedly colour my conclusions.

[72] Objective 4: To explore the construction of the concept of RI by experts in the nanomedicine innovation chain.

3.5.1 My belief system and philosophical stance

I believe that we are multidimensional beings and we can hold multiple viewpoints and we juggle between them depending on the context that we are in. Also, these viewpoints and positions do change with time as learning gets deeper and broader. My roots in the eastern philosophical tradition and teachings influence my belief systems. I believe in the impermanence of moments, that we construct our realities and that there is no distinction between the self and the non-self, i.e., I believe in the non-dual philosophy of existence (how much I practise it in everyday life, is a different question). However, this makes me understand that I predominantly hold a critical realist stance.[73] In Justin Cruickshank's (2011) words, *"knowledge* [and I extend it to perception] *is fallible and open to revision and replacement through empirical research".* In other words, nothing is permanent and everything is changeable.

3.5.2 My interviewing style

This philosophy and my academic training and leaning towards the subjects of physical and life sciences where experiments, observations and inductive reasoning are the foundational aspects, give me the ability to be a detached observer *when required and when possible*, the ability to represent the as-is facts and viewpoints and firmly ground them to the literature, rather than get coloured by my own personal construct of reality. However, during the interview process, sometimes it has not

[73] Critical realism is one philosophical form of post-positivism conceptualised by Roy Bhaskar. The critical realist perspective appealed to me as a concept to present my philosophical stance towards this research study because it can justify my understanding of science (there exists a reality which is not dependent on our thinking and that we might not be able to assess objectively – the unknowable unknowns will remain – but we can continue seeking it).

been possible to remain detached from the conversation and my previous work experience did spill forth. Therefore, conscious detachment, i.e., "manufactured distance" (McCracken, 1988, p. 22-23) from the views expressed while analysing the content and creating themes has been possible, although during interviewing, in a few cases and for a few times it was not so and the balance between obtrusiveness and unobtrusiveness could not be maintained. Overall, it has been easy for me to be "unobtrusive" (McCracken, 1988, p.21) during the interviewing process, probably because of my position as an international student in a country which has many marked differences in cultural, political, and policy arenas, in addition to science and technology issues compared to my home country.

3.5.3 My training background

My own role as a downstream 'scientist'[74] would make it seem that I am biased towards trying to establish the fact that nanomedicine might pose novel and unforeseen risks, however, I have used this bias to provoke discussions.

I come into this research as a lay person or may I say a research-cum-action person trained in transdisciplinary research and participatory approaches, culturally trained to appreciate indigenous and non-expert knowledge and views, and exposed to the global frameworks, standards, and benchmarks related to sustainable development. I lacked the theoretical background to argue about specific philosophical or epistemological meanings and concepts which I gained during this research. I accept all prevailing concepts, guidelines, tools, methods, standards, and codes of

[74] Though I might not be able to classify myself as either as a scientist or a social scientist.

conduct of directing science, research, technology, corporations, and governments via proactive and adaptive governance with the normative goals of co-evolution and co-existence of humans and the planet earth. It is generally believed that an 'optimum solution' can be arrived at by assessing and comparing risks and negotiating trade-offs, but my position is to ask for whom the solution is optimum, human kind or the environment,[75] and over what time scale – short-term or long-term. Synthetic oestrogens and antipsychotic medicines are beneficial for mankind, but their longer-term implications for other species in the environment have been shown to be disastrous (Kidd et al., 2007). Similarly, diclofenac as a veterinary medicine is beneficial but resulted in the near-collapse of the vultures, one of the key scavengers, in the Indian subcontinent (Oaks et al., 2004).

3.5.4 Reflection

My own journey has been an aim to be legitimate: to gain acceptability in the nanoscientists' (both medicine and environmental) world, and acceptance in the world of the social scientists. My eternal quest and need has been to be well informed which is necessary for legitimisation; however, I am yet to gain legitimacy in either of the worlds. This is helpful in some ways that it keeps me free of 'disciplinary' biases arising out of allegiance to a particular discipline.

[75] Here again, I declare my allegiance to Bhaskar's philosophical stance which was anti-anthropism, i.e., against both anthropocentricism (man central to the universe) and anthropomorphism (attributing human characteristics to the cosmos).

3.5.5 Confidentiality and anonymity

When emails were sent to request interviews, they contained the anonymity and confidentiality clause, which to my opinion helped to get the trust of the professionals. Interviewees were once again assured of anonymity and confidentiality while the interview was being conducted. A few interviewees requested the transcribed interview so that they can review the transcripts and hence the transcribed interviews were shared with them. In the introductory mails, the experts were given the option to change their mind regarding the interview and the use of interview data in publications. Interviewees were grouped into categories assigned an alphanumeric code assigned on the basis of their expertise area and the chronology of conducting the interview. For example, NMS 1 means scientist doing research in nanomedicine and the first interview of that group, NMS 13 means nanomedicine scientist and the 13th interview (in chronological order) of the same group. The abbreviations are mentioned below:

NMS - nanomedicine scientist; NMEn - nanomedicine entrepreneur; HTOC- Human toxicologist; ETOC – Ecotoxicologist; RC - Research Council; SS - Social scientists; PP - policy makers. Representatives from regulatory bodies and industry have been named as ‘Regulators’ and ‘Industry’.

3.6 Conclusion

The environmental impacts of nanomedicine might seem to be a very long-term societal risk, and the repeated mention in the literature of the stringent regulatory controls on pharmaceutical development and use, their biodegradability in the body, the negligible mass (especially of nanomedicines), and benefits versus risks of

medicines may make this research seem overly precautionary. However, the engaging responses from the experts I interviewed gave me the motivation and the satisfaction of pursing the 'neglected' question of the potential environmental implications of nanomedicine and developing RI for nanomedicine.

From my perspective, the mixed methods methodological approach adopted for the thesis is a robust and effective means of doing the research. First of all horizon scanning of nanomedicine research and development, done through a comprehensive review of available information such as scientific publications, subscription databases, and clinical trials website, gives a more realistic (in contrast to the idea of human enhancement widely discussed in the nanoethics field) idea of likely / promising future applications in the medical field. This also helped to identify the case study which could be used to fulfil the objective of estimating future environmental concentrations of nanomedicines. The selection of the widely researched probabilistic mass flow model, used for estimating concentrations of nanomaterials in the various environment and technical compartments such as water, soil, sewage treatment plants, and incinerators, was also done with care and deep thinking. This approach was selected in order to provide a 'good' estimate and to "plug" as many knowledge and data gaps as possible (within the available timeframe and data availability), as well as with the goal of helping to direct future research in the nanomedicine and environmental implications area. Moreover, in the widely prevalent positivistic philosophy of science, being able to provide some numbers regarding nanomaterial release or exposure from nanomedical uses satisfies the majority of the scientific community.

The application of nanotechnology in the health care field is an emerging discipline, coupled with the concept of responsible innovation as a means to govern innovation being a recent conceptualisation. As a consequence, definitions are yet to be formulated and concretised, regulatory frameworks yet to be customised, and 'novel' concepts of innovation governance yet to be tried out in the 'real' world and thus strengthened. In such a case, gathering viewpoints from eminent experts belonging to major stakeholder groups becomes imperative to add value to the research (since expert judgement has been the preferred way for taking decisions on the results of risk assessment of chemicals and nanomaterials to date).

The critical realist philosophical stance, and for a novice researcher like me, the general inductive methodology of analysing qualitative material for Objective 3, was appropriate. For objective 4, the directed content analysis methodology was found to be suitable so as to inform a newly conceptualised framework of responsible innovation. Moreover, being truly in allegiance with the ethos of qualitative research, whereby individual perspective and thoughts are important, helped me to analyse the empirical qualitative data as a goldmine of information rather than get stuck in the details of 'who' and 'how many' said 'what'. This mixture of approaches and of methods was needed as a result of the innovative nature of the research undertaken.

This thesis is a pursuit to be as holistic as possible (which is due to my own situation of being a multidisciplinary researcher from a developing country with a varied work experience). The four objectives of the research gave the opportunity to explore (albeit not completely) the interconnectedness, non-linearity and complexity that exist in the health care sector. The thesis helps to identify what else in needed with regard to nanomaterial risk assessment and what is important to guide innovation in the

health care sector to truly reflect the kind of responsibility, i.e., forward looking responsibility that philosophers like Hans Jonas and others have conceptualised for the technological age.

This thesis represents a fraction of the work I undertook during my PhD research. Many of the questions which were asked in the interview remain to be analysed; I am confident it will be sufficient material for another PhD thesis in analysing these data, or for a number of publications. I hope that this mixed methods thesis at an emerging science and technology policy interface can inspire other such theses. To find a home for the thesis is difficult, as I traversed the literature regarding innovation and business management, nanomedicine research, environmental risk, science and technology studies, and public understanding of science, but I think it can fit well into the Environmental Sciences field which is itself a multidisciplinary field, and is used to spanning the science−technology−policy interface.

The following chapter is in its entirety (except some sentences, one table, and one figure) is published in the ‘Journal of Nanobiotechnology’ as:

MAHAPATRA, I., SUN, T. Y., CLARK, J. R. A., DOBSON, P. J., HUNGERBUEHLER, K., OWEN, R., NOWACK, B. & LEAD, J. 2015. **Probabilistic modelling of prospective environmental concentrations of gold nanoparticles from medical applications as a basis for risk assessment. Journal of Nanobiotechnology**, 13, 93.

I. Mahapatra co-designed the study, collected and prepared the input data for the model and was fully responsible for writing the manuscript. T.Y. Sun wrote the code of the probabilistic model, generated the model output, and created all figures (except Figure 4.1) and Table 4.2 for the manuscript. B. Nowack supervised and co-designed the study and gave inputs on the data. J. R. Lead conceived and supervised the study. P.J. Dobson gave inputs on the data. All authors commented on the draft manuscript and I. Mahapatra revised the manuscript for submission.

Chapter 4: Probabilistic modelling of prospective environmental concentrations of gold nanoparticles from medical applications as a basis for risk assessment

Or, what are the future amounts of gold nanoparticles in environment and whether there is any environmental risk from it

"...*In order to make progress, one must leave the door to the unknown ajar"* – Richard Feynman

4.1 Background

There has been an increased focus on developing gold nanoparticles (Au-NP) based applications in fields ranging from electronics to medicine. Between 2000 and 2013, gold nanotechnology related patents increased exponentially, with about 1600 patents published in 2013 (World Gold Council). The number of publications related to Au-NP in the health sector in Thomson Reuters' Web of Science data base also show an exponential increase from 54 to 9083 publications between 2004 to 2014, of which 2150 articles were published in 2014 alone (search conducted on 28 Dec 2014) (Thomson Reuters' Web of Science). The unique chemical and physical properties of Au-NP (Eustis and El-Sayed, 2006; Trudel, 2011; Masitas and Zamborini, 2012) make them excellent candidates for exploitation in the medical field to help in disease diagnosis and treatment. Furthermore, their ease of synthesis in a variety of sizes and shapes and their amenability towards surface functionalization creates the possibility for multi-functionality including imaging and targeted drug delivery (Arnaiz et al., 2012; Kircher et al., 2012; Lukianova-Hleb et al., 2014; Setua et al., 2014; Shilo et al., 2014).

Drug delivery applications based on Au-NP are forecast to have a 21% share of the USD 136 billion total market of nano-drug delivery applications by 2021 (Cientifica

Ltd., 2012). The enormous range of potential applications of Au-NP and their increased future use could result in greater risk of environmental release and exposure at low concentrations, as is the case with many pharmaceutical products (Roberts and Thomas, 2006; Ramirez et al., 2009; Jobling and Owen, 2013; Miller et al., 2015). Proliferation and increased application of single use and disposable cheap medical diagnostic devices (Keel, 2013) could add to this environmental burden.

Uptake, biodistribution, accumulation and biomagnification of Au-NP by environmental organisms have been studied by many investigators (Ferry et al., 2009; Judy et al., 2011; Sabo-Attwood et al., 2012), and it has also been shown that Au-NP can be toxic to animals and plants (Geffroy et al., 2012; Perreault et al., 2012b; Tsyusko et al., 2012; Kim et al., 2013) thus indicating that these supposedly biocompatible materials could present a significant hazard to plants and wildlife. Summary of eco-toxicity studies of Au-NP are in Annexe, in Table A3 and Table A7.1 and Table A7.2. Au-NP have been shown to have different modes of action for creating toxic effects dependent on their properties and the organism studied (Cui et al., 2012; Coradeghini et al., 2013) and show promise as an antibacterial agent (Zhao et al., 2010).

In this study environmental concentrations of Au-NP for the United Kingdom (UK) and for the United States of America (US) from selected medical applications that are currently on the market or have the potential to be introduced in the near future were estimated by developing a conceptual environmental exposure model and by combining this with the hazard data. Probabilistic material flow analysis has been used (Gottschalk et al., 2010a) to track the flow and fate of Au-NP during use and

disposal. Similarly, to quantify ecotoxicological risks probabilistic species sensitivity distribution (pSSD) was used. Risk levels for the ecosystem were derived by comparing the modeled predicted environmental concentration (PEC) to the predicted no-adverse-effect concentration (PNEC). The PNEC for the aquatic and terrestrial environmental compartment was derived from the hazard data for the corresponding environmental compartments (Gottschalk and Nowack, 2013).

4.2 Methodology

4.2.1 General model layout

The geographical regions of the UK and US (excluding dependent areas) have been used as the units of analysis for the study. Census data of the US (2010) and UK (2011) have been used to arrive at the population for the PMF model. The populations of the UK and US were approximately 63 million and 300 million respectively in the census years chosen for this study with both countries having a higher population of females (ca. 1.1 and 5.3 million more females than males in the UK and US respectively).

Similar to the approach proposed by the Guidelines for Environmental Risk Assessment (ERA) of human pharmaceuticals (USFDA, 1998; EMA, 2006b), (hereinafter referred to as ‘Guidelines’) where the consumption data of a drug per year is the key input factor, the model input in this study is based on population based estimates of use and consumption of the selected medical applications in a given year and disregards the manufacturing and processing facilities as a potential

source. Relevancy of consumption based estimates have been shown in studies on measured environmental concentrations of pharmaceuticals where investigators have concluded that households and long term care homes remain the major contributor of pharmaceuticals to waste water (Le Corre et al., 2012; Herrmann et al., 2015). Moreover, information of pollution and environmental risks from pharmaceutical manufacturing industries is limited (reviewed in Larsson, 2014) and hence manufacturing and processing facilities as a potential source were omitted in this study, though limited information does not mean that there are no environmental risks from pharmaceutical manufacturing facilities. Other reasons for not including the manufacturing facilities in the model include: 1. some of the health care applications considered in this study, and which contribute significantly to the total consumption of Au-NP, are in research phase and therefore there is no data available; 2. lack of publically available data for production volumes of particular therapeutics from a manufacturing plant; and 3. the global and regional distribution in the pharmaceutical supply chain makes it impossible to estimate the fraction of Au-NP in the geographical regions of interest.

Surveys show that the majority of unused medicines are disposed in the sink or toilets and to the household waste (Braund et al., 2009; Leal et al., 2010; Fenech et al., 2013), hence sewers and solid waste constitute important technical compartments.

The model is a step-wise process where the selected application's post usage life cycle has been mapped through the technical compartments of sewage treatment plants (STPs), waste incineration plants (WIPs), landfills and the environmental compartments of soil, water and sediments. In addition to Au-NP based therapeutic

agents which are in early stages of clinical trials, Au-NP concentrations in medical devices approved by regulatory agencies or in late stages of product development were estimated. A deviation from the Guidelines is the use of excretion rates from preclinical studies as opposed to assuming 100% excretion. Possible variable retention of Au-NP in STPs was considered. PECs in various compartments and risk assessment results considering 100% excretion are provided in the Annexe to this Chapter as Section 4A.2: Alternate Scenarios. The data and values used to arrive at gold amounts per use are based on broad estimates derived from the available literature and the patient population and hence the study is a bottom up, high release scenario study. I have assumed Au-NP to be spherical in shape and have used mass concentrations to estimate consumption amounts.

Transfer coefficients (TC) have been used to model the behaviour of Au-NP in various environmental and technical compartments included within the model (see Tables A6.1, A6.2, A6.3 in the Annexe for details). The data used in the model have high uncertainty, compounded by large variability and hence Tian Yin Sun (collaborator from Bernd Nowack's group at EMPA) built probability distributions for the majority of input data. Estimated consumption values of products which have the same life-cycle pathway have been summed by adding their individual probability distributions. Table A4 in the Annexe illustrates the probability distributions for all the data used in the study.

To estimate the volumes of the environmental compartments, it was decided to use the ECHA's guidance on environmental exposure estimation for chemicals for a regional scale model (ECHA, 2012). The mass and volumes along with the assumptions of the transition and final environmental compartments are detailed in

Tables A6.1, A6.2 and A6.3 in the Annexe. Seawater is not included in our model. The assumptions of a well-mixed, homogenous and stationery system have been applied in this study which is a standard approach to arrive at crude estimates of environmental concentrations at a regional level (Gottschalk et al., 2009). The model tracks the Au-NP mass and not the total gold mass. Loss of the nano-property (e.g. by vaporization) therefore constitutes an elimination flow. Figure 4.1 shows the components of the environment and technical compartments which were explored in the model.

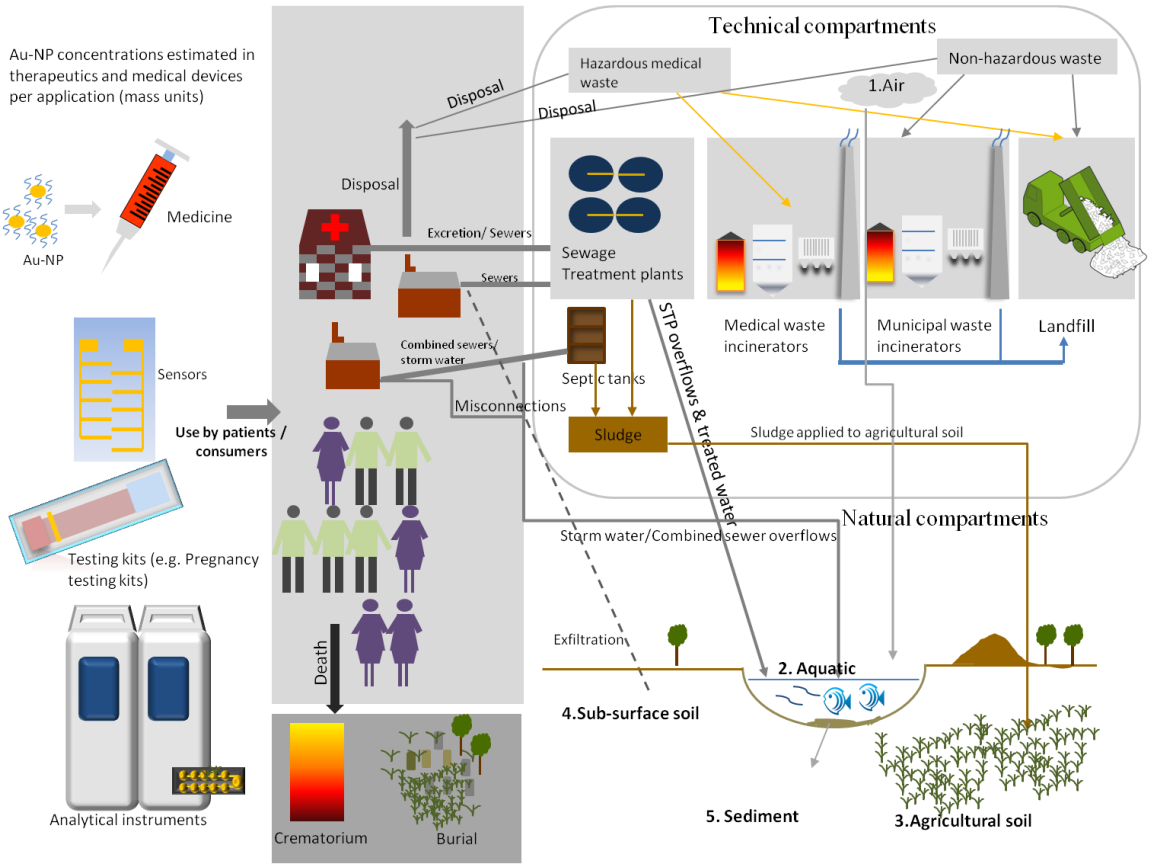


Figure 4.1: A schematic of the material flow pathways used in the model.

Au-NP are used in various medicines and medical devices. In the model, Au-NP flows are tracked post use. The medical devices containing Au-NP can be discarded as part of hazardous medical waste or non-hazardous waste. Waste treatment (incineration plants equipped with various configurations of air pollution control devices) and disposal (landfill) are the two treatment and disposal options used in this model to manage such wastes. Bottom ash and fly ash from incinerators will be disposed of in landfill. Medicines containing Au-NP will, when excreted, enter the sewerage system and flow to sewage treatment plants or septic tanks. Overflows from STPs and leakage from sewer pipes will likely result in flow of Au-NP to surface water and sub-surface soils respectively, and will possibly impact aquatic organisms. Sludge from STPs and septic tanks (containing Au-NP) can be used for agricultural purposes and will likely effect soil organisms. Au-NP emitted to air will get deposited in the natural compartments of water and soil. Au-NP can remain in the body of the patient and after their death Au-NP can be either present in the ashes from the crematorium or can remain locked away because of burial practices.

4.2.2 Methodological approach for input data

Since “nanomaterials” and “nanomedicine” do not yet have universally accepted definitions (refer to Sections 1.2.2 and 1.2.3 for more discussion) an extensive

literature search was carried out to identify relevant peer-reviewed scientific publications of Au-NP or gold colloids in the medical field, administration doses, distribution and excretion. The aim was to identify Au-NP enabled medical applications which are approved, in clinical trials or show promise of translation from pre-clinical models. The journals, such as Nature Reviews: Drug Discovery, Science: Translational Medicine, Nanomedicine: Future Medicine, Nanomedicine: Nanotechnology, Biology and Medicine, Advanced Drug Delivery Reviews, Journal of Controlled Release, The BMJ were some of the key journals which helped to identify new R&D for medicines and medical devices in the field of nanomedicine. Key word lists and tables that were included in some review articles helped to expand the search terms and were used to record various applications and products related to nanotechnology in health care. The subscription databases 'Citeline'[76] and 'Adis R&D Insight' [77] were used between the periods 17-21 December 2012, 18-19 January, and 26-27 April 2013. The key search terms used in these subscription databases were: colloid*, contrast agent, dendrimer, emulsion, gold, liposom*, micelle, nano*, nanocap, nanotechnology, nanoparticle, pegylated, polyethyleneimine, polymer*, silica, superparamagnetic. These search terms were also used in the clinical trials.gov database. All search results were scanned for information which could be relevant for the study. The information provided in these databases (such as company name, published literature), was used to conduct follow-up searches (through Google) which helped to identify the key Au-NP applications that could be used in this study. Final selection of applications used in this study was done after cross-checking company annual reports, press releases,

[76] http://www.citeline.com/

[77] http://www.springer.com/gp/adis/products-services/adisinsight-databases/r-d-insight

USFDA and EMA websites and conference presentations and proceedings. Then extensive review of manufacturer's websites, EMA and FDA websites to check for approval status and additional searches were conducted through Google to add further details to the identified nanomedical application and add information on nanoscale dimensions, dose, treatment regime, biodistribution, and excretion. United States Patent and Trademark Office's website and 'Patent Buddy' websites were relied upon for finding out related patents to arrive at assumptions to help estimate the amount of gold (Au) per test or per patient. However, there was a lack of detail in many papers (could be due to Intellectual Property issues), requiring a trawl through their reference list to identify additional relevant articles and identify additional leads to source the Au NP dimensions and amounts. Systematic Google searches (with various combinations of possible search terms were used because simple search terms many times failed to give adequate results) were also conducted to finally arrive at 'plausible' assumptions regarding Au- NP dimensions and amount. Due to obscurity of information, extreme scrutiny was done to derive 'plausible' data from a variety of sources.

Reports published by the UK and US Government Department and Agencies have been relied upon for estimating population, environment and technical compartment data. For arriving at 'model' or affected (by Au NP-containing medicines) population estimates, sources of information included data from the World Health Organization (WHO), www.cancerresearchuk.org, and U.S. federal agencies such as National Institutes of Health (NIH), National Cancer Institute's SEER database, and the Centres of Disease Control and Prevention (CDC), to name a few. For the UK, data was extracted from the website of the ONS (Office of the National Statistics) and

reports from the NICE (National Institute of Health and Care Excellence) and the NHS (the National Health Services) of England, Scotland, Northern Ireland, and Wales. Where possible and practicable, the most recent data available have been used. Broad assumptions have been used with the intent to come up with best plausible estimates.

The environmental transfer coefficients have been estimated by reviewing scientific literature related to environmental fate and behaviour of nanomaterials and in a few cases conventional air and water pollutants. The environment and technical compartment data was primarily gathered from reports published by government departments and agencies, such as the United States Environmental Protection Agency (USEPA), Department for Environment, Food & Rural Affairs (DEFRA), Environment Agency (England and Wales), Scottish Environment Protection Agency (SEPA), Northern Ireland Environment Agency (NIEA), reports of consultancy firms engaged by these departments and agencies, Eurostat database and publications by the European Commission, the United States Census Bureau, United States Department of Agriculture, United Stated Geological Survey. However, many data, such as misconnections of household sewer pipes to storm water systems, leakage from sewers, overflows from Sewage Treatment Plants (STPs), biosolid application on land, hazardous waste, incinerators and their types were carefully gathered by an extensive Web search and through reviewing literature published in wide variety of sources, including ‘grey’ literature. Some data which was not at all publically available were gathered by soliciting information from experts. When data from multiple sources conflicted, a range was used covering all the reported values or the

approach of the best available data was adopted to arrive at the estimates used in this study.

In the case of data unavailability for Au-NP fate and behaviour in a particular environment compartment, data reported in the scientific literature for other nanomaterials have been used to arrive at the transfer factors (more details in Section 4.2.3). When data reported from various sources widely differed, the reason for the choice of a particular value has been provided (refer Annexe to this Chapter, pages 351−353).

All input data was acquired by adopting multiple approaches and using different calculation strategies and the process was seldom easy or straightforward. Details regarding consumption data and assumptions and references therein are included in Section 4A.1 and Table A5 in the annexe to this chapter. As most of the data used are estimates (based on broad assumptions) with known and unknown uncertainties, probabilistic modelling approach was used to address the uncertainty in the data. Different probability distributions were created with the aim to address data uncertainty and variability arising due to (generic Au-NP rather than specific considerations given to size, coating, functionalisation) the modelling approach chosen in this study. In the cases, where there is a single data point for a certain parameter; this single value was deviated ±50% and a triangular probabilistic distribution was created. Additionally, triangular distributions were applied where data estimates were calculated in a manner that a minimal, mode (mean) and maximal values were available. When a certain parameter had a range (i.e. upper and lower bound), uniform distribution was applied. Only in one case (overflows from STP for UK), standard deviation was provided and hence a log normal distribution

was applied. See Table A4 for probability distributions used for various transfer factors used in this study.

4.2.3 Transfer factors

Therapeutics based on Au-NP, after use, will end up either in solid waste, when the containers with the remnants of the therapeutic and associated procedural implements are disposed of as part of HMCIW and/or in the sewerage system when it is excreted from the body in urine or faeces. *In vitro* diagnostic devices used in hospitals and other health care settings will likely be part of HMCIW. Over-the-counter (OTC) single use medical devices are likely to end up in household waste. Therefore, waste water (WW) or sewerage, HMCIW and household waste are defined as the key potential sources of entry of Au-NP from medical products to the environment.

4.2.3.1 Au-NP flow into sewage treatment plants and surface water

Not all houses are served by a centralised STP. The connection rates to STP are 96% (DEFRA, 2012) and 74% (USEPA, 2008) for the UK and the US respectively. Untreated sewer overflows, misconnections whereby grey water from households is connected to the storm water drainage systems, and exfiltration from sewerage pipes can result in untreated WW reaching surface waters, groundwater and subsurface soil directly. Au-NP from WW can also enter the environment due to failure of decentralised STPs. Since the connection rate to STPs for the UK is 96%, we have neglected the contribution of individual septic tanks and cesspools to the pollution load. However, for the US, nearly 25% of the total population is served by

decentralised systems and the USEPA suggests a failure rate of 6% annually of these systems (USEPA, 2004). Therefore, for the US I have considered failures of decentralised systems as a source of Au-NP reaching the environment. Additionally, discharge of untreated WW due to the dilapidated state of sewerage infrastructure (ASCE, 2013) and polluted outfalls from combined sewers during rains (USEPA, 2008) can add to the pollution load of surface waters.

4.2.3.2 Behaviour of Au-NP in surface water

Data was non-existent with regard to Au-NP fate in surface waters and therefore two extreme scenarios were modelled to represent worst case conditions for both compartments (sediment and surface water). It was assumed that Au-NP entering the surface freshwater compartment were either 100% deposited to the sediment to derive sediment concentrations, or remained 100% in the water phase to derive freshwater concentrations.

4.2.3.3 Behaviour of Au-NP in Sewage Treatment Plant

Only one published study is available where an estimate of the removal efficiency of Au-NP in STPs has been provided (Kaegi et al., 2013). This study found 99% removal rate of polymer coated Au-NP of sizes 10 nm and 100 nm in activated sludge batch experiments irrespective of coating, sizes and treatment. We have therefore used a removal efficiency of 99% for wastewater treatment. However, we acknowledge that removal efficiencies will differ based on the WW treatment systems used (Jarvie et al., 2009; Johnson et al., 2014).

4.2.3.4 Au-NP flow into waste compartment

Household waste is non-hazardous in nature and hence in addition to incineration, discarding to landfill is another preferred mode of treatment. OTC disposable *in vitro* diagnostic devices containing Au-NP will be part of the household and similar waste category as defined in the European Union Waste catalogue (Eurostat, 2010). In the UK, the proportion of landfilled and incinerated waste for the category of household and similar waste is 85% and 15% respectively for the year 2008 (Eurostat, 2013). For the US, the proportion of household waste sent to landfill and incinerated is 82% and 18% respectively of the total waste discarded after the recovered fraction (USEPA, 2013).

Wastes from health care settings are both hazardous and non-hazardous in type. Hazardous waste from health care facilities are generally sent for high temperature treatments like incineration and pyrolysis, or alternatively non-burn low temperature treatments or chemical treatments to disinfect the infectious waste (Tudor et al., 2009). These alternative treatment technologies use wet or dry steam at temperatures lower than 200°C and use chemical disinfection methods. We have assumed that Au-NP will not be transformed or destroyed when waste is treated via non-burn alternative treatment technologies and will eventually end up in landfill.

4.2.3.5 Behaviour of Au-NP during Waste Incineration

No information is available about the fate of Au-NP in incinerators. Depending on the type of waste, type of incinerator and operating temperatures, configuration of the air

pollution control devices (APCDs), and the particle size, it is likely that Au-NP will partition into bottom ash, APCD residues and stack emissions from APCDs.

Emissions from incinerators are under strict regulatory control; therefore it has been assumed that all municipal waste and HMCIW incinerators will have associated APCDs. Both the UK and US use dry or semi–dry scrubbing systems with fabric filters or electrostatic precipitators (ESPs) as the main types of APCDs in the municipal waste incinerators (USEPA, 2010; DEFRA, 2013b).

The temperatures in HMCIW incinerators having secondary chambers can reach as high as 1100°C, which is higher than the melting temperature of bulk gold. Melting temperature depression related to particle size, both for free Au-NP and substrate supported Au-NP, has been proven by many investigators (Buffat and Borel, 1976; Dick et al., 2002; Nanda et al., 2007; Lee et al., 2009b; Luo et al., 2012). Furthermore, the presence of chlorine generated from Polyvinyl chloride in the incinerator can increase metal volatility and release into gas phase (Kakumazaki et al., 2014). The vapour pressure of gold at 1095°C is about 1 x 10^{-5} torr (1.33*10^{-3} Pa) (Honig and Kramer, 1969) and that means typically around one monolayer of gold will be vaporized in 0.1 seconds. Hence, Au-NP entering the HMCIW incinerators will either melt or vaporize. In both cases the nano-property of the gold is lost and the Au-NP is no longer distinguishable from the other gold forms. We have used both the case of 0% and 100% elimination of the gold mass. In the case of 0% elimination, we assume Au-NP to be distributed 81% in the bottom ash and 19% in the fly ash using the values found by Walser et al. (2012a) for removal of Ceria nanoparticles in municipal waste incinerators. Of the 19% of Au-NP in the fly ash, we assume 50% of the Au-NP pass through the wet scrubbers and the remaining 50%

through the fabric filter for both the UK and US. This assumption was extrapolated from the type of APCD installed in the HMCIW incinerators in the US (RTI International, 2012) since no data was available with regard to APCDs for HMCIW incinerators in the UK.

The operating temperatures in municipal waste incinerators are around 850°C, so we assume that 81% of Au-NP mass will be removed in the bottom ash and 19% in the fly ash of which 99.99% will be removed by the ESP and fabric filter as APCD residue. These residues are treated as hazardous waste and are finally disposed to secured landfills or abandoned underground mines (Amutha Rani et al., 2008). Bottom ash from municipal waste combustors can be used in the construction sector (Ørnebjerg et al., 2006). However, due to non-uniformity in available data for the selected regions and to simplify the model, we have neglected bottom ash recycling rate and have presumed that 100% of the bottom ash from both types of incinerators will be landfilled.

We have not included the leachate from landfill and subsequent contamination of the ground water compartment because studies on the fate of nanoparticles in landfills are not yet available. Moreover, research studies done on organic contaminants describe the analytical challenges of measuring contaminant concentrations in the complex leachate matrix; studies have also shown the importance of various parameters, such as groundwater flow, soil mineralogy, and weather that can influence metal transfer to groundwater. The few studies done with regard to the presence of pharmaceuticals in groundwater report very low (sub nano gram level) concentrations for most widely used drugs meant for human use. Even where

concentrations were high immediately below the landfill site, it was reported that attenuation happened within a short distance (e.g. 150 m) (Holm et al., 1995).

The technical compartment of cremation has been considered in the model boundary with the assumption that some percentage of Au-NP might remain in the human body post treatment when Au-NP has been administered as a last line treatment. The temperature in crematoria is not high enough to vaporize or melt Au-NP (Mari and Domingo, 2010) and hence we assume that untransformed Au-NP will form part of the ash.

Recycling of waste has not been included due to the prescribed and prevailing practices in the health care sector and the limited data availability. It has been assumed that the lab-based in vitro diagnostic devices exemplified in this study will not be part of the WEEE waste category and hence will not be included in the targets set by the amendment of WEEE which came into effect February 2014 (EU, 2012a). Recycling of metals is a possible option after cremation (e.g., http://orthometals.com/)). However, data is scarce and since the amounts will be negligible, we have neglected this pathway in the study.

Therefore, human body, landfills, sediments, subsurface soils and burial grounds have been considered as the final sinks of the product life cycle post usage.

4.2.4 Ecological risk assessment

To derive species sensitivity distributions for environmental effects of Au-NP, an extensive search of the ecotoxicological literature was conducted. Fourteen relevant

studies were found published between 2008 and February 2014. Twenty six data points across five taxonomically different environmental organisms – bacteria, fish, algae, crustaceans and ciliates – were included in the assessment. The endpoints used were mortality and malformations, growth inhibition and reproductive performance. These endpoints were selected to maximize utility of the data points from the available published literature and because these endpoints can impact species survival. We considered all endpoints reported in a study even if they used different particle size and coating with the aim to create a generic Au-NP species sensitivity distribution to compare with the PEC of Au-NP which considers the mass of Au-NP. If in a study only one concentration has been tested on an organism and it had shown no effect for the selected toxicity endpoint, we have used that concentration as no-observed-effect concentration (NOEC), acknowledging that this could in reality be higher. When a range of concentrations were tested (Bar-Ilan et al., 2009; Asharani et al., 2011), the highest concentration at which no statistically significant adverse effect was observed was used as the highest-observed-no-effect-concentration (HONEC). The raw data were converted to species sensitive values below which long-term negative impacts on the species were considered to be excluded using two assessment factors (AF) based on the REACH guidelines (ECHA, 2008). The first AF was used to convert acute toxicity to chronic toxicity (AF time = 1, in the case of chronic and long-term test; AF time = 10, in the case of acute and short-term test). All but two data points represented acute or short-term exposures. The second AF was used to convert the various endpoints to NOEC values (AF no effect = 1 for NOEC, AF no-effect = 2, if $L(E)C_{10} \leq L(E)Cx < L(E)C_{50}$ and AF =10, if $L(E)_{50} \leq L(E)Cx \leq L(E)C_{100}$). In studies where effect concentrations

were reported in terms of molar concentrations, we have converted the values to mass concentration (µg/L), because regulatory limits are expressed as such. The studies selected and the associated end points arranged species wise are detailed in Tables A7.1 and A7.2 in the Annexe. Probabilistic species sensitivity distributions were constructed for soil and freshwater as explained in an earlier study (Gottschalk and Nowack, 2013).

4.3 Results and Discussion

4.3.1 Estimation of nano gold consumption from prospective medical application

Table 4.1 details the estimated quantity of Au-NP from nano-enabled medical applications. As the table depicts, very small amounts – in the range of milligram to less than a few kilograms – are estimated to originate from *in vitro* medical devices or devices used for detection of specific disease biomarkers. Larger quantities of Au-NP are estimated to be released from applications used for treating or managing a particular disease, for example, for the treatment of gum infections, cancer and diabetes. The amount of Au-NP per patient was estimated to range from 0.05 mg to 5000 mg for the whole treatment cycle, the higher values corresponding to the treatment modality of photothermal ablation of cancer using gold nanoshells. A study (Booker et al., 2014) conducted in Northwest England estimated the consumption of anticancer drugs from hospital records and showed total consumption of all the identified anticancer drugs to be around 350 kg. Thus, the annual Au-NP consumption amount in the range <1kg to 250 kg could be reached in the near future

for the UK for treatment of breast, lung, pancreatic and bowel cancer. This is because these diseases have high incidence rates, however, it needs to be kept in mind that we have used high release scenario of 100% patient access and treatment by the same Au-NP based therapeutic for all patients.

Table 4.1: Prospective amount (per annum) of Gold nanoparticles (in grams) in selected medical applications (high release scenario).

The table presents total gold nanoparticles consumption per annum for the UK and US using a worst case scenario. Data rounded off to 2 significant figures for values below 1 or rounded off to the nearest integer or ten. Refer to Supporting Information for details related to assumptions and references.

Application	Consumption		Waste compartment
	UK	US	
Lab based lateral flow assay to detect the presence of Methicillin Resistant and Methicillin Sensitive *Staphylococcus aureus* in blood	0.34	6	Hazardous Medical/Clinical/Infectious Waste (HMCIW)
In vitro lab based diagnostic test kit for detection and genotyping warfarin metabolism	0.36	3	HMCIW
In vitro lab based diagnostic test kit for detection of single nucleotide polymorphism to detect risk from venous thrombosis	1	3	HMCIW
OTC pregnancy and ovulation test kits to detect hormones in urine	3 to 100	20 to 460	Municipal solid waste
Lab based in vitro rapid test kits for qualitative detection of antibodies to HIV-1 and HIV-2 in human serum, plasma and blood	2 to 80	20 to 830	HMCIW
Home based *in vitro* HIV test kits	20	90	Municipal solid waste
Lab based *in vitro* tests for detection of CD4 cells and viral loads for HIV patients	60	540	HMCIW
Lab based diagnostic test kits for infectious diseases	70	350	HMCIW
Removal of *Staphylococcus aureus* from the nasal passage of patients to reduce risks of nosocomial infections	30 to 53300	110 to 164640	HMCIW
Treatment of periodontitis	270 to 106560	940 to 365160	Waste water
Sensors for diagnosing diseases from breath samples	0.01 to 1590	0.03 to 4620	HMCIW

Treatment for solid tumors (colorectal, pancreas, breast)	70 -(480) - 1100	310- (2020) – 4600	Waste water
Last line treatment for patients with solid tumors (colorectal, pancreatic and breast)	*420*	*1500*	Waste water
Treatment for patients diagnosed with head & neck and lung cancer	140290 to 233820	744750 to 1241260	Waste water
Last line treatment for patients with head & neck and lung cancer	*104710 to 174520*	*468250 to 780410*	Waste water
Transbuccal insulin delivery platforms	128250	841620	Waste water

The Au-NP consumption data could be estimated due to the strict regulatory governance framework associated with approval of pharmaceutical products for human use and also because of the availability of disease incidence and prevalence data for widespread diseases, such as cancer, diabetes. In contrast, estimating Au-NP quantities from *in vitro* diagnostic devices was challenging due to the dependence on the patenting literature, wherein specific details are obscured and also because of the less stringent regulatory pathway for *in vitro* medical devices. Hence, the estimated data relied on vast number of assumptions and data was extrapolated from various literature sources. Some overall and broad assumptions are mentioned below:

- It has been assumed that each product by a company for a particular application serves 100% of the market of the US and UK (i.e. no competition) and all patients, irrespective of socio-economic status and other access to health care issues, have access to these products. For example, when a therapy is in clinical trials for head and neck cancer, the latest publicly

available data for number of people diagnosed with head and neck cancer in a particular year have been used as a prospective population for treatment. Innovative medicines might create excitement with regard to possibility of increasing the life expectancy of a patient; hence it was assumed that all deaths could be prevented if this medicine is used as a last line treatment under the auspices of "expanded access or compassionate use"[78]. Therefore, mortality figures of people suffering from a particular type of cancer were used. I acknowledge that not all people will have access to these 'trial' drugs and devices, however, the objective was to model high-emission worst-case scenario and hence these numbers were included. Various disease types and stages of cancer have not been taken into consideration. It is assumed that all patients get treated in the same year, since the model (in the current state of development) doesn't allow for time-based-releases.

- Attempts were made to reduce risks due to double counting (Exception: There is double counting of two applications selected for testing of *Staphylococcus aureus*). However, the inclusion of this data does not impact significantly the share of these applications in the total consumption amount.

- Estimates of health and health care related statistics are based on the most recent data available in the public domain, except for incidences of Venous Thromboembolism for the UK.

[78] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm

- In most cases, dose of the therapeutic agent is used to arrive at the input data, and the gold amounts that would be present in drug delivery equipments, containers containing the drug, etc. have not been included in our estimates.

- Census data of the US (2010) and UK (2011) have been used to arrive at the prospective population.

The details of the data used and associated assumptions (specific to an individual medical application) to calculate annual consumption of Au-NP from medical applications selected for this study are detailed in the annexe to this chapter. However, an estimate of Au-NP with detailed calculation steps and related references is shown in Box 4.1 as an example. Broadly, the steps to arrive at Au-NP consumption estimates were:

- Assumed, or reported particle size and mass of Au-NP (best plausible assumption from available literature sources) ;
- Assumed the amount in one device or amount required for one diagnostic test or amount in a dose;
- Estimated the patient population or consumers using the particular device or medicine in a year;
- Multiplied the population with the amount of gold calculated per medical device or therapeutic.

Box 4.1: Home based test kits for diagnosing HIV/AIDs

Approved by US FDA on 3 July 2012 (OraSure Technologies Inc., 2015)

Assumptions to estimate amount of Au per application

1. Au-NP size = 60 nm (Nazareth et al., 2012)
2. 15 µL/test device = $8.52*10^{-7}$ g/test strip (BioAssay Works LLC)

Assumptions for annual total number of tests

Since this is a home based test based on oral fluids, we assume 50% of people from age 15 to 64 years conduct one home based HIV test per year. Though legally the self-testing kit is to be sold to population aged 17 years or more, we have used 15−64 yrs because of the class intervals provided in the population tables.

- Population in the age group of 15 to 64 yrs for the US (Year 2010) = 203 554 000 (U.S. Census Bureau, 2011)
- Population in the age group of 15 to 64 yrs for the UK (Year 2011) = 41 706 000 (ONS, 2012)

  Hence, total amount of gold in a year (US population) = 50% * 203 554 000 $*8.52*10^{-7}$ g = 86.71 g

  Total amount of gold in a year (UK population) = 50% *41 706 000 * $8.52*10^{-7}$ g = 17.77 g

4.3.2 Mass flows of Au-NP

The annual mean prospective Au-NP use estimates for the UK and US are 540 kg and 2,700 kg respectively. The yearly disease incidence rates of HIV/AIDS and cancer were found to be relatively stable over the last few years (Cancer Reasearch UK; CDC, 2011; Prejean et al., 2011; Siegel et al., 2014; Yin Z et al., 2014), so the data estimated in this study (which uses incidence and prevalence data compiled in the recent national disease registries and are for the years between 2007-2014) can be assumed to remain constant for the next 5 years. By combining the estimated maximal possible consumption of Au-NP with the technical and environmental transfer coefficients, we were able to obtain Au-NP flows from the end user to technical compartments and then further to receiving environmental compartments. Currently this represents an unrealistically high use of Au-NP and therefore our PEC values also represent highest possible concentrations. If Au-NP based applications for the health care sector are realised over the coming years, it may result in very high market penetration. For example, seven *in vitro* diagnostics, based on Au-NP for determining pregnancy and ovulation, were approved by the USFDA between 2009 and 2012. In our current assessment, only two uses dominate the overall Au-NP flows, a cancer treatment and an insulin delivery platform. The overall flows are therefore to a large extent following the flows of Au-NP used in these two applications, with all other uses having only a minor influence on the mean values but influencing the overall distribution and therefore the extreme values.

Figure 4.2 and Figure 4.3 shows that the most prominent Au-NP flows arise from consumption, leading to accumulation in the human body for both the UK and US. Based on pre-clinical data, we assumed 35% (Goel et al., 2009) and 85% (Gad et al.,

2012) accumulation of Au-NP in the body for the two cancer therapeutics used as model input data. For other Au-NP based applications we assumed 100% excretion (Longmire et al., 2008; Zhang et al., 2012c). Of the total yearly consumption of Au-NP, around 160 kg and 850 kg of Au-NP respectively for the UK and the US would remain in the body of treated patients.

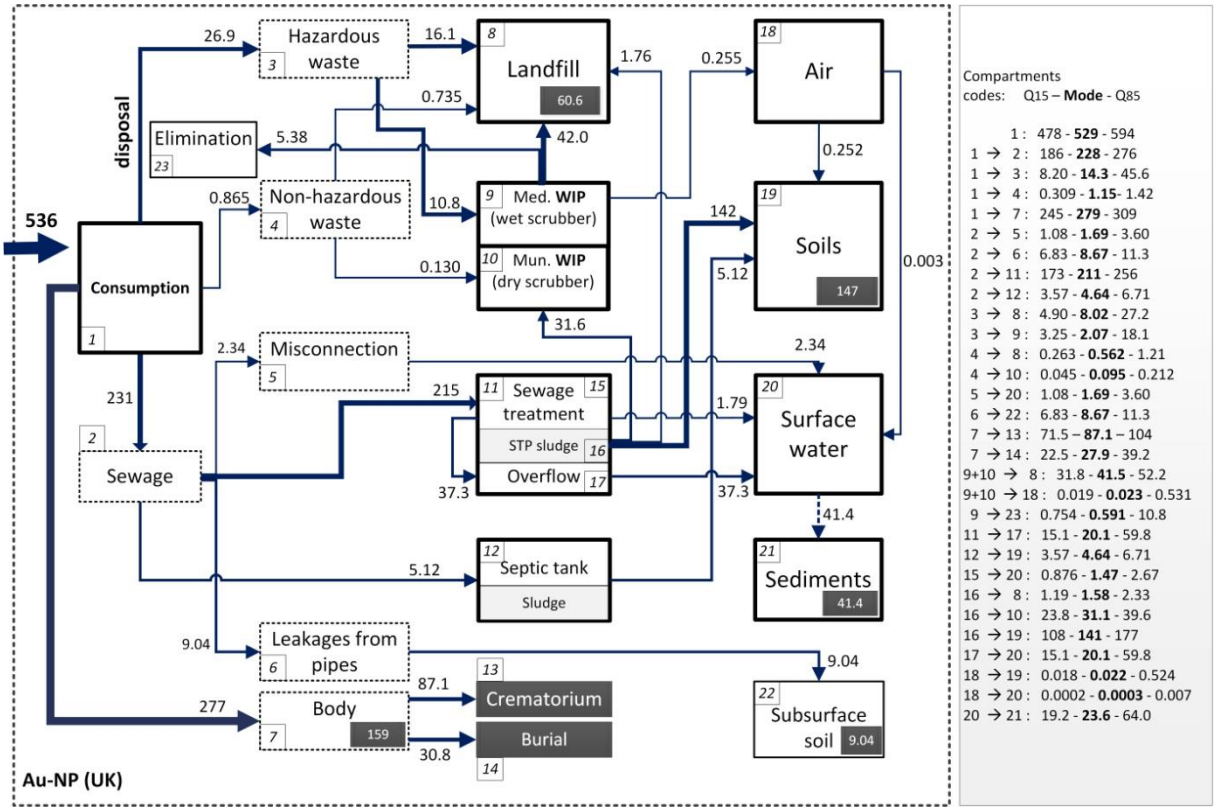


Figure 4.2: Modelled annual prospective mass flows (in kg) of Au-NP in the UK.

Technical and environmental compartments are expressed as boxes and flows are expressed as arrows. The flow volumes used are mean values from the probability distribution of each flow. Each box (compartment) is given a code. Mean values, mode, quantile 15 (Q15) and Quantile 85(Q85) values are also given. These are indicated with compartment codes on the right side of the flowchart. The flow volumes are visualised by the thickness of the arrows. The compartments which we assumed to be the final sink are indicated by a black square box (body of living patients, crematorium, burial, landfill, soil, sediments and subsurface soils). Complete Au-NP suspension in surface water and complete Au-NP sedimentation from surface water to sediment are assumed in the calculation of mass flow (indicated by dashed arrow) and concentrations.(Diagram prepared by: Tian Yin Sun)

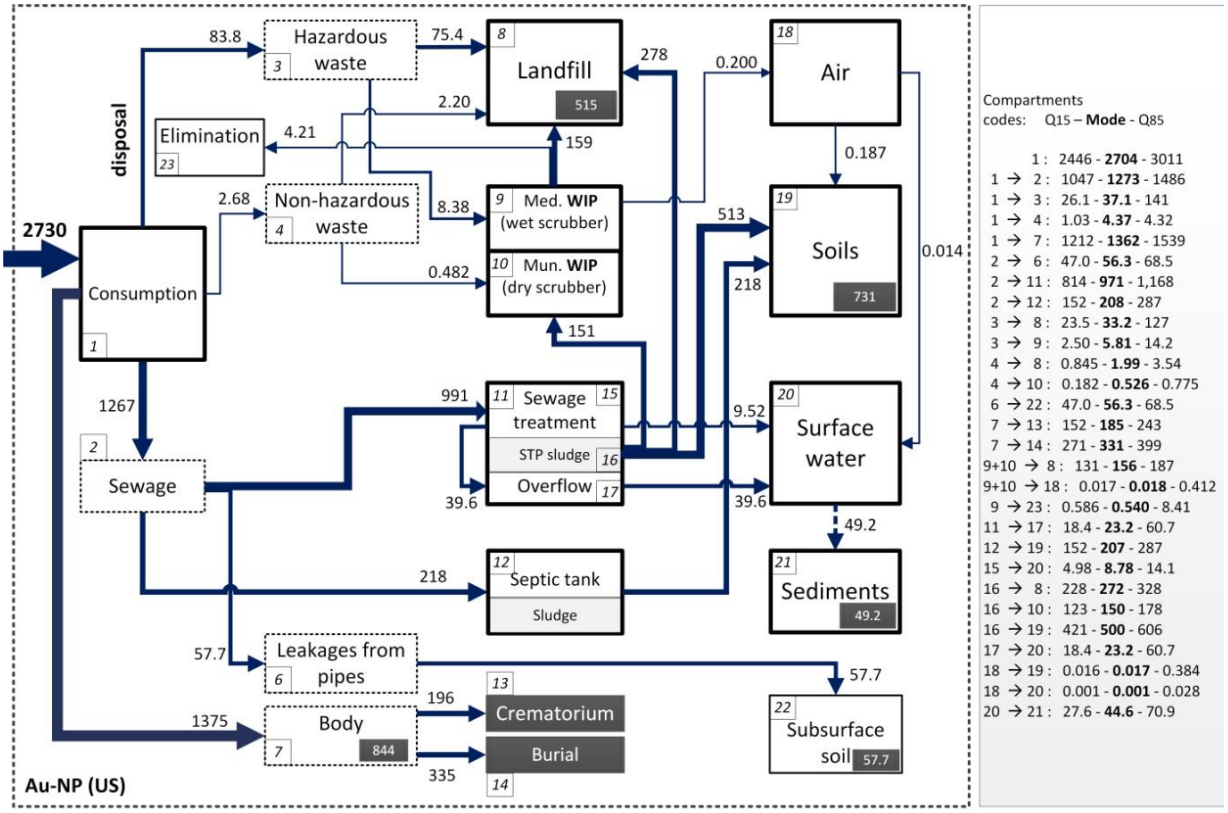


Figure 4.3: Modelled annual prospective mass flows (in kg) of Au-NP in the US.

Diagram prepared by: Tian Yin Sun. Refer to legend under Figure 4.2 for further explanations.

The second largest flow of Au-NP for both the UK and US is via sewage to STPs. About 230 kg and 1300 kg of Au-NP from the total consumption for the UK and US, respectively, end up in sewage. In the UK, small amounts of Au-NP are directly transported to surface water due to misconnections and overflows. No data about misconnection for the US could be found, hence we have not modelled this value, but it is a potentially important source of uncertainty. In addition to misconnections, leakages from sewer pipes result in Au-NP mass transfer to subsurface soils. Au-NP reaching the STP might additionally not flow into the STP processes due to overflow discharges during rainy seasons. Compared to the US, overflows for the UK are more significant; direct discharge to surface waters accounts for nearly one fifth of

the total Au-NP initially reaching STPs; whereas for the US only 0.04% of the total Au-NP by-passes the STP and reaches the surface waters.

Significant removal of Au-NP into the sludge, for both regions, results in significant quantities of Au-NP entering STPs, ending up in biosolids, which is partially further distributed onto agricultural soils as a fertilizer. Total Au-NP inputs in soil were modeled to be around 150 kg/y and 730 kg/y for the UK and US respectively. For the UK, around 32 kg of Au-NP present in the sludge reach the municipal waste incinerators (MWIs)) and a negligible quantity pass to the landfill i.e. the majority is applied as sludge to land. For the US, of the 990 kg of Au-NP present in sludge from centralized treatment works, around 280 kg and 150 kg were estimated to reach the landfill and MWIs compartments respectively. Au-NP from decentralized systems, such as septic tanks, cesspools, can be released to land and/or surface water, or underground water, based on the implementation status of relevant regulations. We assumed all Au-NP passing through the decentralized systems end up in sludge treated soils.

The third major flow of Au-NP is to the hazardous waste compartment for both regions. For the UK, 60% of the 27 kg of hazardous waste was estimated to reach landfill, with the remainder in hazardous medical/clinical/infectious waste (HMCIW) incinerator, whereas for the US, 90% of the 84 kg of Au-NP in the hazardous waste end up in landfills. These values indicate that clinical waste treatment via incineration is not a prevalent practice for both regions, and hence there is a possibility of Au-NP becoming accumulated in landfills in the future. However, these values need to be treated with caution because of the scarcity of national scale data with regard to waste management from health care facilities. Comprehensive and

updated reports for medical waste for the US were not available and hence extrapolated data reported in non-peer reviewed literature sources was used (details in the annexe to this chapter). For the UK, only one peer-reviewed paper (Tudor et al., 2009) containing data for the year 2007 was available. Furthermore, the difference in the health care and biological waste (H&B) generation data in the Eurostat database, updated on December 6, 2013 and DEFRA (DEFRA, 2013a) report for the years 2004, 2006, 2008 indicate the need for coherent definitions and reporting. H&B generation data in the Eurostat database for the year 2010 was approximately 3 times more than the waste generated in 2008. Since there was no publication from DEFRA for the year 2010, the data reported in the Eurostat database could not be verified and the reason for the increase was undecipherable. This indicates the poor state of environmental reporting, monitoring and updating between national scale and regional scale databases and between organisations in the EU.

4.3.3 Au-NP concentrations in technical and environmental compartments

Table 4.2 shows the predicted Au-NP concentrations in STP effluent, surface water, STP sludge, and yearly concentration in sediments and biosolid treated soils for the UK and US. The values presented are mean values, mode values (the most probable values) and their 15th and 85th percentiles (Q15 and Q85) from each distribution. When comparing the two regions, predicted Au-NP concentrations were higher in the UK in nearly all the compartments when compared to those in the US, except for STP sludge which shows similar mean concentrations. The predicted

environment concentration (PEC) in surface water in the US is the lowest among all the modeled technical and environmental compartments for the UK and the US.

Table 4.2: Predicted Au-NP concentrations in technical and environmental compartments.

The mean, mode (most probable values), quantile 15 (Q15) and quantile 85 (Q85) for the predicted concentrations in the technical environmental compartments are provided on the table. Black values designate concentrations; grey values designate yearly increases in concentrations. Au-NP concentrations in surface water and sediments represent no and complete sedimentation respectively. The results are expressed up to two significant digits. Table prepared by Tian Yin Sun.

		UK				US				Units
		Mean	Mode	Q_{15}	Q_{85}	Mean	Mode	Q_{15}	Q_{85}	
STP Effluent		**440**	**360**	220	670	**140**	**130**	71	200	pg/L
Surface water		**470**	**270**	210	730	**4.7**	**4.0**	2.7	6.8	pg/L
STP sludge		**120**	**130**	94	150	**150**	**150**	120	170	µg/kg
Sludge treated soil		**300**	**300**	230	370	**150**	**150**	120	170	ng/kg·y
Sediments		**290**	**170**	130	450	**5.0**	**4.5**	3.0	8.0	ng/kg·y
Hazardous waste		**77**	**78**	23	130	**65**	**69**	20	110	µg/kg
Medical WIP	Fly ash	**270**	**30**	36	530	**260**	**32**	36	530	µg/kg
	Bottom ash	**200**	**25**	27	410	**200**	**26**	27	400	µg/kg
Municipal WIP	Fly ash	**72**	**70**	53	92	**39**	**38**	31	47	µg/kg
	Bottom ash	**55**	**52**	39	71	**30**	**27**	22	37	µg/kg

In the UK, the predicted Au-NP concentration in surface water is higher than in sewage effluent. This is due to the fact that a significant amount of Au-NP is estimated to be released directly to surface waters via overflows. In contrast, the lower Au-NP concentration in STP effluent and the lower PEC in surface water for the US can be explained by the much larger STP effluent volume produced per capita. According to USEPA, 625 L of STP effluent is produced per capita per day (USEPA, 2000) whereas for the UK, it is 150−180 litres per capita per day (British Water, 2009; 2013) (see tables in Annexe: A8.1, A8,2, A8.3). The mean modeled Au-NP concentration in surface waters for both regions is in the range of 5 to 470 pg L^{-1} which is similar to the background gold concentration reported in freshwaters

(reviewed by McHugh (1988)). PECs in surface water of Germany for iron oxide nanoparticles based MRI contrast agents were estimated to be 400 and 3140 pg L^{-1} for the year 2015 for two different scenarios used by the authors (Filser et al., 2013). Measured environmental concentrations in surface waters of various anticancer drugs in use are in the range 500 to 41000 pg L^{-1} (Booker et al., 2014), indicating that the results of our model are at a similar level.

Predicted mean concentrations of Au-NP in STP sludge are 124 µg kg^{-1} and 145 µg kg^{-1} for the UK and US, respectively. The PEC in sludge is considerably less than the measured total gold concentration of 790 µg kg^{-1} reported in a Swedish study (Eriksson, 2001). The measured concentrations of some widely used antibiotics and bacteriocides in dewatered municipal sludge is listed in Table 4.3 (Gottschall et al., 2012). If Au-NP find its use as antibiotics (WGC, 2010; Zhao and Jiang, 2013), then the predicted concentration in sludge will be more. This study did not use the data for potential antibiotic usage of Au-NP.

Table 4.3: Concentrations of some antibiotics in dewatered municipal sludge. Adapted from Gottschall et al. (2012).

Class of Pharmaceutical	**Compound**	**Concentration (µg kg^{-1} dry weight)**
Antibiotics	*Azithromycin*	228
	Ciprofloxacin	3260
	Norfloxacin, Ofloxacin	1010 ,1400
	4-Epitetracycline	334
	Tetracycline	513
Bacteriocides	*Triclocarban*	4940
	Triclosan	10900

The second highest concentration of Au-NP is in biosolid treated soils, although yearly concentrations are only in ng kg^{-1} levels. However, continuous application of biosolids on agricultural land might lead to Au-NP accumulation in soil over years.

The lower predicted concentration of Au-NP in US agricultural soils is because of the larger area of the country and hence larger mass of biosolid treated agricultural soils in comparison to the UK.

The Au-NP concentrations for water and sediment concentrations are for worst-case scenarios, i.e., we did not model any fate in the environment but assumed that for the water compartment no sedimentation and for the sediment compartment complete sedimentation. Only a full environmental fate modelling including a mechanistic modelling of heteroagglomeration, sedimentation and transport will enable to predict the actual concentrations but these models (Praetorius et al., 2012; Liu and Cohen, 2014; Meesters et al., 2014) will rely heavily on input data to the environmental compartments that are provided by the material flow modelling carried out in this study. The environmental concentrations calculated in this work are valid for a regional assessment and are based on well-mixed compartments and follow as such the ECHA guidance (ECHA, 2012). A next step in the exposure assessment would be to regionalize the emissions which also allow to identify hotspots (Gottschalk et al., 2011; Dumont et al., 2015).

4.3.4 Risk assessment with probabilistic species sensitivity distribution

Aquatic species show a wide range of responses to Au-NP, with no observed effect concentrations (NOECs) ranging from 0.12 µg L^{-1} up to 26800 µg L^{-1}; a spread of five orders of magnitude, although most values are in the 1000 µg L^{-1} range. The most sensitive species was the single cell green algae, *Chlamydomonas reinhardtii*, (an acute toxicity study done using 2 nm Au-NP capped with D-manno-pyranoside

terminated PAMAM (polyamidoamine) G0 generation dendrimer) (Perreault et al., 2012b). PAMAM dendrimers of different cores and generations (G2 to G6) have been shown to exert toxic effects in fish, freshwater crustaceans and algae with L(E)C_{50} values in the range 0.13 to 194 µM (reviewed in (Suarez et al., 2011)).

Figure 4.4 shows the cumulative probabilistic species sensitivity distribution (pSSD) for Au-NP in water. The results lacked sufficient resolution to decipher which taxa are most affected, and what particle properties are related to toxicity, though it seems fish (*Danio rerio*) were the least sensitive species when exposed to Au-NP in an aquatic environment. Publications with properly designed experiments (Wheeler et al., 2002; ICMM, 2007) or environmentally relevant exposure concentrations for studying toxic effects of Au-NP on environmental organisms are sparse. Barring a few, the studies selected do not report the L(E)C_x (lethal / toxic effect shown by x% of the organisms at a particular concentration) value, or the statistical method used to arrive at the reported data, do not mention acceptable control performance, and lack characterization of the NPs throughout the exposure duration. These results indicate the high variability of input model data, reflecting the varied toxic potential of Au-NP of different sizes and coating to different species. Therefore, reliable toxicity studies with specific Au-NP used for medical applications are needed for improved environmental risk assessment to influence policy makers for aiding regulatory decision making and responsible innovation (Stilgoe et al., 2013). It is also necessary to study the environmental stability and fate of the coatings of the Au-NP once released to wastewater or the environment.

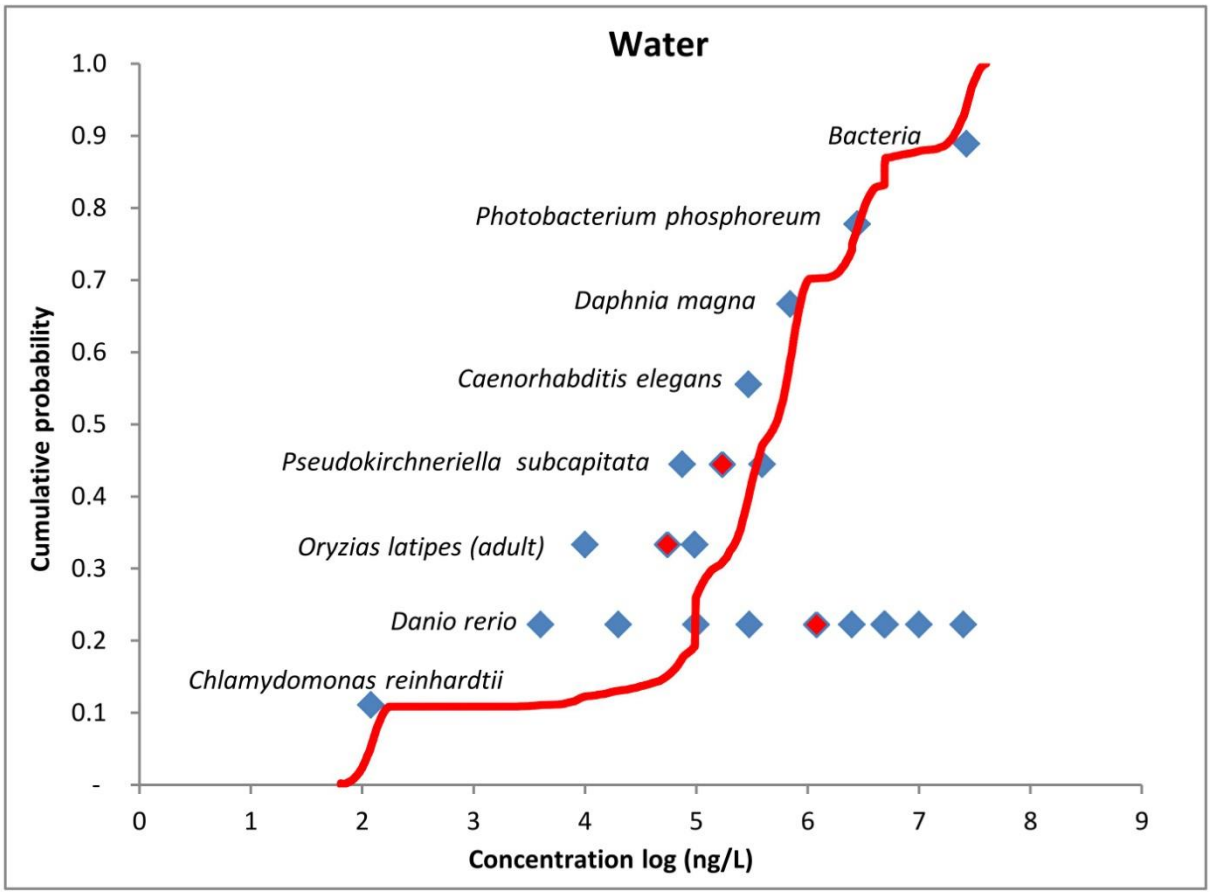


Figure 4.4: Probabilistic species sensitivity distribution (pSSD) for Au-NP for the water compartment.

Probabilistic species sensitivity distribution (pSSD) for Au-NP in fresh water (red line) compared with the raw sensitivity data used (blue diamond). The red diamonds are the geometric means of the raw sensitivity data if there are more than one data available. The number of blue diamonds for each species corresponds to the number of raw sensitivity data available and used. The raw sensitivity data indicate the no observed effect concentrations (NOEC). Diagram prepared by: Tian Yin Sun.

By using probability distributions in place of single values we attempted to address the variability and the uncertainty which is inherent in toxicity studies. The hazard assessment we performed is for a “generic” Au-NP, considering all different sizes and coatings, representing the full width of currently used Au-NP in toxicity studies. This enables us to compare in a next step this “generic Au-NP SSD” with the modelling of

the flows and concentrations which is also for a “generic Au-NP” because data on specific forms of Au-NP is not available.

Figure 4.5 shows the probability distributions of the PECs and the pSSDs for Au-NP in the aquatic and terrestrial environment for both the UK and US. The PEC and pSSD for surface water and soils are compared and risks may arise where the PEC and pSSD overlap. It is clear that there is no overlap between the PEC and pSSD in both environmental compartments considered for the UK and US. The narrowness of the PEC probability density curves is due to the fact that few of the Au-NP application categories dominate the total consumption resulting in a narrow distribution of the total input into the system.

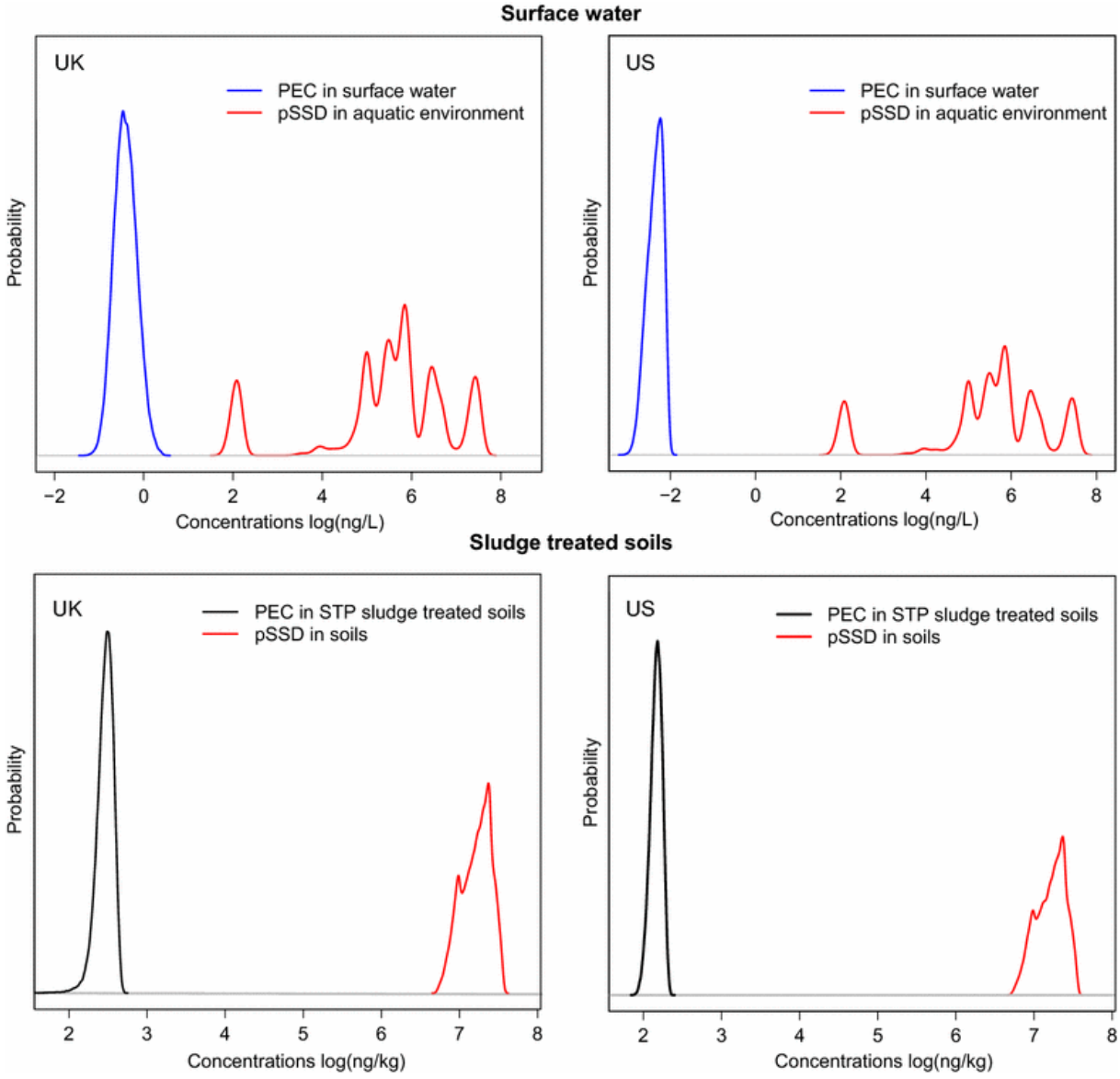


Figure 4.5: Predicted Environmental Concentration (PEC) and Predicted No-Effect Concentration (PNEC) distribution for surface water and sludge treated soils compartment for the UK and the US.

The PEC and pSSD distribution is in blue (water compartment) or black (soil compartment) and red colour respectively. Probabilistic species sensitivity distribution (pSSD) which reflects the no observed effect concentration data compared to the probability distributions of predicted environmental concentrations (PEC) of Au-NP in surface water and sludge treated soils in the UK and the US. Environmental risk could occur where the PEC overlaps the pSSD (not the case for Au-NP). Diagram prepared by: Tian Yin Sun.

Many human pharmaceuticals occur in the aquatic environment in ng L^{-1} concentrations (Ashton et al., 2004; Thomas and Hilton, 2004; Roberts and Thomas, 2006) and studies have shown accumulation of these chemicals in aquatic organisms (Liu et al., 2015a; Liu et al., 2015b; Miller et al., 2015) and their adverse effects (Sanchez et al., 2011; Jobling and Owen, 2013). The very defining property of nanoparticles – size and surface area – coupled with their ability to interact at subcellular levels to generate subtle biochemical changes (Shvedova et al., 2010), their novel properties and gaps in knowledge regarding relationship between chronic and acute toxicity, calls for the inclusion of sub-lethal toxicity endpoints for regulatory decision making. In one scenario we also included selected sub-lethal endpoints in the pSSD (results are provided the Annexe as Section 4A.2: Alternate Scenarios) but the risk assessment does not significantly change.

Because nanomaterials have been found to undergo transformation both inside the human body as well as the environment (Lowry et al., 2012), their fate can change accordingly in real world situations. However, for Au-NP, chemical degradation is rather unlikely due to the inert nature of gold but transformations of surface coatings will strongly affect environmental fate. This will be important when the results from our material flow modelling are used in environmental fate models which include a specific description of fate processes (Praetorius et al., 2012; Liu and Cohen, 2014; Meesters et al., 2014).

In an ideal situation environmental risk assessment should be based on a full characterization of the material and its transformation products; in the case of nanomaterials such complete risk assessments are not yet available (Owen and Handy, 2007). The complex challenge can currently be addressed in a number of

ways, for example by using expert judgment and multi-criteria decision analysis (Linkov et al., 2007; Owen et al., 2009) and species sensitivity distributions (Garner et al., 2015) for different types of a nanomaterial. The probabilistic risk assessment using both probabilistic species sensitivity distributions and probabilistic mass flow models enables us to consider the complete current knowledge in a systematic and comprehensive way and has been applied to other ENM before (Gottschalk et al., 2013; Coll et al., 2015). Both exposure and hazard data are limited and the model provides a way to deal with this uncertainty. Extensive literature search combined with communications with experts in the field has helped us to arrive at plausible estimates. The results from the model can be used to provide a baseline for realistic and environmentally relevant exposure/toxicology studies and can help in iterative problem formulation and solution, as more concrete data becomes available. The modelling performed here suggest that freshwater (and hence sediments) and biosolids treated soils would likely receive highest loads of Au-NP for the UK. Risk from Au-NP to aquatic organisms and soil organisms seems to be unlikely in the near future at a regional scale, although variations will exist temporally and spatially and can also be influenced by the presence of natural Au-NP (Hough et al., 2008). The study models for high loading of Au-NP and depends on worst case assumptions with regard to environmental transformation and fate, hence real concentrations in the environment are likely to be much lower. Developing environmental fate models and models addressing temporal and spatial issues can be a possible next step to arrive at more robust estimates of Au-NP concentration in the environment. Hazard assessment data for soil organisms is severely limited and so uncertainty is particularly high indicating that more Au-NP toxicity research is needed for soil

organisms. Empirical fate and transformation data of Au-NP for incinerators as well as freshwater systems are non-existent and research is needed for Au-NP transformation in STPs with different treatment processes using Au-NP with surface coatings used in medical applications.

Chapter 5: Perceptions of potential of environmental risks from nanomedicine

Or, what experts opine about possible risks to the environment from wide scale future use of nanomedicine

"What is certain is that nothing is certain, not even that is certain" – Joachim Ringelnatz

"....I have approximate answers and possible beliefs and different degrees of uncertainty about different things, but I am not absolutely sure of anything and there are many things I don't know anything about...." – Richard Feynman

5.1 Introduction

As discussed in Chapters 2 and 4, nanomedicines are now being designed with new properties to make them more bio-available, capable of being activated by external stimuli and able to cross biological barriers in the body. They have the *potential* to be of immense benefit for improving human health despite their high cost (currently) and the technical difficulties. It is believed that in the next couple of decades nanotechnology enabled health care applications will have significant influence on diagnosis, prevention and treatment of diseases (ETP, 2006; 2009). Due to their unique chemical and physical properties, such as superparamagnetism and increased luminescence and optical scattering via plasmonic effects, nanoparticles will find increasing application in medicine. However, there is also the possibility that their use could result in toxicities with different modes of action (compared to bulk materials or (macro)molecular drugs) and the diversity of nanoparticle sizes, surface coating, and functionality can result in varied toxic potential (across different cell types and organisms).

The risks to human health for medical applications are being addressed by the appropriate agencies such as the USFDA (Zolnik and Sadrieh, 2009), EMA (Ehmann et al., 2013) and national medicinal agencies[79] in Europe. However, the risks to the environment from such medicines after excretion from the body are sparingly discussed, despite the fact that, as discussed in Chapter 2 (Section 2.2.1), pharmaceuticals products (PPs) have been detected in various environmental compartments. PPs have been detected in surface waters of 41 countries (Hughes et al., 2013), and it has been found that low level chronic exposure to PPs can have adverse and sometimes unexpected effects on non-target organisms (Porsbring et al., 2009; Volkova et al., 2015).

This raises the question as to whether nanomedicines, when they find their way into the environment through excretory processes or from manufacturing, will cause harm to the organisms in the environment. Very few studies have reported on the interaction of nanomedicines with the non-biotic components of the environment and some (limited) ecotoxicology studies have been done with the sorts of nanomaterials used in nanomedicines although it is important to note that these studies have not been done with actual nanomedicine formulations approved or in clinical trials. Details of some ecotoxicity studies were presented in Chapter 2 and the annexe to it.

In order to understand quantitatively the potential environmental impacts of nanomedicine usage, in Chapter 4 preliminary environmental concentrations of a selected nanomaterial used in medical applications, were investigated post usage of the nanomedicine without considering the inputs to environmental systems that might

[79] For example, Medicines & Healthcare products Regulatory Agency (MHRA) in the UK at https://www.gov.uk/government/groups/mhra-innovation-office

result from manufacturing. The chapters (2 and 4) also described the limited data available to characterise risks and hazards from the nanomaterial used in the medical applications and provided the justification for selecting a probabilistic mass model as a first pass worst-case high-usage estimate of environmental concentrations resulting from usage of a selected medical product (Au-NP based medical applications). The results of the quantitative study showed, based on available data, that Au-NP are unlikely to create risks to the organisms in the water and soil compartments at a regional scale in the near future.[80] However, many assumptions and extrapolations were done to arrive at the results because of the novelty of the field and scarcity of relevant data.

Over the years, scientists have been called upon to serve in various committees instituted by the government (Jasanoff, 1990). Scientists do contribute to discussions on policy issues and regulations, although the choice of expert might not be non-partisan and might have an underlying political agenda. Regulatory agencies, like the environmental and medicines regulatory agencies, also comprise many scientists. Moreover, regulatory agencies need to be prescient with regard to hazards and risks from emerging technologies and their applications so as to regulate them before it is too late, as was the case with DDT and others (EEA, 2013). Also, in the case of high uncertainty and knowledge gaps, expert judgment is one of the ways to evaluate and characterise risks. Furthermore, the hazard identification step in risk assessment is qualitative in nature although to characterise risks, quantitative data are needed. Hence, as part of the thesis, the perspectives of

[80] A specific timeline could not be established because the probabilistic model used is not dynamic; input data was annual consumption amount of the most recent year for which prevalence of disease data was available. However, wherever available and needed, disease prevalence for the last few consecutive years or more was checked - the prevalence rate was found to be stagnant over the years.

scientists, regulators, policy makers and representatives of industries along the nanomedicine innovation pathway on the potential environmental impacts from nanomedicine and their perspectives on the adequacy of current risk assessment frameworks were gathered via semi structured interviews to supplement the quantitative modelling exercise conducted in Chapter 4. The findings of this qualitative study are the focus of this chapter. It is important to note here that the interviews were not done to validate the model results presented in Chapter 4, they were conducted with the aim to gather opinions of eminent experts to provide a more holistic and broad-ranging overview of experts views regarding the environmental, health and safety challenges of nanomedicine. Moreover, the interviews were conducted between May 2011 and September 2013 and the modelling study was done in the period of December 2012 to April 2014.

There are varied views on risks posed by nanomedicine. In a study by Petersen and Anderson (2007), experts rated human health risks from medical applications to be high, whereas in a study by Siegrist et al. (2007) experts considered risks to be low from use of nanomaterials in medicines compared to risks associated with nanomaterials in other areas such as food packaging and sunscreens. Similarly, Capon et al.'s (2015) study showed that use of nanomaterials in medicines was considered less risky by academics and industry representatives when compared to the use in food, cosmetics and pesticides. Moreover, to ensure safe and sustainable propagation of new and emerging technologies, all possible impacts of emerging technologies should be identified and described with respect to a particular

application sector[81] in order to avoid fictitious science and social science (Nordmann and Rip, 2009). Description of these impacts may be theoretical or hypothesis-based, but they need to be explored and deliberated upon so that concerns are assessed, and also to enable policymakers to agree on and develop research directions and priorities for a roadmap.

To date, there have been no studies gathering expert viewpoints across the nanomedicine value chain regarding the environment risks from nanomedicine. However, one study from Portugal, intended to understand how nanomedicine researchers perceived ethical issues in nanomedicine, reported that of those researchers (17 out of 22) who expressed potential risks from nanomedicine, 6 (of the 17) mentioned environmental risks of nanomedicine (Silva Costa et al., 2011). In this chapter, I discuss the responses of the experts (from research, industry, regulatory/policy) on: (i) the potential environmental hazards and risks from nanomedicines, and (ii) the adequacy of the existing risk assessment framework for assessing environmental risks from nanomedicine.

Before describing the methodology in Section 5.2, I define some terms used here. Althaus (2005) has described the concept of risks as used in various disciplines (e.g., sociology, history, medical). For example, logic and mathematics see risk as a calculable phenomenon, science and medicine sees risk as an objective reality, whereas sociology views risk as a societal phenomenon and psychology sees it as a behavioural and cognitive phenomenon.

[81] For example, comprehensive identification and description of benefits, risks and uncertainties related to biotechnology and food, and biotechnology and pharmaceutical products rather than implications of biotechnology as a whole.

I have elicited expert responses on the type of risk assessment which is housed within the science and medicine fields as discussed by Althaus (2005), and with special emphasis on environmental risk assessment (ERA). Environmental and human health risk expressed simply is hazard **x** (multiplied by) exposure; where hazard and exposure are assessed in the laboratory using standard protocols and methods and quantification done using certain assumptions and postulates. Therefore, risk is the likelihood or probability of an event which is not desired. ERA is conducted primarily for chemicals and pollutants and it helps decision makers to set environmental quality standards (EQS).

Various regulatory agencies (and across jurisdictions) use the terms in risk analysis interchangeably.[82] To avoid confusion, in this thesis the risk assessment framework I use has four steps:[83] hazard identification (toxicity studies to evaluate toxicity); hazard characterisation (dose-response assessment); exposure assessment (amount of toxicant inhaled, ingested, or absorbed); and risk characterisation (risks in terms of population).

Risk assessment helps regulatory agencies to take decisions based on evidence and supposedly 'objective' analysis.[84] In the case of pharmaceuticals and medical devices, regulatory agencies need to take into account the benefit-risk ratio of the product. Also, potential environmental harm is not sufficient at present to stop or prevent approval of a drug (EMA, 2006a) in the EU. In cases where environmental

[82] For example, in the EU, the ECHA describes risk assessment as hazard assessment, exposure assessment and risk characterisation. It can also be represented as exposure assessment, effects assessment (hazard identification and dose-response) and risk characterisation.
[83] https://www.epa.gov/risk/human-health-risk-assessment
[84] A recent study by the EMA showed that even medicinal assessors are influenced by demography and their own attitudes. For details see: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/02/WC500123226.pdf. Moreover, hazards are generally socially constructed. Hence, though, risk assessment is said to be objective and a scientific process and hence is claimed to be positivist, risk assessment or any scientific process is value laden and subjective.

harm is foreseen, proper information and communication of risk management steps is advised by the USFDA (USFDA, 1998; 2015). The study presented here adds clarity to the exploratory discussions on environmental risks from nanomedicine by presenting views from experts in academia and representatives from government agencies, regulatory bodies and industries, allowing any divergence of opinion between groups to be identified.

I discuss briefly in the next section (Section 5.2) the methodology of collecting and analysing the data, and then, in Sections 5.3, the views of the experts on potential environmental implications of nanomedicine are elaborated, clustered in major themes as per the questions in the questionnaire. In Section 5.4., I discuss the overall viewpoints of experts and how they vary among the categories of experts. In Section 5.5, I conclude by confirming with Stirling's (2007) arguments that in the case of uncertainty and ignorance, risk assessment is not fool-proof and is, in fact, is irrational and does not fulfil the mandate of evidence based policy, leading to the conclusion that a different approach to governance of nanomedicine is required. I suggest the increasingly popular concept of responsible innovation as one way forward to govern emerging technologies and products, since, as will be discussed in Chapter 6, this maps well to the existing paradigms of risk assessment from medicines.

5.2 Methodology

The thesis's overall methodological approach was discussed in Chapter 3, however, here I recapitulate briefly the method of collecting the qualitative data which forms the

basis of this chapter. I conducted 62 expert interviews from the nanomedicine innovation chain, using a pre-set questionnaire shared in advance with the interviewees, and queried them on potential environmental hazards and risks, exposure scenarios, adequacy of current risks assessment frameworks for nanomedicines, gaps in knowledge and challenges in the nanotoxicology domain which can impact a regulator's ability to formulate new regulations or change existing regulations. Risk can only happen when there is an exposure, i.e., risk is very specific to a context and hence both hazards and risks were explored. The abridged sets of questions asked are presented in the annexe to Chapter 3.

In the analysis presented in the sections below, I have not discussed the exposure pathways of medicine. This has been covered conceptually in Chapter 2 and Chapter 4, Figures 2.4 and 4.1 respectively. Also, responses to the question on knowledge gaps in the nanotoxicology domain are not detailed in the succeeding sections because of the many publications dealing with this issue (e.g. Oberdorster et al., 2005; Handy et al., 2008; Handy et al., 2012; Grassian et al., 2016). Briefly, detection of nanoparticles in the environment against a background of naturally occurring colloidal particles, the characterisation of nanoparticles, linking exposure in natural environment to toxicity, the dynamic nature of nanomaterials (such as aggregation, agglomeration, dissolution), fate and transformation in the human body and the environment were mentioned by the interviewees, which corroborated with the available publications and as discussed in Chapter 2. Moreover, this thesis presents a small slice of the discussions that were encountered, and elaborating on all these different dimensions would make the scope of the PhD unmanageable.

A general inductive approach (Thomas, 2006) was adopted to analyse the data in order to form a "clear link with the research objectives and the findings from the raw data" (p.238). Due to the exploratory nature of the study, there is no theoretical framework against which the findings can be corroborated. However, the findings have been explained by frequent reference to studies in the field of nanotechnology and chemicals where experts' opinions have been surveyed. For example, the findings are related to outcomes from quantitative studies on expert judgements on risks from chemicals (Kraus et al., 1992; Neil et al., 1994; Slovic et al., 1995; Slovic et al., 1997; Mertz et al., 1998), expert perception on nanomaterial regulations, risks and benefits (Scheufele et al., 2007; Besley et al., 2008; Corley et al., 2009; Engeman et al., 2012; Beaudrie et al., 2013; 2014), and surveys related to perceptions of risks related to nanomaterials and nanotechnology by industry and other stakeholders (Helland et al., 2006; Conti et al., 2008; Helland et al., 2008).

5.3 The conversations

5.3.1 Viewpoints of expert interviewees on environmental hazards and risks from nano-therapeutics

5.3.1.1. Hazards possible but risks unlikely*:* The experts interviewed generally believed that nanomedicines can cause environmental hazards, though they generally were of the opinion that they would not cause risks (as environmental concentration would be less). They reasoned that the nanomedicines would undergo transformation in the body as well as in the environment which could make them less hazardous. The prevalent idea of experts was that pharmaceutical manufacturers

follow “good manufacturing practices” (GMP) and nanomedicines will be very expensive, so wastage will be less, though studies have reported the presence of pharmaceuticals downstream of pharmaceutical industries. For example, a recent study reported that the monitored amount of PPs in effluents from WWTPs receiving waste water from pharmaceutical industries was 10 to 1000 times higher than typical WWTP effluents (concentration less than 1 μg L^{-1}) not receiving discharge from pharmaceutical industry waste water (Phillips et al., 2010) and hence discharge from pharmaceutical industries can be an important source of PPs in the environment, contrary to the opinion expressed by the experts.[85] However, literature published by industries report lower concentrations from their manufacturing and formulation units. For example, by using a mass balance approach, Roche (at Basel, Switzerland) estimated the concentrations of APIs to be in the range 0.01 to 38 μg L^{-1} in their effluent (Hoerger et al., 2009). Moreover, experts mentioned that hazards and risks (if any due to use of medicines) will be local, i.e., in hospital waste waters, though the bioactive nature of medicines was explained as the source of the hazard, i.e., medicines are designed to either kill cancer cells, or to influence specific biochemical pathways, and hence they can influence similar biological pathways in non-target organisms. They gave the popular examples of oestrogens and anti-cancer drugs to substantiate their viewpoints. One of the experts, for example, when asked whether nanomedical products might pose ecotoxicological hazards and risks said:

“I would say yes. For instance, concerns over oestrogen whether it comes from birth control pills or whether it comes from the farming industries that get into waste streams has affected apparently some fish populations. And is there any reason to expect that just because it’s a

[85] The monitored concentrations of PPs in the receiving waters of pharmaceutical manufacturing units in both developed and developing countries have been reviewed by D.G. Larsson. LARSSON, D. G. J. 2014. Pollution from drug manufacturing: review and perspectives. *Philosophical Transactions of the Royal Society of London B: Biological Sciences,* 369.

nanomaterial and inorganic that somehow it might not behave as a drug? Things that interact with biological systems as drugs [do] *can obviously interact with biological systems of other animals, there's no reason* [to believe] *that it might not also affect things at a mechanical level in the environment."* [Industry 04]

Several experts expressed that risks to the environment would be negligible due to low volumes and dilution and few were confident that nanomedicines would not cause any risks in near future. However, many experts gave a balanced (and explanatory) response. A downstream expert identified the problem with pollution from pharmaceutical industry.

"So, for the industries that are making the drugs, it's how efficiently I suppose these materials are actually going to be used, what sort of waste there is, because where industry is concerned, it's likely that that waste is going be dumped and so, I think disposal of waste in the manufacturing industries that are making the drugs would be the primary environmental hazard." [HTOC3]

The expert went on to add that from clinical use the risks would be negligible; however, if use of the therapeutic is widespread and frequent then there could be likely exposures and risk.

"With regard to actual clinical use, I think it's going to be a lot lower as far as environmental hazard is concerned. If it's a material that's excreted from the body then you have got hazard as far as the water ways are concerned but again, it goes back to the level of usage. If it's a very minimal use then I think that the impact is not going to be that heavy. If it's something that would be used, for example, to treat everyday cold and which everybody would be taking on a regular basis and it is excreted from the body then you've got a much more substantial problem. So, it's similar I suppose to women taking contraceptive pills and there have been concerns about the hormones that are going into the waterways and how that affects feminization of fish but you've got millions of women taking it on a daily basis and so that's where you have the problem. I think, unless nanomedicines are actually used to that extent, then I think that that's not going to be quite as much of a problem. In the near future, it's very least but the manufacturing side of things, I think is more problematic." [HTOC3]

A typical response, generally by scientists, industry representatives and toxicologists on the question of potential environmental hazards and risks of nanomedicine followed the structure that nano-therapeutics can cause hazards, but the amounts are negligible, they can be biodegraded or transformed in the body and the environment and then compared it with other industries or natural nanoparticles. For example, an industry representative said:

"It's very difficult to say that some of them won't get into the environment. Whether they get in, in the same form that they went into the body is another matter. The body can do an awful lot of metabolism. So, there could be changes there. The whole environment issue is a bit strange because there are nanoparticles out there, all around us, and nano seems to scare some people" [Industry 08]

The industry representative went on to say that the quantities will be insignificant and that medical products go through rigorous toxicity testing for humans and later made the comments more neutral by adding that the toxicity is not tested on environmental organisms like blue-green algae. Finally, they said:

"I think it's [hazards and risks are] *very unlikely and the environment is a huge place, there is a massive dilutional effect ….you can't say no* [to hazard and risk], *but I think it would be very unlikely."* [Industry 08]

A social scientist emphasised on the phrasing of the question and said risk potential would be there, even if minimal, so the possibility of no risk is unobtainable:

"Yes, of course, it has the potential. This question says do you think nanomedical applications might have the potential to pose environmental health risks. But it would be very, very odd to say no to that question, wouldn't it?" [SS03]

This expert asked what other interviewees had stated and I shared that most of them had said that as the quantities are likely to be minute, risk is unlikely. This interviewee went on to say: “So, it would be reduced risk but still some risk.”

5.3.1.2. Possibility of risks more from nanomaterials used in other industries:

The experts interviewed expressed more concern for nanomaterials used in cosmetics, textiles and other application areas. Several experts compared the risks from nanomedicine with other industries or compared with global environmental challenges, such as climate change and air pollution.

“Nanomedicines I think is probably an absolutely tiny component compared to what else has been chucked out from other industries.” [NMS 16]

Some upstream scientists and representatives of medicine regulatory agencies emphasised that benefits versus risk of medicines should be assessed. They also said that nanomedicines might result in reduced environmental concentrations of medicines because of higher efficacy and targeting capacity in comparison to conventional drugs. One regulator, for example, said:

“Nanoparticles are not the only pollutants, so maybe in the future you can have minute portions releasing into the environment instead of big quantities of aluminum, big quantities of other materials which are equally polluting. So I think it is important to keep the perspective. Nanostructures might at the end of the day reduce pollution from medicines, in many ways, in addition to potential benefit to public health.” [Regulator 2]

However, despite the suggestion of negligible concentrations of nanomaterials in the environment, some upstream academics and industry representatives expressed concern about the health risks and consequently environmental risks of engineered

nanomaterials which can be aerosolised or are in powder form. This probably may be due to many publications on health risks from CNTs (reviewed by Donaldson et al., 2006; Aschberger et al., 2010) and historic and epidemiological studies on inhalation of fine particulates and worker exposure to air contaminants in the workplace. Other studies (for example, Petersen and Anderson, 2007; Engeman et al., 2012) also have reported that experts and industry representatives generally view inhalation exposure and dry powders of nanomaterials to be of high risk. Another probable reason could be that risk science has matured in the case of human health impacts of air borne pollutants and acceptability of the risk assessment methodology has also been achieved for such exposures and hence experts from academia and industry managers drew upon their knowledge to explain the possible risks of nanomedicine if in powder form or if nanomedicines are administered through the nasal route. However, a key question here is whether this is "folk theory" (Rip, 2006)?[86] Experts emphasised that the (nano) medicines they were working on are generally in liquid or are nanoparticles only when in aqueous media. For example, an upstream academic expert who also has established a company said:

"First of all the nanoparticles that we make, they are nanoparticles only once they are in contact with aqueous media. So when they are not in contact with aqueous media they are not particularly nanoparticles. The nanoparticles that we should be concerned about are those that can be aerosolised, those that can be in the atmosphere. You can breathe them in. Most of the NPs under development are not those types so they are not being made as dusts and fine powders. They usually are made as an aqueous dispersion ...and they will only cross the biological barriers once they are introduced into the body and they are normally introduced by ingestion or by injection, those are the two main routes." [NMEn07]

[86] A point to note is that very few conventional medicines (e.g. medicine for asthma, migraine) are administered through the nasal or inhalation route and hence I question whether this could be a "folk theory". Folk theory as per Arie Rip is a "pattern that evolves in ongoing practices, and serves the purposes of the members of the various practices"; however, they are based on some experience but not systematically checked. RIP, A. 2006. Folk Theories of Nanotechnologists. *Science as Culture,* 15**,** 349-365.

Moreover, no novel environmental risks from nanomedicine were suggested by most experts which is similar to Silva Costa's (2011) study where nanomedical researchers did not think that ethical issues specific to nanomedicine need to be considered.

5.3.2 Views of expert interviewees on environmental hazards and risks from medical devices

Most experts mentioned that medical devices made with nanotechnology wouldn't be hazardous to the environment as the nanoparticles would be embedded within a non-nanomaterial and consequently there wouldn't be any direct exposure. Hansen et al. (2008) developed a categorisation framework for nanomaterials which classed consumer products where nanoparticles are suspended in solids as having no exposure. This conviction that embedded or bound nanomaterials would not cause harm or raise less concerns has been reported by Weil in her survey of 22 firms in the US Midwest (Weil, 2013) and by Capon et al. (2015) in their survey of Australian scientists, representatives from industry and government, and lay persons. However, some experts mentioned that general wear and tear can cause some exposure. The possibility of human health risks from wear debris of medical implants have been reported and novel mechanisms of effects elucidated (for example, DNA damage caused by influencing the cellular signalling pathway without comprising the structural integrity of cells or the cell barrier) (Bhabra et al., 2009; Sood et al., 2011).

Interestingly, some upstream experts and representatives from regulatory bodies mentioned designing medical drugs and devices in such a manner that they do not have negative environmental implications, so called safety-by-design or benign-by-

design considerations. For example, one expert from a regulatory agency said regarding design of devices:

"*Scientists are, for example, coating those nonbiodegradable devices in a way that once they go into the environment they become susceptible to light and destroyed by light. So the beauty of the nanoparticles, even the activable implantable ones, is that you can play with the physical properties, the optical properties whereby as soon as it goes out of the body they can be self-destroyed.....if it was really the amount, the cumulative amount in the environment would pose a hazard, you can find a way to make them vulnerable to the environment, so difference in temperatures, for example, can break the particle or light exposure can break the particle"* [Regulator 02]

On the other hand, in a study by Doerr-MacEwen and Haight (2006), where experts from academia, industry and government from North America and Europe were consulted to gain their perceptions on environmental risk management from pharmaceuticals reported that incentives of green drug manufacturing strategies were ranked low both in terms of effectiveness and feasibility (7th and 8th rank respectively out of 8 environmental risk management strategies suggested in the study) for risk management. The following interesting remark was made by an industry representative who participated in Doerr-MacEwen and Haight's study: "Structure and function are inextricably linked. The attrition rate for drug candidates is already very high based on safety, efficacy, stability, and manufacturing requirements. Adding yet another requirement with respect to biodegradability for the structure of these molecules will probably result in a massive increase in the attrition rate of drug candidate" (p.862).

Using biodegradable substrates (though substances after biodegradation can give rise to toxic products) and not using plastic casings for lab on chip devices was

another design feature mentioned by the interviewees. A social scientist mentioned that rather than having end-of-pipe solutions and more regulations, it is better to have a technological fix to make a product less risky to the environment. The case of small amounts of nanomaterials from medical devices was also discussed by the interviewees. They also shared that contaminated medical devices are incinerated at their end-of-life and hence are not likely to pose hazards and risks. I did not enquire further whether the experts meant hazards and risks to human health or the environment, because mostly these responses were preceded by discussions regarding safety to human health. Many experts mentioned the need to have proper disposal instructions, but were confident of the current disposal guidelines of medical devices and its implementation success. However, while collecting data for Chapter 4, the poor state of reporting for medical waste and my interaction with the head of waste management in an NHS hospital indicated that the current disposal guidelines were not being implemented properly. This person mentioned that it was difficult to emphasise the importance of segregation of the various types of wastes and eventually most waste (domestic as well as recyclable, which became mixed with hazardous waste) were likely to be disposed as hazardous waste.

5.3.3 Views of experts on adequacy and adaptation of current environment risk assessment framework for nanomedicines

Downstream experts and a few upstream experts commented that in principle the current risk assessment procedure is applicable for nanomaterials and that only some adaptation is required for test systems, standards, and protocols for hazard identification and characterisation and exposure assessment. A need for

modification of current test media and protocols has been shown in some studies (see for example Casey et al., 2007; Park et al., 2013) and establishment of suitable dose metrics has been discussed for conducting various exposure assessment studies (Oberdorster et al., 2005; Oberdörster, 2010; Simkó et al., 2014; Delmaar et al., 2015). However, the majority of experts interviewed including some downstream experts were unaware of the ERA guidelines for human pharmaceuticals or the need for ERA as a step (if needed) in the drug approval process.

An eco-toxicologist aired their disagreement with the current broader scientific consensus about the inadequacy of current regulatory toxicity endpoints to reflect systemic effects of nanoparticles. The expert emphasised that new toxicity endpoints specific to nanomaterials are not needed and that current endpoints meant for bulk chemicals are sufficient as follows:

"I think the endpoints are fine. So, I don't think there's any need for different endpoints for nanomaterials. I think probably the tests are fine as long as they're performed in the right way. So, I think when performing the test, the people need to think about the fact that they have got nano form of the material and you want the test to reflect that. I really don't think we need new endpoints for nanomaterials. We just need to think about refining the test so that we are able to do them with nanomaterials and that the results are meaningful in the natural environment." [ETOC 3]

The interviewee continued:

"I know a lot of academics say that we need new ecotox for nanomaterials, but I think the endpoints have been established for years and they are there to protect different taxonomic groups. There's no reason why we should say a biochemical endpoint or histological endpoint for a nanomaterial and not do it for other chemicals. So, I really struggle with some of the academics that are really trying to push subtle [toxicity] *endpoints."* [ETOC 3]

The above excerpts indicate one extreme end of the spectrum of opinions regarding adequacy of existing risk assessment frameworks for nanomaterials and at the other end another extreme viewpoint from an eco-toxicologist was that risk assessment from nanomaterials should be viewed through a completely new lens.

"I know that the whole strife is of course how can we adapt our test methods so that we can test nanoparticles, but I have formulated another hypothesis saying that it is not possible to adapt. I think we need to start on a clean sheet of paper and that's because as far as I read most of the guidelines, now it is ecotoxicity, that's really my area, our underlying assumption is mainly that we are dealing with dissolved chemicals……." [ETOC 1]

These kind of contrasting views and divergences regarding testing methodologies, standards and protocols are not new in the "young science of risk assessment" (Neil et al., 1994 , p. 200). A survey of British toxicologists showed that these scientists disagreed on the extrapolation of animal models to sufficiently predict risks to human health (Mertz et al., 1998). In case of nanomaterial risk assessment, consensus expert opinion is that the risk assessment framework for bulk conventional chemicals can be used for nanomaterials; however, it has been discussed that the properties of nanomaterials are different than bulk materials and hence the procedures for conducting risk assessment will need customisation (Rocks et al., 2008; SCENIHR, 2009; Grassian et al., 2016).

Some upstream experts and industry representatives mentioned that as a rule of thumb they treat nanomaterials that they work with as hazardous, since they do not have complete understanding or knowledge of the toxicity of the nanomaterials they are working with, and hence follow the necessary rules of managing and handling hazardous waste. The representatives from industry and some of the upstream experts in academia indicated that they are using whatever knowledge they have to

deal with risks and proactively engage with the Health and Safety Executive (HSE) to sort out issues.[87] Similarly, some [NMS 09 and NMS 19] emphasised the difficulty of filling the existing COSHH[88] forms (designed for traditional molecular chemicals) and the need to adapt the forms for nanomaterials. This indicates a certain amount of concern and care on the part of the researchers, a kind of moral responsibility as presented by Ladd (1982) which is necessary in the context of knowledge gaps and uncertainty and lack of regulation or specific prescriptions for behaviour which is pervasive in the nanotechnology field, indicating a strong alliance with, for example, the EC's Code of Conduct for responsible nanoscience and nanotechnology.

Only one expert (an eco-toxicologist) mentioned about the threshold or trigger value of environmental concentration (PEC) to do an environmental risk assessment as not being correct for nanomedicines because of the value being a mass based metric and hence not taking into account the unique functionality of the nanomedicines.

When asked about the applicability of the partition water coefficient (log K_{ow} values) to assess the persistence and bioaccumulation potential of nanomaterials, most of the experts (who were not ecotoxicologists) initially interviewed acknowledged their lack of knowledge regarding the question and asked for further explanation. Later I asked this question only to those experts who I felt would be able to answer. The experts who were posed the question on applicability of log K_{ow} for ERA of nanomaterials unanimously responded that log K_{ow} was not a good surrogate and they stated that it was not even fully applicable to conventional pharmaceuticals for assessing persistence. For nanomedicines, they suggested that finding log k_{ow} value

[87] An interesting point to note here is the absence of any mention of the Environment Agency in the discussions.
[88] COSHH: Control Of Substances Hazardous to Health.

is complicated and they responded by saying it will need to be assessed on a case-by-case basis. Experts (all eco-toxicologists and representatives of a regulatory agency) who had an understanding of the concept expressed uncertainty about estimating it in the laboratory. Three eco-toxicologists [ETOC 1, ETOC 3, ETOC 4] stressed that octanol-water partition coefficient was not the right proxy for bioaccumulation and one further added that the distribution co-efficient is not even the right predictor of bioconcentration: "I don't think we should be thinking about the log K_{ow} for nano materials or D_{ow}." [ETOC 3]. The challenges of and issues with measuring octanol-water partition coefficient for nanomaterials have been discussed in Chapter 2, Section 2.3.

Interestingly, some upstream experts voiced that they need to consult with their other colleagues who might be able to tell them how to go about measuring log K_{ow}. Some of the human toxicologists I interviewed did not know about the use of log K_{ow} indicating strong disciplinary orientations. The medicines regulatory agency experts indicated that the criteria of log K_{ow} for medicines is one area that is being looked into. One of the ecotoxicity experts interviewed got back to me later after discussing the issue with a material scientist:

"*the log K_{ow} measurement is a bit of a moot point in terms of nanomaterials – specifically if they are dissolved then they are no longer nanomaterials and should be therefore treated as a normal chemical. Instead there should be a measurement of the affinity of the surface of the nanomaterial to a polar or non-polar liquid…At the end of the day if the energy of the system of a nanomaterial and water is higher than the energy of the nanomaterial/lipid system, then the nanomaterial will sit in the lipid system.* [ETOC 6]

Several experts from academia and the policy makers were unaware of the regulatory requirements regarding environmental risk assessment of

pharmaceuticals. Lack of awareness of regulations has been reported by Marquis et al. (2011) where they conducted a thought experiment with bench scientists researching on nanomedicines to understand the requirements to get approval for a medical product from the USFDA.

Few scientists in their responses mentioned about safety to patients and safety to health care staff and about their own practice in the laboratory regarding following the necessary safety rules indicating that risk framing of scientists is based on their subject expertise or institutional affiliations as has been observed elsewhere (Slovic et al., 1997; Powell, 2007). This might be perhaps due to difficulty to imagine that questions on environmental risks of nanomedicine could be asked though the aim of my research was detailed in the introductory mail and questionnaire and associated documents were sent in advance. Or, perhaps due to the stress and time limitations part and parcel of academic life (Dowling, 2008), they had not had the time to go through the questions.

Few interviewees (across all stakeholder categories) stressed the novel properties of nanomaterials and hence new risks, the lack of knowledge of the fate and behaviour of nanomaterials in the human body as well as the environment, and the associated uncertainties. Below is an excerpt from a detailed discussion:

"The first part of any risk assessment is probably the formulation of exposure assessment. So, some of the assumptions in exposure assessment don't fit the way the nanomaterial would behave for they don't capture the fact that they're dynamic, that they change in time." [ETOC4]

This expert, and some others, believed that the current risk assessment framework for chemicals was applicable for nanomaterials, however, they detailed the

uncertainties and challenges involved in conducting an environmental risk assessment of nanomaterials:

"The basic principles of risk assessment are fine. The devil is in the detail. So, transformation is important. So, you're trying to track or assess risk on the dynamic system and that's challenging because at which point do you assess risk. So, for example, do you want to risk assess materials even though they're modified in the environment or do you want to assess the modified materials. You can do the tox tests and hazard tests, but as in any form of risk assessment, what those mean in terms of real affect is less easy to interpret because of this dynamic nature change." [ETOC4]

A social scientist clearly indicated the need for communicating uncertainties and knowledge gaps: "I think it's important not to just focus on the risks but also to take seriously the prospect of uncertainties and areas of ignorance as well" [SS04].

5.4 Discussion

Use of nanomaterials in health care is perceived to be beneficial by experts (as expressed by the experts interviewed in the current research and in other studies) as well as the public (Bottini et al., 2011). In contrast, environmental pollution risks from nanomaterials are generally of lower concern to experts than animal and human health risks (Besley et al., 2008). Moreover, it is well established that non-human stakeholders, i.e., the environment are rarely paid much attention in risk assessment (Phillips and Reichart, 2000). Furthermore, risk and responsibility are defined and perceived as per a particular socio-cultural-economic situation and is highly contextual to a particular sector (Siegrist et al., 2007; Siegrist et al., 2008). In some sectors like health, tolerability and acceptability of risk could be different when compared to other sectors such as food or transportation.

In few instances, a lengthy discussion took place with regard to risk aversion, especially in the context of the UK. It was explained how the risk aversion attitude is thwarting innovation and making the life of academic scientists more challenging. These same experts expressed unhappiness with the current health and safety guidelines due to their sometimes 'unnecessary' cautiousness. They expressed wariness of the current stringent health and safety aspect in the UK and preferred not to be burdened with more new rules and regulations regarding health and safety of nanomaterials. Some experts explained the hazardous substances handled in chemistry labs and in comparison expressed the possible benign nature of nanomaterials that they were using. Most upstream scientists and industry representatives explained the concept of possible risks and hazards by citing their own research work and the materials they use. The nanomaterials they were using were either present abundantly in nature, e.g. silica or were considered to be biodegradable, like polymers (can be persistent if not biodegradable), proteins, and lipids. Robichaud et al. (2005) used an insurance industry risk quantification protocol and applied it to industries manufacturing chemicals and compared them with nanomaterial manufacturing and found that environmental risks from manufacturing nanomaterials were less or equal to those from other chemicals such as, manufacture of aspirin, petroleum refining. However, novel properties of nanomaterials, their persistence and unique modes of action can cause environmental risks and remain to be studied (the nano(eco)toxicology field is very new).

Additionally, detailed discussions took place on the complexity of nanomaterial systems, the immense possibilities to create a plethora of nanomaterials, their varied

properties which would make it challenging to put them in a particular class or category, the current inability to detect them both in the body and the environment, their unpredictability in the human body and environmental systems, their dynamic nature, toxicity, biodegradability/biopersistence, bioaccumulation and excretion dependant on shape, sizes, surface functionality, and surface chemistry and associated uncertainties and knowledge gap.

Generally it is accepted that downstream scientists or experts involved in risk assessment will have strong views about risks (Powell, 2007), however, in this research it was found that none of the experts were overly concerned about hazards and risks from nanomedical applications. They agreed about the possibility of hazards but expressed their reservation about environmental risks from nanomedicine. However, some of them expressed their satisfaction that research was being done to explore environmental risks from nanomedicine and that it was not a neglected area. For example, to SS 01,[89] I asked: *Are the current [environmental] risk assessment test methodologies and protocols fit-for-purpose for nanomedicine? Are you aware of them?* To which s/he responded that s/he was not aware of them and could not comment on their applicability because s/he is not an expert in environmental risk assessment. S/he added "*I would be worried if they weren't any such protocols. I would be worried if there were no researchers researching into it. It's important that those things are done."*

All experts were enthusiastic about applications of nanotechnology in human health. Some interviewees expressed their answers with disclaimers like benefits and risks need to be compared and also that comparison should be made with other

[89] SS 01 is a well-known scientist involved in the deliberations on science and innovation governance.

conventional chemicals (e.g. endocrine disruptors) and other global environmental problems like climate change.

The experts in my study were not very much concerned about environmental risks from nanomedicine and prided themselves in leading the way with respect to health and safety in their laboratories and workplaces. Some experts gave examples of their proactiveness in engaging with the HSE to discuss ways to handle the nanomaterials which they were manufacturing. They gave the impression that they were very diligent with respect to health and safety and designing safety into products. Industry representatives talked about the risk management controls which they already have in place. Generally industries have indicated they know the best health, safety and environment measures that need to be taken in a given scenario (for example Engeman et al., 2012; Weil, 2013).[90] Ability to work with radioactive materials was frequently cited as an achievement or man's triumph against hazardous materials and hence the confidence that risks can be managed or controlled (ability to control risk generally results in lower perception of risks) with increasing knowledge and technical know-how.

All but one of the research councils shifted the responsibility of assessing the environmental risks to the Natural Environment Research Council (NERC) whose remit includes funding research on environmental issues, and experts from this research council in turn informed that the regulatory agencies dealing with medicines would be most appropriate to be approached on environmental risk from (nano) medicines. Even the regulatory agencies with the responsibility to deal with

[90] I make a similar observation regarding the question on responsible innovation where industry representatives impressed upon me that they were very responsible in taking care of EHS and social issues.

environment issues informed that the regulatory agency dealing with medicines would be in the best position to answer questions related to adequacy of regulatory frameworks. This indicates that the pharmaceutical sector is a very distinct sector with regard to downstream implications with very few overlaps between various governance agencies (both funding and oversight) and it seems responsibility can be easily attributed (or passed) to someone else. However, an interesting point is that research on pollution from pharmaceuticals is funded and issues are addressed by environment agencies.

It was intriguing to note the reverence that scientists had for the pharmaceutical industry sector and the regulatory bodies and the confidence they had in them to follow proper health and safety protocols. Generally, experts have been shown to have more confidence[91] in government agencies dealing with risks (Siegrist et al., 2007) whereas the public appears to have less trust in government regulatory agencies and pharmaceutical industries (Slovic et al., 1991; Capon et al., 2015). The experts interviewed here repeatedly mentioned the stringent regulations in the pharmaceutical sector, the 'smartness and intelligence' of the pharmaceutical industries and the regulatory preparedness, which contrasts with the poor reputation of pharmaceutical companies (e.g., Lofstedt, 2007; Kessel, 2014). However, regulators did not see themselves as being prepared for handling the regulatory challenges that would be posed by nanotechnology products and expressed the need for interacting across disciplines. This observation is very much aligned with what other investigators have reported. Beaudrie et al. (2013) in their survey of 254

[91] It is important here to note that in the risk perception literature trust and confidence have been nuanced. Earle (2010) mentions 'confidence' as calculative trust where trust is based on past behaviour or knowledge about a process. EARLE, T. C. 2010. Trust in Risk Management: A Model-Based Review of Empirical Research. *Risk Analysis,* 30**,** 541-574.

US based scientists, decision makers, and EHS scientists, reported that regulatory scientists did not consider themselves to be fully prepared to manage risks from nanotechnology applications whereas scientists and EHS experts perceived regulators to be more prepared (than what the regulators themselves assessed to be) for managing risks from nanotechnologies. Similar result of uncertainty on part of the regulators was reported in their survey of experts from both the US and Canada (Beaudrie et al., 2014), and also by Helland et al.(2006), who gathered perceptions of 21 experts from academic, health and safety agency and industry.

Another interesting outcome observed from the interviews across the spectrum of expertise was that the questions from one area could promote discussion or even follow-up questions to colleagues from different disciplines. A team of upstream scientists started discussing about what log K_{ow} would mean for their product, a downstream scientist was intrigued when I shared examples of studies which found excretion of the nano-form in the urine and/or faeces. This indicates that an interview process can also prompt reflexivity thereby promoting modesty and pluralism in viewpoints (Stirling, 2006).

5.5 Conclusion

Discussions on nanomedicine to date have focussed on regulation (Gaspar, 2010; Dorbeck-Jung and Chowdhury, 2011) or public perception of applications of nanotechnology and nanomedicine (Priest et al., 2011; Sechi et al., 2014) and public engagement for defining nanomedicine funding strategy (Jones, 2008) or on ethical issues of nanomedicine (Khushf, 2007). No study (except Baun and Hansen, 2008)

has explored the environmental risks from nanomedicine, which is exactly what this study attempts to do.

The instinctive and spontaneous discussion on possible human health risks from nanomedicine shows that the concept of environmental risk assessment seems to be distant and distinct (except for specialist eco-toxicologists). But it was heartening to know that health and safety issues have become mainstream and habitual throughout the value chain, although potentially with some naiveté and over-confidence from academics. However, the research highlights a significant gap in terms of awareness of environmental regulations as well as a lack of orientation towards an ecosystem perspective. Thus, a significant conclusion from this chapter is a call for effective communication and deliberation strategies to reduce this gap, and to raise awareness regarding environmental risk assessment of pharmaceuticals and its need while submitting an application for investigational new drug and potential for nanomedicine to be excreted into wastewater and the environment intact and with the active ingredient still attached which can have potential environmental consequences.

Risk perception is not unidimensional in the sense that risk is not an ‘objective’ fact described only by the probability of harm; rather, risk is a multidimensional concept and is dependent on many factors thereby making risk assessment subjective in nature and hence not value-free, even though guidance documents on risk assessment state that risk assessment is a scientific process. Science is assumed to be objective in the positivistic philosophy; however scientific ‘facts’ are contested many-a-times (Garrety, 1997). Also, social science scholars have shown the influence of micro- and macro-social interests shaping the research and its outcomes

(Jasanoff, 1987; Jasanoff, 1990; Martin and Richards, 1995).[92] For example, the EMA did a study to assess whether and what influences medicinal assessors[93] regarding decisions on approval of medical products and the study found variables such as, gender and number of years of an assessor can influence perception of risks and benefit. Moreover, Stirling (2007) has argued as to why, in conditions of uncertainty, ambiguity, and ignorance, risk assessment, a reductive technique, is neither science based nor rational.

Special risk governance of active and complex nanosystems was called for by Renn and Roco (2006). Furthermore, Renn (2008) had proposed a "risk escalator", where he suggested involving various stakeholders to resolve risk issues when induced by complexity, ambiguity, and uncertainty. Similarly, the precautionary principle can deal with risks in conditions of uncertainty. However, the precautionary principle is rarely discussed with respect to pharmaceutical development because risks from pharmaceuticals to humans are more individualised and can be controlled, and are not as diffuse as environmental risks for which the principle was developed (Callreus, 2005). As has been shown in Chapters 4 and this chapter, environmental impacts from nanomedicine are likely to be negligible for some years. Moreover, robust data and evidence is needed to change existing policies and formalise regulatory criteria which calls for further research to address basic conceptual problems, such as (i) trigger limits in the environment in terms of mass concentrations of (nano)medicine; (ii) establishing bioaccumulation criteria and appropriate test assays, and (iii) what to do in the case of complex nanomedicine. A heartening point is that the medicines

[92] But results of research studies (my observations from reading publications exploring toxicity) indicates to me that they can be interpreted flexibly.
[93] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/02/WC500123226.pdf

regulatory agencies of the US and the EU have not been lagging much behind in terms of deliberating on impacts of new and emerging technologies. Two examples worth mentioning here are the International workshop on Nanomedicine which was organised by the EMA in September 2010 (and where the need for reviewing environmental guidelines was discussed) and the recent Guidelines from the USFDA regarding gene therapy, vectored vaccines, and recombinant products, which shows they are trying to keep up with the science.

However, in such a scenario which is full of uncertainty and ambiguity, it becomes imperative that we shift from governance of risks (from downstream, science and mathematics based approaches) to governance of innovation (upstream, and more democratic approaches) with focus on deliberation, discussion, reflexivity and improving the capability to visualise alternative technology paradigms and scenarios and address the purpose and motivation of innovation. In the next chapter I discuss one method of governing innovation – responsible innovation – and how the same experts as introduced here conceptualise RI.

Chapter 6: Imaginations of Responsible Innovation

Or, how do experts express responsible innovation.

> *"In any case, considerable intellectual uncertainty is inevitable in areas where post-academic science becomes entangled with 'trans-epistemic' issues, such as questions over bovine spongiform encephalopathy, where 'non-scientific' social, environmental and humanistic values are involved."* – John Ziman (1996, p. 753)

6.1 Introduction

In this chapter, I discuss the broader concept of governing innovation and move away from the risk dimension of anticipating environmental implications of nanomedicine which was discussed in Chapter 5. The main reason I do so is because the narrow framing of societal implications in terms of risk limits analysis to regulatory compliance and liability, so overlooking wider societal concerns over nanomedicine use such as equity, justice, and access, all of which are key issues with respect to health care (though it is emphasised that in-depth discussions on these issues in health care are beyond the scope of the current thesis).

Scientific breakthroughs, inventions and innovations in nanomedicine potentially offer a multitude of societal benefits and hence it becomes imperative to think about how these benefits can be realised responsibly. This requires consideration of the following questions: What kinds of purposes and motivations should underlie invention? What kind of nanomedicines should be developed? How can the desired outcomes be defined? Who should benefit from nanomedical developments? What aspects should be considered so that benefits are maximised and risks are minimised or controlled? To address such questions, the concept of responsible

innovation (RI) has gained traction, primarily in the EU, to govern innovation. RI is defined as *"a collective commitment of care for the future through responsive stewardship of science and innovation in the present"* (Owen et al., 2013a, p. 36).

It has been adopted as an approach underpinning research and innovation funding under the Horizon 2020 programme. RI is being discussed in the context of its applications to emerging technologies, such as nanotechnology, geoengineering (Owen and Goldberg, 2010), synthetic biology (TSB, 2012), and Information and Communication Technologies (ICT) (Grimpe et al., 2014), as a means to govern innovation. RI is about steering innovation processes collectively in the present with a view to moderating future impacts and is driven by the concepts of care for the future, responsiveness to the plurality of viewpoints, and being reflective of rapidly emerging knowledge in these emerging areas. It aspires to bring about significant 'cultural change' and reconfigure research and innovation in a way that is based on moral and ethical values.

The history and development of the concept of RI has been discussed in Chapter 2. Here I present a brief overview to reintroduce the concept for the sake of continuity and to demonstrate how this concept informed the theoretical analysis of the empirical data presented in this chapter. The concept of RI has rich foundations including the seminal publications explicating how science and society are 'co-produced' (Latour, 1993; Jasanoff, 2004), how technology is 'constructed' by society (Pinch and Bijker, 1984), how science and technologies are politically entangled (unintentionally or by design) (Winner, 1980), and how involving stakeholders and lay people can help manage negative societal outcomes (Hart, 2005), inform about negative externalities of technologies, e.g. see discussion by Wynne (1998), and

shape research in a democratic process (Wilsdon and Willis, 2004). RI evolved in part due to low confidence of the public and stakeholders in science and mistrust towards regulators (e.g., the bovine spongiform encephalopathy (BSE), or mad cow disease) and the genetically modified (GM) crops debacle in the UK), the shift towards 'post-academic' science[94] (Ziman, 1996) and the increasing understanding and evidence of complexity and previously unimagined multidimensional issues raised by technology and its products.

The accidence (fundamentals) of responsible innovation referred to in this chapter is the framework suggested by Owen et al.(2013b). The authors have created an umbrella concept to ensure desirable and acceptable research outcomes, which can deal with aspects of ethics, need, motivation, purpose, and likely impacts of research and innovation, including sustainable development. Recapitulating from Chapter 2, the four dimensions of RI are presented in Box 1 (Owen et al., 2013b). I have used these four dimensions of RI to analyse the responses of the experts to the questions: Are you aware of the term RI? What does RI mean to you? What should be considered at the innovation stage so that it [a product / process] fulfils the criteria of RI?

In the following sections, I lay out the context of the research and the objective of the chapter, and then I discuss briefly the methodology adopted to collect and analyse the data before moving on to present and discuss the findings. Based on these results, derived from the semi-structured interviews and scrutiny of the emerging

[94] There have been exchanges between scholars John Ziman and Helga Nowotny (and her co-authors) related to their conceptualisations of academic and post-academic science and / or Mode 1 and Mode 2 science. I use the term post-academic science to mean research pursued with industrial partners, and driven by the mandates of funding agencies to support economic recovery and growth or competitiveness agendas.

academic literature on RI, I conclude in Section 6.5 by suggesting a draft concept on how to operationalise RI in the novel nanomedicine sector.

Box 1: Four dimensions of RI (Owen et al., 2013b)

Anticipatory – Considering various plausible scenarios and analysing possible social, environmental, economic implications in advance.

'Reflective – reflecting on underlying purposes, motivations and potential impacts, in terms of what is known (including those areas of regulation, ethical review or other forms of governance that may exist) and what is not known; considering associated uncertainties, areas of ignorance, assumptions, questions and dilemmas'.

'Deliberative – opening up visions and questions to broad and collective deliberation through processes of dialogue, engagement and debate, inviting and listening to wider perspectives from the publics and diverse stakeholders.'

Responsive – using the information and knowledge generated through the above processes to influence the goals, direction and speed of innovation.

6.2 Context

As described in Chapters 4 and 5, many knowledge gaps and uncertainties exist in the field of risk characterisation for nanomaterials. Furthermore, with increased complexity of nanomaterials, the challenges to do a traditional environmental and health risk assessment will increase exponentially. Therefore some guiding principles or concepts are needed to help govern innovation rather than wait for evidence to be gathered to change policies and bring about new regulations. Here, I focus on the concept of RI as a means to govern innovation. My initial thinking on the background and substantive focus of this part of the thesis was to gather the opinions, perspectives and interpretations of RI from various experts with different disciplinary backgrounds involved in aspects of nanomedicine (development,

commercialisation, funding), downstream scientists, policymakers, and regulators, in order to explore their spontaneous responses towards RI, and investigate how it is imagined in the 'everyday' life of experts and scientists. The empirical evidence gathered through the use of questionnaires would be used to conceptualise RI for nanomedicine and could help design research funding calls or prepare targeted and customised dissemination strategies about RI.

Innovation is already governed in the pharmaceutical sector to some extent due to the involvement of the regulator at various stages of innovation; however, the key idea is to minimise risks to human health.[95] For example, conducting clinical trials need approval from national regulatory agencies [96] and around 80% of drug candidates in clinical trial finally fail to get regulatory approval for marketing for poor safety or efficacy outcomes – two key criteria for drug approval (Arrowsmith and Miller, 2013). The stage-gated model of pharmaceutical innovation is explained in Chapter 2 along with the stages where regulatory bodies need to be engaged and various other guidelines that need to be adhered to. These gates can also be imagined to act as stop-go-modify decision checkpoints. Medical devices also follow a similar model; however, the medical device innovation pathway is not accorded such close scrutiny as pharmaceuticals, except for Class III medical devices.[97] This governance of (pharmaceuticals and medical devices) innovation has developed and strengthened over the years, due to effective policies which had political legitimacy,

[95] In fact, regulatory bodies sometimes exercise control on advertisements. For example, the pharmaceutical company Duchesnay recently was sent a warning letter by the USFDA on Kim Kardashian's Instagram post promoting one of Duchesnay's drugs. Available at: http://www.forbes.com/sites/davidkroll/2015/08/11/fda-spanks-drug-maker-over-kim-kardashian-instagram-endorsement/.

[96] http://www.hra.nhs.uk/research-community/applying-for-approvals/medicines-and-healthcare-products-regulatory-agency-mhra-medicines-clinical-trial-authorisation-ctimps/

[97] By Class III device, I use the broader concept whereby higher classification entails involvement of regulatory bodies or notifying bodies before the product can be marketed. Devices are classified in broad categories - Category I, II and III - on their intended use. Examples of Class III medical devices: some surgically invasive devices, implantable devices.

especially in the case of the USFDA. For a detailed account of how the regulations developed in the US, refer to Carpenter's (2010) description of the USFDA, the sought after regulatory body (even for the UK nanomedicine researchers)[98] for drug approval. In the case of medicine, science and innovations have often, in recent decades at least, developed alongside regulations. For example, Carpenter and Tobbell (2011) have discussed the emergence of the concept of bioequivalence for generic drugs as a "joint regulatory and scientific creation" (p.94) and which facilitated further research in pharmacokinetics. However, despite stringent regulations in the pharmaceutical and medical device sectors, the sectors are rife with issues of lobbying, corruption, monopoly,[99] unfair pricing[100], and falsification of clinical trials results (Kessel, 2014). Discussions on these issues are beyond the scope of this thesis, but I alluded to them since the concept of RI is firmly anchored in normative societal goals and the very concept of responsibility calls for forward-looking or moral / virtue responsibility and hence to explore purpose and motivation behind a particular innovation becomes important. To conceptualise how to implement RI in the sector, these larger normative issues need to be considered.

The principal aim of this aspect of the research then was to ascertain what 'meanings' experts attach to RI and how it might be articulated, concretised, and developed in nanomedicine. My intention in undertaking this aspect was that it would provide valuable insight into how RI is conceptualised by stakeholders in

[98] During many of the interviews with upstream scientists, the USFDA was mentioned much more frequently than the EMA. It could be perhaps due to EMA's newer incorporation (in 1995) compared to the USFDA, more awareness in experts related to the USFDA (due to their academic training received during their college years) or because of the US being one of the largest markets for medicines.

[99] See ruling by European Commission where it fined Lundbeck and other pharma companies on antitrust issues. Available at: http://europa.eu/rapid/press-release_IP-13-563_en.htm

[100] For example, refer to the much discussed decisions by Turing Pharma and Mylan to voluminously increase the price of their products, Daraprim (5000% increase in price) and Epipen (400% increase in price since 2009), respectively.

nanomedicine, and how this challenging concept might be implemented by those involved in research, development and deployment or distribution of technology, products and services. I present the methodology briefly below and then I elaborate the results.

6.3 Methodology

Detailed discussion of the methodological approach used to collect data on stakeholder opinion is discussed in Chapter 3. Briefly, by means of semi-structured interviews, sixty-two experts from the nanomedicine innovation chain were asked to share their ideas on what the term responsible innovation could mean to them, and what criteria could be important to innovate responsibly and who could be responsible for defining such criteria. Their responses are analysed and presented here. The question on RI was framed in an anodyne manner and also posed in an unobtrusive, value-free way. Most of the experts I interviewed were willing to express what RI 'meant' to them and sometimes wanted an explanation from me about the term both before and after the question was posed. In some cases, I explained, very briefly, that RI was a new term being discussed in the policy circles and it was about governing innovation by the involvement of various stakeholders and thinking about future impacts in advance. In some cases, I refused to provide a lead and encouraged the interviewees to express their opinion.

I did not seek to be prescriptive in defining 'responsibility' or 'being responsible' to interviewees during these structured encounters in order to gain, as far as possible, their own perspectives on RI. However, the discussion and conclusion sections of

this chapter have been influenced by my background of belonging to a developing country, working with corporations and communities on sustainability issues and the discussions which I was witness to in the RI and nanomedicine conferences that I attended. I made no attempt to quantify the various types of responses by means of proportions or percentages. I simply sketch an array of responses clustered into major themes which either emerged from the textual data and /or were part of the *a priori* codes which were assigned, aligned with the analytical lens of the four dimensions of RI, to interrogate the data. However, not all textual material could be arranged under the particular themes. Some of these non-clusterable responses, which are otherwise relevant to capture the plurality of thoughts, have also been presented in the analysis and the discussion that follows. It needs to be remembered though that the specific context in which these responses were elicited was the interview situation where the interview was about nanomedicine development and challenges of translation, environmental implications, and adequacy of the existing governance framework, with RI being only a small proportion of the total interview.

The framework of responsible innovation was being developed and improved in the science policy circles during the period of 2009−2013.[101] The interviews presented here were conducted from 12 May 2011 to 12 September 2013. Since the completion of fieldwork in 2013, academic debate on RI in various fields have been growing and is cross-disciplinary in character, with researchers and the academics from various disciplines including ethics and philosophy contributing to the discussion. Nonetheless, it remains the case that very few have commented on RI's

[101] Refer to an article by Richard Owen titled "A new era of responsible innovation" published in October 2009 at: http://planetearth.nerc.ac.uk/features/story.aspx?id=460&cookieConsent=A and in 2013, a document on RRI by the EC, a book (which forms the basis of this chapter) edited by Owen et al. and an open access paper (Developing a framework for responsible innovation) in the Journal Research Policy, were published.

application and deployment in the nanomedicine field and very few nanomedicine researchers and/ or nanotechnology based industries have been involved in the discussion of RI. Certainly at the time of writing I am not aware of such an exercise where perspectives of experts have been collated on RI via semi-structured interviewing whether for the nanomedicine sector or indeed any other sector. To analyse the diverse responses, I have drawn from the broader research done on discourses in sustainable development, risk perception, public engagement, science, technology and society studies, and ethics to interrogate the empirical materials presented here.

There was a scarcity of literature with regard to perception on RI of various expert stakeholders, and these results are just preliminary to act as a guidepost with the aspiration that it will strengthen the concept of RI. The views presented are representative and grounded in the interview transcripts. At the heart of this chapter is to my attempt to engage conceptually with the concept of RI along with the empirical data and re-conceptualise it so that can be made operable in everyday life. In Section 6.4, I present my analysis of the comments of the experts interviewed when they were asked what RI meant to them. The subheadings in this section illustrate the key themes teased out from the interviews which explain experts' 'take' on the meaning of RI.

6.4 Stakeholders' imaginations of responsible innovation (RI)

Amongst the experts I interviewed, only the social scientists and the Research Council members (except the expert from one RC) were aware of the 'story behind'

RI or had heard the term. Thus, I introduced a term in the questionnaire / interview which was not familiar in the wider community, i.e., was more of an analyst's concept rather than an 'actor' concept (Collins, 2008). Despite the unfamiliarity of the phrase, the initial views expressed and responses of the participants can add value to the concept of RI and provide important insights regarding how to translate RI into day-to-day actions or to provide broad guidance to help make it implementable by stakeholders in order to embed them into practice. The interviewees' views on what RI is were not completely aligned to the framework of RI being proposed by Owen et al.(2013b), nevertheless the description of RI given by interviewees was not completely opposed. Their enthusiastic and sometimes engaged response to the question indicated that this concept (RI) can be used to re-brand research policy, can bring about change in research practice, and greater collaboration with end-users of nanomedical products. However, some nanomedicine entrepreneurs and industry representatives were also cynical or sceptical when the question was posed, or cut off the question with a clipped answer 'don't know' when they were asked whether the term was familiar to them. It might be because either they were mentally saturated with the risk related discussions around nano or that they were not certain and didn't want to discuss further. It could be also because they found the question irrelevant to their work as developing medicines is regarded as a panacea for research in new technologies. There were interviewees who wanted to check with me if what they had said was correct or not. Their interest to know the term itself shows they are willing to engage in the debate regarding RI and that they can be tagged as 'responsible nanoresearchers' (Kjølberg and Strand, 2011, p. 107).

Out of the four dimensions of RI, anticipation and deliberation came forth very clearly in most of the expert discussions. However, the dimensions of reflexivity and responsiveness were mentioned less frequently. This is in contrast to Shelley-Egan and Davie's (2013) study where they found the framing of responsibility was in terms of responsiveness (where being responsive is defined as gaining public trust due to public pressures) in the industries in Europe. Other dominant themes emerged, such as: innovation to safeguard human health being a responsible endeavour and the challenges of controlling innovation in a globalised world (Section 6.4.1); being realistic about (and accountable to) the technosocial imageries that are created with regard to new and emerging technologies (Section 6.4.2); and being conscious of the environmental impacts (Section 6.4.3). The findings from coding the transcripts by the *a priori* codes of the four dimensions of RI are discussed in Section 6.4.4.

6.4.1 Innovation in health care 'is' responsible innovation

Upstream scientists and representatives of industries undertaking applied scientific research on nanomedicine had a range of perspectives on RI. In line with the tenets of social constructivism (Berger and Luckmann, 1991), respondents' attitudes towards this novel concept seem to have drawn upon their own values, beliefs, worldviews (socio-cultural-political attitudes), and disciplinary training. Thus some upstream experts and some representatives from industry interpreted the concept in a partial way, by maintaining they were already 'responsible' as evidenced by their developing novel medicines at the nanoscale. From this perspective, responsibility is construed by applied scientists to be the introduction of novel medical procedures,

products and processes that target disease and thereby safeguard human health. Although scientists and the public are treated as a 'binary opposition' (Cook et al., 2004) in the major discourse on public engagement or public understanding of science, if we consider scientists to be members of the public, then the idea that taking care of human health is a responsible endeavour can be juxtaposed or extended from research done on public perception where it was found that people perceive more benefits rather than risks from nanotechnology applications in medicine and health fields when compared to nanotechnology applications in other fields, such as geo-engineering and cosmetics (Pidgeon et al., 2009; Priest et al., 2011; Capon et al., 2015). This is not only the case for nanotechnology, as generally less negative perception is attached to medicine than other areas. For example, Slovic (1999) identifies medicines as a special case with regards to risk perception as follows : "*Nuclear and chemical technologies (except for medicines) have been stigmatised by being perceived as entailing unnaturally great risks"* (p.689). Similarly, researching and developing products or processes which are meant to meet societal challenges are generally framed to be responsible (see Shelley-Egan and Davies, 2013).

Due to the long time required to bring a pharmaceutical product to the market, academics researching on nanomedicine and with experience in patenting and entrepreneurship shared their discomfort or reservations regarding the term innovation. On average, it takes 13.5 years for the development of a new molecular entity (this excludes the time to identify and validate a drug target) and the average cost from discovery to bringing the NME to market is approx. 1.8 billion dollars (Paul

et al., 2010). Upstream scientists often framed their responses to my questions with this in mind, with one expert noting:

"*Sometimes it is not an "innovation" anymore, because you go through too many tests and it becomes 'old' by the time we are done with it, that's what happens, this lag of innovation, like I say for example, liposomes were first invented in 1965,* [the] *first animal experiment done in the 70s and the first product in* [19]*96, so almost 30 years* [later]. *Can you call the liposome 'responsible innovation'? Yes, but it is old, it is not an innovation any more, from my point of view. But I think that is 'responsible innovation' in my field, it is really long and it is all about making sure it works"* [NMS 03]

Interviewees also suggested that they were delivering a societal goal by working in the medical science and innovation sector. The following quote shows that R&D in medicines and medical device field are intrinsically seen as delivering noble societal goals and hence viewed as responsible ventures. As one nanomedicine scientist said:

"Because I think in nanomedicine, we are doing things for society to try and improve healthcare for patient benefit. It may consequently reduce health care budgets and do other things" [NMS 08]

Interviewees also reflected on how innovation processes were by their nature global in scale and reach, with multidisciplinary teams working across organisational (Heinze and Kuhlmann, 2008; Guo et al., 2015) and national boundaries (Shapira and Wang, 2010), and knowledge flows across multiple industrial sectors (Park et al., 2005). Innovation in the medical sector is distributed with parts of the R&D process located in various geographies and in different sized firms – large and small − and institutions (Ramlogan et al., 2007; Demirel and Mazzucato, 2012). In many cases, and especially in the biotechnology sector (and now evidenced in the nanomedicine

sector), universities and small firms do the basic research and the incumbents scale up, develop and market the products (Arora and Gambardella, 1994). This globalised nature of innovation process was adduced by some interviewees as a major challenge to govern innovation:

"....you cannot control it [i.e., innovation], you cannot control it, it's a highly chaotic process" [NMS05]

A representative of a Research Council shared:

"……with synthetic biology, one of the things we've been talking about is [that] *we must have good air vents and good manufacturing practice and yeah* [have] *they got those in North Korea? I don't think so. So I think it's that sort of 'how on earth do you govern this on a global basis?', because the system of innovation is global. "* [RC 01]

Representatives from regulatory authorities for medicine stated that they don't label any medicine as innovative (this indicates, when describing RI for this sector, one has to first describe what innovation means to the medical sector) and said:

We don't describe innovation per se, because we are not free thinking scientists, the only way we describe innovation is as defined in the legislation, scientific or technical which do not cut into whether it is responsible. Yes or no, first whether it is an innovation or second what is the purpose of it, we do not give a label of innovation to anything, because for us innovation is a way to give access to the services of the centralized procedure..... [Regulator 2]

However, while the thesis writing was under way (in late 2015), it was noted that a general description of innovation was provided on the website of the European regulatory agency interviewed for this research study. More details on definitions of 'innovative or new' drug can be found in Chapter 2 and it's annexe. As I infer, it is an issue related to semantics finally: the regulatory agencies have generally used the term 'new' (in the sense of not having been regulated previously) rather than

‘innovative’ for drugs and label them likewise. A second framing of responsible innovation which emerged clearly was responsibility as accountability and of fulfilling promises, which I discuss below.

6.4.2 Framing RI in terms of Fulfilling Promises and Accountability

Expectations from technology are sometimes raised prematurely to unrealistic levels by scientists and the media (e.g. civil nuclear energy to solve all problems, cancer caused by virus), and influential voices direct these visions to influence policy or enhance funding, e.g., Mary Lasker and Hollywood celebrities helped increase funding for cancer; the National Cancer Act was passed in 1971 in the US, this was labelled as ‘War on Cancer’. Thus, creation of public support or raising awareness to show the importance of a particular identified issue, can have dramatic effects, indicating that ‘context, power, and purpose [can] shape outcomes of technology choices in society’ (Stirling, 2008). Technological solutions have been widely depicted as a magic bullet capable of fixing many of the ills plaguing society or to enhance societal output, for example, GM crops as a means to ameliorate hunger (Borlaug, 2000). Generally, new and emerging technologies have followed the so-called Gartner’s hype cycle, which is characterised by innovation triggers followed by inflated expectations and then a trough of disillusionment and finally reconciliation and adjustment of expectations to achievable real-world outputs. Nanomedicine has also gone through a similar hype-cycle as evidenced in the early but widespread metaphors, e.g., nano weapon, smart bombs (Loeve, 2015) used to make the case that nanotechnology can revolutionise health care. However, expectations raised are

yet to be fulfilled. The so-called 3rd and 4th generation of nanomaterials (Roco, 2004) are yet to be introduced into the market; in fact in the nanomedicine field, only a handful of nanomedicines which are in clinical trials could be categorised to fall under the category of 2nd generation nanomaterials – see Table 2.2.2 for examples of types and details of nanomedicine in market and clinical trials and a recent review by Etheridge et al (2013). However, in the case of medicines, this delay could be primarily due to the long time frame required to develop medicines, perform clinical trials and get authorisation to market them.

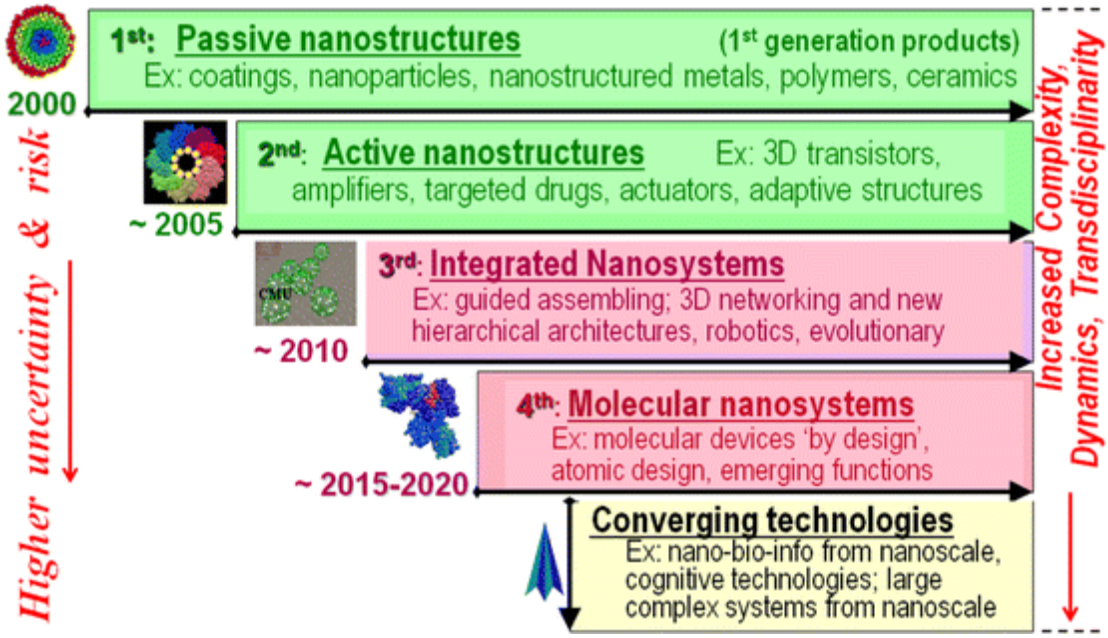


Figure 6.1: Nanomaterial categories as conceptualised by Mihail Roco (Taken from Roco 2004).

Upstream experts were aware of the hype promoted around it; one of the experts researching on developing nanomedicine commented:

"To me, it [RI] *means that you don't overplay your hand if you like. You don't promise what you can't deliver, and in parallel obviously* [consider] *the safety implications."* [NMS 12.2]

A nanomedicine expert commented that one should be very cautious in raising expectations in the medical field because a hypothesis which has been proven in the laboratory (and is entering clinical trials) can be personalised easily and can create ethical dilemmas for the researchers:

"....you have to be careful there, because people don't know what you are talking about, and they get hyper very quickly, it is very contagious, in a positive way sometime, so people call you up and request 'can I inject that into my son because he is dying', etc. etc [NMS 03]

Another upstream expert articulated that one can be responsible for only certain things in the innovation process. This expert identified his/her domain of influence as the science s/he was doing and emphasised that one should reflect on the possibilities of the innovation and not create hype and raise expectations which cannot be fulfilled.

". .....in my case, the technical scientific side of it, because you know you cannot be responsible for all other stuff. So, I think, I have a responsibility as well. You are innovating - you have a responsibility not to prematurely raise expectations beyond a responsible level. [NMS04]

This interviewee added further that engaging with the press and public should be undertaken bearing in mind the same level of thoroughness with which one justifies a research idea to the funding body or prepares a response to one's harshest of critics:

I have seen examples where people have had a bright idea, they think it might have a beneficial impact on health and the next thing they are talking to the press. I mean, it ends in disappointment, and I think it is your responsibility while you are innovating to be very, very self critical and say "No, it is a terrible thing to raise false expectations in terms of [a] cure....You say what you can actually back up, so everything you say [if] *you are talking to a*

journalist, or on paper, you should say as if you are saying [it] *to your worst critic or the peer review panel at EPSRC."* [NMS04]

The discussions with various interviewees covered many other areas which can be related to accountability. Upstream experts mentioned that RI means delivering products as per commitments to funding bodies, not unnecessarily pushing one's personal agenda, trying one's best to translate a potential invention to clinical practice being aware of translational opportunities, consideration of safety implications of products, and being accountable to funders and the taxpayers. An upstream scientist emphasised the importance of being able to let go of one's research idea or theory if it was found to be not be very useful in terms of innovation:

....."Responsible innovation to me is making something which is useful, and being in academia actually I would try to be accountable for the tax payer's money I am spending. That's what I feel. For example, there are some hypotheses which can fail and some are successful and if somebody says that this hypothesis may not work, I am so flexible I can leave that at any moment. I wouldn't really kind of push it because it's my baby and I brought up this concept and it has to work....." [NMS 06]

Another upstream scientist who had established a company echoed similar thoughts. This expert stressed the importance of translating discoveries to marketable products, and expressed their strong reservations about scientists who pursue their own research interests in science without spending the time and energy to take an idea to the end stage/ application stage:

"……I think you've got to go chasing fundamental science but if you actually hit something that might be developable that you actually try to develop it…. If your intention is actually getting it just to spend the government's money… I can say they're irresponsible if when they had the chance, they decided to go and do something else." [NMEn12.1]

The importance of translation could be attributed to the change which has happened in academic research, where, in addition to intellectual merits, scientists are expected to solve problems related to societal concerns and/ or to come up with a marketable product. Also, the shift in many countries has happened towards (funding of) more 'useful and relevant' research (Davis and Laas, 2014; Leitch et al., 2014).

Also, there have been calls for "social responsibility of scientists" (Krogsgaard-Larsen et al., 2011) where scientists have been implored to regain public trust and show allegiance to solving the major societal challenges, for example, societal issues as recognised in the Lund Declaration.[102] Mike Eaton, an Executive Board member of ETP Nanomedicine suggests that *"it is important that researchers take scientific social responsibility for their research. It should have real impact on science, as well as societal benefits or benefits for patients.....researchers should be mindful that their research, often paid by taxpayers, must deliver some value to society and that the debt be repaid*...." (Eaton, 2012). Similarly, Mitcham and Frodeman talk about adoption of a professional code of ethics for scientists "*that increasingly affirm social responsibility above and beyond any contractual determinations*".[103]

Minimising use of resources, value addition, transparent and frank communication with patients were some other conceptualisations of RI that emerged from the stakeholder interviews. It was often expressed by academic entrepreneurs that scientists should realise the translation potential of a discovery early on and should be enthusiastic to carry it through from bench to bedside. The importance of knowing the steps of innovation was expressed by an upstream scientist, which also indicated

[102] http://ec.europa.eu/invest-in-research/pdf/download_en/isi_contribution.pdf
[103] http://www.issues.org/16.4/p_frodeman.htm

that in a more general sense scientists in academia might not be aware of the entire value chain of innovation in the pharmaceutical (and medical device) sector. An excerpt from a long discussion below:

"Well, to me responsible innovation is about innovating in a cost effective manner with a minimum number of exploitative experiments on the way, so there is always a tendency for people, for example, to do enormous number of animal experiments. I don't think that's very helpful if you are going to do just lots of bad animal experiments: make sure that you understand what you are doing first and then [that] *what you do is of the essential variety and* [that] *you minimize the number of animals that have to be committed to the study, which is better for animal welfare, so I think responsible innovation also means being less science based, I mean, more aware of* [the] *translation process as well. So, you are after all managing resources from A to B. So, you got to know what you are doing. So there is an element to me and that is sort of actually having an adequate knowledge base to know what innovation means…..have you managed it to mature enough so you can sell it? Have you taken the resources you were given and added value to them so that you could sell? You achieved that and you have innovated responsibly, I would say. If you have not, you have not.."* [NMEn10]

An expert discussed responsibility in terms of transparency, of communicating clearly the likely risks from new products and contextualising it to people participating in clinical trials. It indicates that lay people should be given information, so that they can take decisions for their safety and health. The expert said:

"….[a] clinician had to explain [to the patient] what the clinical trial is and in cancer, less than 3% of patients ever respond to an experimental drug. So, if you say to a patient 'would you like to have this experimental therapy? There's more than 95% chance that it won't help you, and that there is quite a reasonable chance that you'll have some unexpected toxicity that will inhibit your quality of life.', [If] those statistics are put in front of the patients and then the procedures are explained to them and so that's part of responsible development, and people then have the right to opt out" [NMS 08].

6.4.3 RI framed in terms of 'Environmental Sustainability'

Representatives of industry, a few upstream scientists, the majority of downstream scientists, policymakers and funding agencies expressed their understanding of 'responsible innovation' in terms of environmental sustainability. When asked what the main aspects of RI could be, interviewees mentioned less toxicity, designing products which can be recycled or biodegradable, proper waste management, and considering impacts of their products along its lifecycle. There are many possible explanations for this: it might be due to disciplinary background (which I elaborate more in Section 6.5); or, it might be a consequence of 'framing' (Entman, 1993) as the introductory emails with the request for an interview communicated the central research aim of the study was of exploring environmental implications of nanomedicine. Also, public policy discussions on societal implications of nanotechnology got narrowly framed as environmental, health and safety (EHS) implications (Doubleday, 2007c; Sykes and Macnaghten, 2013) of nanotechnology. Or, it can be due to 'environment' becoming prominent and central to major discourses on development and growth and increasing visibility in the media albeit after four decades of the evidenced environmental crisis resulting from indiscriminate chemical usage.[104] More recently, the international focus and concern regarding climate change has added substantially to the environmental discourse. Inclusion of ecological concerns at the product and policy conceptualisation stage can be evidenced in global and regional policies (EU's Sustainable Development Goals)[105]

[104] This can be contrasted with the findings of Chapter 5, the spontaneous responses to the question on adequacy of risk assessment framework for nanomaterials and human health.
[105] Sustainable Development Goals and the Agenda2030.

and via national policies and institutional decision-making (e.g. General Electric's ecomagination[106]).

The discussion below, which includes excerpts from all the various stakeholder categories, is indicative of framing of RI in terms of environmental sustainability. An upstream scientist articulated RI as anticipating the benefits and risks along the life cycle of a product and being responsible with regard to sourcing of environmental resources: This expert said:

"I suppose for me it's just the life cycle analysis. It's that you consider risk and benefit from the outset…If it turned out that manganese was a wonder medicine, I think people would understand we're not going to take all the manganese from one country…" [NMS16]

Similarly, one eco toxicologist commented that RI is about exploring the unintentional and possible toxic effects of a product and the need to know the environmental footprint of the product value chain

"…. from cradle to grave and thinking about what is it, what could the risks be, what could be the unwanted side effects, where could they occur, how much CO_2 do I put into to this complex compared to what I get out of it. So it is a lot of LCA kind of thinking …" [ETOC1]

Interestingly, a representative consulting industry commented about persistence of a novel therapeutics which could have disastrous consequences on the environmental species.

"*.....You don't want to develop a wonderful new drug, say, it is a nanodrug, if it's going to stay in the environment and kill all the fish. It's* [i.e. RI] *that sort of thing"* [Industry 03]

[106] Available at: http://www.ge.com/about-us/ecomagination

A policy maker discussed RI in terms of anticipating possible uses of the innovation, knowledge of the various forms of the product and the supply chain, its fate at various stages, and environmentally sound disposal.

"…kind of a full awareness of how the nano product that you are creating is going to be used, gaining an understanding of, you know, ……..an awareness of what other sort of potential uses could be and awareness of the lifecycle of products, so, you know, what happens to it at different stages in its life, how you dispose it off, consideration for supply chain management, you understand the risks are being sort of transferred along the chain." [PP1.2]

However, the inherent tensions which have existed with regard to inclusion of environmental considerations and safety issues in the development of new technologies and products and the dominant framing that EHS issues needs to be taken care of and that innovation should not be impeded by EHS issues is reflected in the extract below:

"So, when we think about RI, what it means to us is trying to make sure that environmental health and safety issues are considered as part of the innovation process. So, we don't want environmental health and safety to be a barrier to innovation. We think if it's considered in tandem with innovation then it's just a win−win for everyone." [RC02]

Recently, scholarship has emerged to establish the 'business case' for sustainability, but other than a few case studies from well established business corporations (e.g. Interface Corporation's revolutionary idea to change its business model from product to service delivery and in turn make significant reductions in its environmental footprint)[107] and literature on monetised savings achieved primarily by utilising energy

[107] For a case study on Interface Corporation: http://www.thenaturalstep.org/project/interface/

conservation measures, the so called low hanging fruit environmental sustainability, a strong case it yet to be built.

In the preceding sections I discussed the key framings of RI which emerged as a result of the content analysis of the interview transcripts – innovation to meet societal challenges is considered to be responsible innovation, transparency and accountability to 'agents' involved in the nanomedicine innovation value chain and taking into consideration environmental implications. I now discuss the results arrived at by coding the transcripts as per the four dimensions - anticipatory (and anticipation), reflective (and reflexivity), deliberate (and inclusion), and responsive (ness) - proposed by Owen et al. (2013b).

6.4.4 Using the analytical lens of the four dimensions proposed for RI

Very few responses of interviewees could be categorised under the dimensions of 'reflective' and 'responsive' when using the analytical lens of the four pillars of RI to the emergent themes. This can be due to the 'implicit' assumption that purpose and motivation are clear in case of medicine and medical device research and development. The relative absence of the reflective dimensions in the analysis of the interviews could also be due to political and economic factors, such as time constraints on academics in an increasingly neo-liberal educational environment (Dowling, 2008), funding constraints and a highly competitive funding scenario, and publishing pressures. Moreover, in case of innovation in medicines, the R&D process is a stage-gated process whereby the results at a particular stage act as feedback for the further development pathway of a new molecular entity (NME) or

medical devices. The purpose and motivation (i.e., first-order reflexivity) behind particular drug development in firms are announced via websites, annual reports, R&D is discussed in strategic meetings, goals set and discussed, timelines prepared, teams identified from various departments and other similar actions taken and hence they *partially* fulfil the responsive and reflection dimensions of RI. Similar strategic and structured approach to innovation has been reported by Asante et al. (2014) in their ethnographic study of understanding product innovation in the financial sector. However, they observed that financial innovation strategies were limited in terms of second-order reflexivity, in other words, discussions on whether such kind of financial instruments should at all be needed to be introduced into the market place.

Kuzma and Kuzhabekova (2011) analysed business firms by using corporate social performance and found that larger and established business firms take up voluntary initiatives to report non-financial performance. Such larger and established business firms generally address the concept of responsiveness by: responding to employee suggestions, customer feedback, third-party auditors and queries raised by NGOs; problems raised in Corporate Board meetings and their solutions, compliance to relevant and applicable regulations, community needs assessment and formulating and implementing programs in the communities in which the firms operated is expressed as responsiveness of the firm to various external and internal inputs (for example, see AngloGold Ashanti[108] and Novo Nordisk's[109] corporate annual reports). Shamir (2008) argues that the ever increasing voluntary and compulsory codes of conduct are a step towards directing corporations to take responsibility for their

[108] AngloGold Ashanti's integrated annual report for 2014 is available at: http://www.anglogoldashanti.com/en/Media/Reports/Annual%20Reports/AGA-IR14.pdf

[109] Novo Nordisk's annual integrated report 2014is available at: http://3blmedia.com/News/Novo-Nordisk-Publishes-2014-Integrated-Annual-Report-Emphasising-Long-Term-Thinking

actions and products. He adds that ‘morality of corporation’s gets guided by markets’; however, the concept of health is so central to human existence that it results in less bargaining and influencing power of the markets served by these corporations.

Many of the views expressed by interviewees could be categorised under the dimensions of ‘anticipation’ and ‘deliberation’ of RI. Interviewees discussed about conducting toxicity assessment, thinking about future implications, conducting environmental life-cycle assessment, engaging with various stakeholders, and green design of drugs. This indicates that the risks and the risk framework are embedded in modern society, and responsibility is entwined with risks (Giddens, 1999). Solutions can be framed in a manner whereby some realities can be made “thinkable while closing off certain possible future scenarios” (Lash et al., 1996, p. 257), consequently influencing deliberation and responsiveness towards a particular vision of development.

6.4.4.1 Intentions and anticipation of benefits and risks of new products / technology

Anticipatory and reflective capabilities are important for prospectively governing innovation having high levels of uncertainty and unknown trajectories of development. Anticipation doesn’t mean predicting the future as Guston (2014) argues, it is about cultivating the capacity to think about possible futures and implications to enable future governance and current decision making. Experts shared precluding toxicity while designing new products, being aware of the product’s lifecycle and the associated risks at various stages, and the need to develop

something which is ‘good’ and ‘useful’ for society. The discussions reflect values oriented towards the existing concepts of green chemistry (Anastas and Warner, 1998) and social innovation or entrepreneurship (e.g. Ashoka Foundation, Skoll Foundation)[110] among the interviewed stakeholders in the nanomedicine value chain.

The responses indicated a strong disciplinary orientation and work experience – nanomedicine scientists talked about ‘dual use’ of science and technology (POST, 2009), occupational exposure of people administrating medicines to patients and exposure in the laboratory for researchers and scientists; toxicologists and eco-toxicologists mentioned ‘benign by design’ (the concept of designing for reduced toxicity and end of life and recyclability) and impacts across the life-cycle of products; social scientists talked about public engagement. There is a considerable body of literature regarding exposure of health care providers in occupational settings. For example, chemotherapeutic drugs have been measured in body fluids of health care workers in occupational settings of hospitals and pharmacies (Sugiura et al., 2011). Furthermore, genotoxic effects and adverse reproductive outcomes like low birth weight, spontaneous abortion, congenital abnormalities and low fertility have been evidenced in health care workers administering chemotherapeutic drugs to patients (reviewed in Connor and McDiarmid, 2006). To address workplace issues in hospitals, guidelines were developed by various health and safety agencies (e.g. NIOSH and HSE) for safe handling of hazardous drugs in hospitals and other health care settings. Safe laboratory practices are predominant across universities and other research centres and hence experts mentioning about exposure in laboratory and workplace settings indicated that the tradition of complying with health and safety

[110] For example, see http://www.schwabfound.org/content/what-social-entrepreneur

issues has finally permeated in everyday conversations (also discussed in Chapter 5), but, of course concerns remain regarding their applicability to or effectiveness for nanomaterials, and potentiality about their implementation. An upstream scientist commented:

"I can imagine what it [RI] *means....We can innovate but we have to be aware of the implications of what we're making and how we are going to dispose of it, how it's going to affect the environment, and how it's going to affect the patients. The people who are most at risk are the people who are either making it or administering it because they are going to come into contact with the most of that product."* [NMS 19]

The two excerpts below indicate how their disciplinary orientations influence the perspectives of scientists. An human toxicologist mentioned toxicity and further added how one can design a nanofibre so that it is not hazardous: *"Well, to me it's very simplistic…to be responsible is to think about these things (i.e. toxicity) beforehand and at every stage you can and build benign into the design …."*. [HTOC4].

By contrast, an ecotoxicologist commented that responsible innovation means that the life cycle of the new product is taken into consideration and the environmental footprint of a product is considered anticipatorily:

"...you take in your new development of something, it could be a chemical substance, or product or an article or whatever that you consider it from cradle to grave and thinking about what is it, what could the risks be, what could be the unwanted side effects, where could they occur, how much CO_2 do I put into to this complex or compared to what I get out of it. So it is a lot of LCA kind of thinking depending on how we define LCA….." [ETOC 1]

Similar thoughts were echoed by the representative of an environmental policy making body and this interviewee added about being aware of the implications of the product along the entire supply chain and the potential uses of the product:

" .... a full awareness of how the nano product that you are creating is going to be used, gaining an understanding of / awareness of what other potential uses could be, awareness of the life cycle of products, so, you know, what happens to it at different stages in its life, how you dispose of it, consideration for supply chain management, you understand [that] *the risks are being transferred along the chain."* [PP1.2]

As mentioned earlier, the Research Councils (except one RC) were aware of the discussions on responsible innovation, of which program managers from EPSRC, ESRC, NERC and TSB had more knowledge of the concept. Their conceptualisation of RI included scientists' thinking about potential implications of their research and various pathways of technological development:

"...It is getting scientists to think about the potential impact and consequences of their research before undertaking it. So, this isn't the impact agenda, it's almost Oppenheimer, in the nuclear bomb type issue just to escalate things a little bit... So, some scientists will say, "Well this is just in an interest of curiosity, I'm going to look into this area and I'm not going to be worried about the consequences." What responsible innovation is trying to do is to get people to think about those potential consequences and then to think about the directions of their research as a result of that" [RC 01]

As evidenced in other studies (Helland et al., 2008; Köhler and Som, 2008; Dahlöf, 2010), industry consider themselves to be following high standards in terms of managing risks from new products. Engeman (2012) and Becker (2013) in their surveys on risk perception by nanotechnology industries found that industries believed they are capable of self-regulation and can manage risks from new products. Experts from industries interviewed here remarked that they are cautious

in their approach when experimenting with new products and new lines of business and that they practise managing risks in their everyday work and already follow high standards of corporate responsibility in terms of human rights, environmental sustainability, occupational health and safety standards, product labelling:

"I think for us, it's all about supply chains, all about responsible supply chains, ethical supply chains, marking our products, about looking at toxicity data, so rather than going ahead with animal tests, for example, all about looking at materials not far off our core competence. So, it's not something completely new. We wouldn't just dive into a new venture not knowing what will the health and safety implications are, etc." [Industry 07]

Another industry representative responded by commenting that they use the term 'Responsible Business'. This representative added that though they were not working with nanotechnology[111] they have comprehensive rules and standards to assess risks from new products and generally the idea of any new product development is approached strategically. The response from the industry representative is indicated below:

"Yes I have heard of this [i.e., RI], *although as far as I am aware we don't often use it as a term in XX.*[112] *We use the term 'Responsible Business' however, and we continually review the risks of our products, including rigorous assessment of the risks associated with new innovations and technologies. XX is not currently using nanotechnologies as far as I am aware, but if we were then we would probably have a development programme to look at the special properties and risks associated with these. By analogy, we are doing the same at the moment with different types of biotechnologies since XX has clear interest in this area."* [Industry 02]

[111] Approximately one year after this conversation, the industry announced its interest in the nanomedicine field. However, I was aware from various newsletters XX's plans to enter the nanotechnology space and hence the industry was approached to be interviewed. The discussion about fragmented information in big corporations is unfortunately beyond the scope of the thesis.
[112] XX is the name of the company which is anonymised here.

6.4.4.2 Communication and deliberation with stakeholders

The preceding Section gave examples of how interviewees articulated RI in terms of anticipations. In this section, I mention the conceptualisation of RI in terms of inclusiveness of and deliberation with stakeholders. One of the four dimensions of RI deals with collective imagination - to explore different possibilities of research and alternative paths of developments by scientists and innovators engaging with various actors in society. The experts interviewed here expressed the view that innovating responsibly means engaging with the public and communicating about the research they are doing, transparent and truthful communication of promises, risks and benefits with patients, having dialogue and involving stakeholders at different checkpoints in the innovation phase. However, historic importance given to public understanding of science (PUS) by the Research Councils in the UK (see for example, Pearson (2001) and Gregory and Jay Lock (2008), especially in Europe (Hagendijk and Irwin, 2006; Sykes and Macnaghten, 2013), and long term contributions from eminent scholars such as Brian Wynne and John Ziman about the importance of public engagement in science. More recently, the increased emphasis on public dialogue on new technologies like synthetic biology and nanotechnology could be the trigger for the interviewees to respond as such. The EPSRC conducted a public dialogue on nanomedicine at four locations in the UK (Bhattachary et al., 2008) and many of the experts I interviewed were aware of this public engagement exercise. Furthermore, the nanomedicine scientists interviewed were funded by the EPSRC and quite a few had been closely associated with the public meetings. T hese meetings helped shaped the research call for nanotechnology for health care. Similar research done elsewhere might give different results.

Deliberation and dialogue with people from different disciplinary backgrounds as well as laymen can resolve impasses that can be reached due to lack of evidence and need for action (Wynne, 1998; Scholz et al., 2000). However, the 'public deficit' model (i.e., public are not aware of science and technology issues – public are ignorant) (Wynne, 2006) and that people are passive recipients and not active in co-constructing knowledge could be evidenced in the mindsets of the experts interviewed, but most were politically suave when addressing the point. The excerpt below from a well-known nanomedicine scientist (NMS08) indicates the need for having dialogue with the public, but suggests that public communication is a skill and that only select scientists, capable of doing so, should be engaging with the public:

"… my philosophy in this area is that we need public engagement, for people to have an opinion. There needs to be honest and open dialogue from the very beginning and there needs to be explanation by people that are both experts and also articulate so that they can frame where we are and what the issues are……" [NMS 08]

Some experts expressed that it is a scientist's responsibility to communicate with the public, talk to media and others beyond work remits and mandates, though it seemed that the aim was more to inform the public, i.e., a one way communication rather than engage in a participatory process to set research agendas. The following interview excerpt indicates the above:

"……..responsibility is to communicate what you're doing, especially if you're funded with the tax payers' money…. So, that's why I'm happy to talk and go to newspapers…. [NMS 15]

The same expert indicated the possibility of ridicule from peers, which could create challenges for interested scientists to talk about their science and research:

"It's not ego frenzy for me, as some of my colleagues think it is, I have the responsibility to say what we're doing and why you guys are funding us....." …. [NMS 15]

The enthusiasm to communicate with the public, talking to media and others beyond work remits and mandates indicates the influence of widespread policy discourses on societal implications of science and technology, especially in Europe (e.g.,Hagendijk and Irwin, 2006; Sykes and Macnaghten, 2013). It has been argued that scientists have a responsibility to communicate with the public, and pragmatically, science communication also helps to raise a researcher's profile with funders (Weigold, 2001; Petersen et al., 2008). There are a variety of barriers to public communication by scientists; some reported by Petersen et al.(2008) were: lack of control over media, distortion of the science content to makes it sensational, and difficulty of communicating uncertainties.

It was also mentioned by interviewees that engaging with the press and public should be undertaken with caution and bearing in mind the same level of thoroughness with which one justifies a research idea to the funding body or prepares a response to one's harshest of critics. The following excerpt also indicates that scientists' responsibility is not to raise expectations without having robust evidence of how the concept or technology works.

I have seen examples where people have had a bright idea, they think it might have a beneficial impact on health and the next thing they are talking to the press. I mean, it ends in disappointment, and I think it is your responsibility while you are innovating to be very, very self-critical and say "No, it is a terrible thing to raise false expectations in terms of [a] cure."...You say what you can actually back up, so everything you say [if] *you are talking to a journalist, or on paper, you should say as if you are saying* [it] *to your worst critic or the peer review panel at EPSRC."* [NMS04]

Doubleday (2007b), Fisher (Fisher and Mahajan, 2006; Fisher, 2007) and others (Schuurbiers, 2011) have shown how social scientists' involvement with scientists working in the laboratory helped work on new solutions and influenced decision making. It also promoted second-order reflective learning whereby scientists "reflected on their background theories and value systems" (van de Poel and Zwart, 2010, p.180). The following quote illustrates second-order reflective learning of an upstream scientist regarding lay person's ideas of control and choice in case of health decisions at an individual level:

"*....we have an interesting experience of talking with patients, doctors and you have to be careful there, because people don't know what you are talking about, and they get hyper very quickly, it is very contagious, in a positive way sometime, so people call you up and request 'can I inject that into my son because he is dying', etc. etc., so it becomes hard, so you are careful on moderating public expectations in many ways. But we are trained to do it and it is a very, very useful exercise for us because there are certain things sometimes that you forget because you live too much in the lab and you forget that real life is different in many ways, more practicality, etc. For example, I was involved 2 years ago, in a public consultation paid by EPSRC and I was one of the experts… to convince the public about theranotics, they said 'what are you talking about; you are going to inject something without telling me I was sick and then curing me. You knew I was sick, you kind of lose control of the things, what's the point....Before that experience, I was a very big fan of this theranostic thing, now I am not anymore, and only because, I don't know but I think he was a taxi driver who really got crazy, he was absolutely right about it, we didn't think about it in that sense."* [NMS 03]

One of the Research Council members interviewed shared similar observations from their involvement in the public dialogue on nanomedicine in the UK and they expressed that scientists realised that they are members of the wider community and hence effected changes in their research:

"We had, as I mentioned, a scientist at each of the four sites, and you could see some of them, after they were listening to the discussion, actually realising that they weren't just scientists, they are members of the community, they are members of the public, they are mothers, etc., and that this technology could affect them in their private lives as well. So, at least one researcher changed her research direction because of that.....". [RC01]

Macnaghten et al. (2005, p. 278), eloquently put forward in their article, in which they presented the role of social scientists in the governance of nanotechnology, an explanation that supports the empirical data presented here: "*Rendering scientific cultures more self-aware of their own taken-for-granted expectations, visions, and imaginations of the ultimate ends of knowledge, and rendering these more articulated, and thus more socially accountable and resilient*..."

One representative from an industry explained RI as involving various stakeholders:

"...and how I define it [responsible innovation]*? I think it's* [RI] *about engagement of stakeholders from the public to the market that have an interest…. I fear that stakeholders is such an overused term but I think it's engagement of all the stakeholders in an innovative spectrum"...* [Industry 04]

When asked whether stakeholders in the innovation spectrum would include the public, the interviewee noted the importance of existing regulatory and other institutions to conduct a dialogue with the public. In other words, rather than scientists or innovators communicating with stakeholders directly, the institutions of governance that already exist and are entrusted with the responsibility to safeguard public health, for example, Health and Safety Executive of the UK, Food Standards Agency (UK) should be the ones conducting public engagement:

"……There are public bodies that look after regulating safety, regulating the environment and regulating medicine and the reason these public bodies are there is because some of these subjects are very complex that the average person in the public, unless they're engaging

with a professional context won't be able to say anything particularly useful without a lot of time spent." [Industry 04]

This expert gave the example of how the GM crop discussion got mired into problems and the public assumed that the engagement was only meant as a marketing strategy of GM crops. The expert emphasised the importance of strengthening existing institutions which are entrusted with the responsibility to take care of consumer health and safety and the environment:

I think, what we saw in the case of GM crops was the desire to engage the public……some of its substantially beneficial issues, but in a sense by engaging the public in the way they did, they diminished the value of the public institutions that are looking after the public in terms of health and safety, in terms of the environment and while it may have been a good idea to engage the public, it was sort of Pandora's box of problems simply because the public wasn't attuned enough to the science behind GM motivations and they assume that the engagement was for the sake of marketing relevance and for the sake of trying to really educate, so that the public is aware…… .....I think that really, they represent the public and should be empowered, and having a dialogue with them is probably more important than engaging in a dialogue with the public directly." [Industry 04]

One way communication with the public regarding innovative products from new technologies is seen as a reinforcement of the 'public deficit' model (Wynne, 1991) and can be seen as 'preparing the path' (Guston, 2014) for public acceptance of new products and technologies. In other words, communication with the public is generally seen as a means to create public acceptance of technology (which the above excerpt also indicates) as has been reported in the literature, particularly in the context of GM crops, rather than a true effort to engage in dialogue. This also reinforces the linear relationship of science technology and societal impacts (Doubleday, 2007a), where science and technology are producers and society is treated as a consumer of these products with no say in the design of technology or

research. The excerpt below indicates the deeply entrenched outlook that the role of experts is to educate the public:

"Well what I have to say in terms of governance, this agency in particular, whenever there are innovative approaches coming across, we did it for gene therapy, we did it for pharmacogenomics, we did it for nanotechnology, when the time is mature, we have these big conferences, which mark the start of formal activities, normally, so we have had all these disciplines that I mentioned to you, and we have had one in 2010 for nanomedicines. So, we involve the stakeholders systematically, I even made a webinar, webex, with 100s of patients explaining what is coming, what it is about, and to explain that these are early days, so we are looking carefully into it, so really to prepare, I would say to the ones who are interested, to sort of prepare a mind state to be curious, and want to understand rather than be afraid and reject, so we are already doing this for few years now". [Regulator 02]

One of the experts mentioned the concept of industrial symbiosis (Jacobsen, 2006) whereby materials and energy flows are interconnected between industries which can be brought about by engaging various groups. This interviewee further mentioned that everyone cannot be engaged at all levels of product development and that the engagement needs to be staggered and strategic:

"However, to have it responsible would really mean that everybody is involved in that sort of thought process because you may have a by-product that you're generating that actually could be used for something else and having that sort of the wider approach means that it could be that somebody else can come in and say, "You know what! This is going to have this impact", which somebody else hasn't thought of. It also means that your external community probably needs to be involved at some point. However, there would need to be that sort of the barrier (barrier is the wrong word), but there's no point involving external representatives (members of the public or NGOs or other industries) throughout the whole process, however, at check points, it is quite useful to bring that in". [ETOC06]

Similar to the findings of The Royal Society's (2006) survey of scientists and engineers on science communication, in our study only a few experts (these few were in fact some of the social scientists interviewed) mentioned the need to involve the public regarding the ethics and directions of science and research.

6.5 Views on who should be responsible

Responses to the question as to who should be responsible for RI were varied. Responsibility was attributed to: manufacturers, scientists developing a technology, innovators, expert peer review panel, regulators, shared responsibility of business and regulators, shared responsibility of funding agencies and researchers, and publishers. It was also expressed that everyone in the value chain should be (collectively) responsible.

Interviewees also expressed concerns with the 'use' or potential misuse of a specific innovation; examples were provided where particular technologies can be used beneficially or for destructive purposes. It was observed that to drive home their point the experts used some everyday objects or familiar routine work or some anecdote to lay the foundation before moving on to give more 'scientific' examples related to the topic of the interview.

"...just to take a simple example, if you develop a shovel for doing agriculture, [the] *shovel can also be used to hit people over the head. It has been used to hit people over the head, so you can talk about what I am using the shovel for, to dig the ground, but you are kidding yourself if you think it cannot also be used for other things. So I am working on biosensors for asthma and I am quite happy about that because this is what I call responsible science, but I am kidding myself if I think the same sensor could not be used to detect sarin nerve gas, and therefore [be] used by the military. So there is a train of thought that can take me from where I am here working on responsible science to over there, where it can be used for* [an] *irresponsible purpose."* [NMS 05]

However, scientists and industry representatives generally prided themselves on being responsible and emphasised the potential for dual use of science discoveries. For example, an expert said:

"So, I think it is very difficult to put science and technology in a box, nuclear energy you can use it for nuclear weapons and if you can use it for energy you can solve the global GhG

[greenhouse gas] problem, it's the same technology, so responsible science, you don't know when you are doing the science, it's very hard to constrain..." [NMS 05]

This same expert went on to say that the science and engineering communities are not inherently malicious:

.....I mean 99% of the scientists and engineers wouldn't do that kind of thing [experimenting on themselves to test a hypothesis without ethical clearance], because they would not go down that route because they are responsible, as are most academics, they are not the most irresponsible part of the population, so you got to trust them to some extent..." ..... [NMS 05]

The experts shared that it was their responsibility to identify potential negative impacts and have acceptance of these impacts:

"....So, I find this part of the responsible innovation for me is to have responsibility towards your technology, the technology you're developing. So in the sense that your technology has to have a positive impact, you have to be responsible to identify and accept any negative impact...." [NMS 15]

The kind of responsibility that has been suggested by the experts according to Vincent (2011b) is role responsibility, which is related to the duties attached to an individual in a specific social and institutional setting. However, role responsibility is what Ladd (1982) argues against and suggests instead the importance of moral responsibility of professionals. Other scholars like Goodin (1986) has argued the difference between duty and responsibility, where he suggests the former to be more constraining than the latter and that fulfilling ones duty doesn't leave any room for ambiguity. The concept of responsibility is new (Jonas, 1985 , p.123; EC, 2013d) and hence various conceptualisations of responsibility are being discussed in the literature. Most of the nanomedicine researchers I interviewed perceived themselves to be responsible scientists, and considered themselves to be pursuing excellence in science. Many of the nanomedicine scientists said they are doing responsible

research, however, pointed out that it is how their research is applied which is more important to be considered and that how science and research is finally used cannot be controlled. This indicates that when responsibility was perceived as accountability to something, it made scientists uncomfortable, as could be also evidenced in the findings of the EU project, NanoCODE.[113] Work Package 2 of the NanoCODE project was about "Consultation of stakeholders to assess attitudes, expectations, needs and objections regarding the EC-CoC N&N [Code of Conduct for responsible Nanoscience and Nanotechnologies]". [114] It was found that the principle of 'accountability' was contested most when compared to other proposed principles of the EC-CoC for N&N. Around 17% of the respondents to the survey disagreed strongly by relating it to legal ramifications (Forloni, 2012) and the recommendation was to replace 'accountability' with 'responsibility '(EC,2013).

The toxicologists researching on human and environmental health implications of nanomaterials, the policy makers and regulatory bodies overseeing environmental, health and safety issues, the social scientists associated with nanotechnology, and the Research Councils (except one) appeared to be interested in science policy issues, and were concerned about possible risks from nanomaterials and the associated uncertainty. The representatives of the Research Councils expressed interest in improving their funding strategies and processes and perceived themselves to be responsible for funding the 'right' research.

[113] NANOCODE (A multistakeholder dialogue providing inputs to implement the European code of conduct for Nanosciences and nanotechnologies (N&N) research)) funded by the European Commission under its 7th Framework Programme. The survey and consultations regarding the proposed Code took place between August 2010 and January 2011. Available at: http://cordis.europa.eu/project/rcn/92804_en.html. Accessed on 25 December 2015.

[114] The Code of Conduct is available at: http://ec.europa.eu/research/science-society/document_library/pdf_06/nanocode-apr09_en.pdf

A representative from one of the Research Councils, representatives from the regulatory agencies responsible for approval of drugs, the notified bodies[115] and experts from industry[116] and the nanomedicine researchers expressed that they are responsible, follow excellence in their work and take care of safety, sustainability and environmental implications. These observations are similar to the findings of Wiek et al. (2007) in their agent network study conducted in Switzerland. These investigators found that the representatives of industries, researchers and the public research institutes perceived that doing or funding research in emerging technologies integrating the three dimensions of sustainability – economic, environment and social – is their responsibility. Furthermore, around 95% of the respondents in the Swiss survey felt that government regulatory agencies are responsible for regulating risks to human health from emerging technologies (Wiek et al., 2007). However, no one perceived themselves to be fully responsible for a particular function / role in the study. To the question on who should be responsible for RI, an expert from an industry responded:

"...this has been an interesting question for me and I think a few years ago, I probably wouldn't have known and at least in medical devices, we have the notified bodies, like BSI, better responsible for implementing and reviewing safety and compliance on behalf of the MHRA and EMA and so, there are national public bodies that are in charge of looking after safety and efficacy, although more safety than efficacy ...." [Industry 04]

Distrust towards industries taking adequate measures to ensure safety was also expressed:

[115] the third-party verifiers of safety and efficacy of medical devices in the EU.
[116] Industry representatives who chose to guess the answer to the question on what RI can mean or who gave the idea that they were familiar with the term, albeit in a different sense

"..I think the majority of this making sure (that a particular product is safe) *should come from the government, before it goes to, you know, biotech, pharma or the big corporations....."* [NMS03]

Innovation is a multi-actor process involving various interactions (including negotiations, compromises and repeat negotiations) between the actors and institutions; as a consequence, distribution of responsibility throughout the innovation chain is important. For example, in REACH legislation, downstream users (e.g. formulators, end users: producers of articles) are responsible to liaise with upstream producers / importers / suppliers of a chemical to ensure that the purpose of use of the particular substance is included in the registration dossier and the Chemical Safety Report is prepared by the supplier or upstream user according to the information provided by the supplier. Figure 6.2 describes the REACH requirements for downstream users (ECHA, 2015). In case of nanomedicine, for example, if metal nanoparticles are sourced from particular suppliers, it can be under REACH (in case of Europe) even though the therapeutic as a construct can be regulated by national medicines agencies in member states of the EU or the EMA.

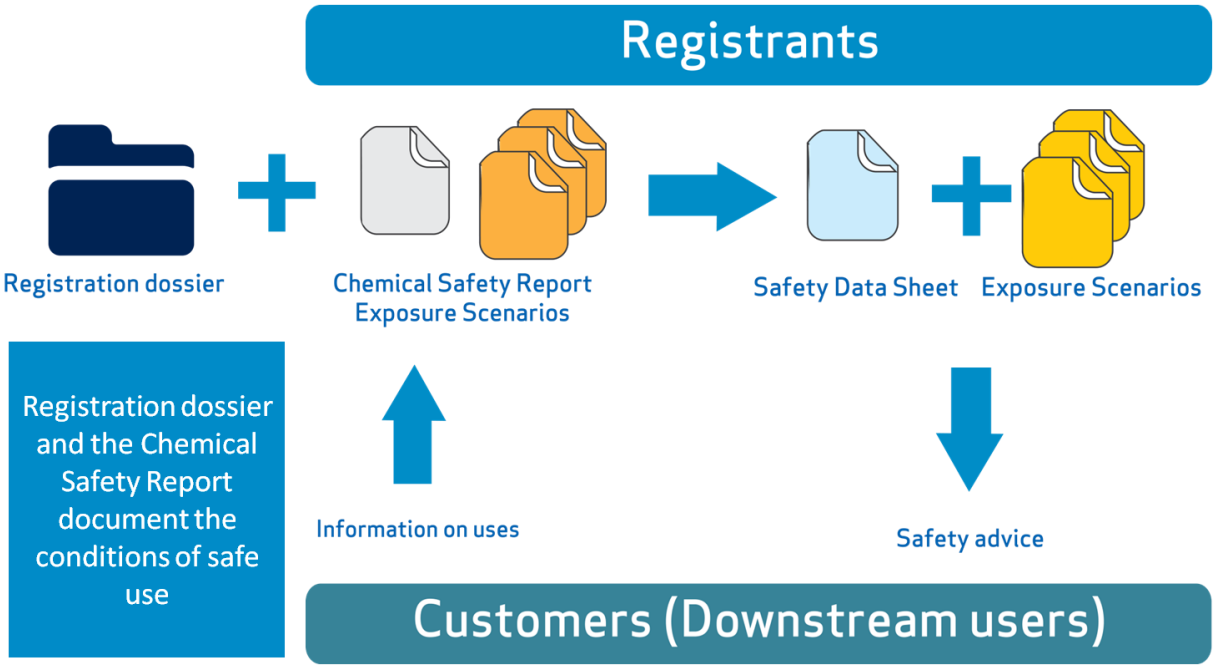


Figure 6.2: Communication along the supply chain in REACH regulation.

To assess the use of the substance throughout its life cycle, the registrant gathers information on the uses of the substance in the supply chain, e.g., from downstream users. The safety data sheet outlines safe use for specific groups. The ECHA has the Chemical Safety Report with them containing human and environmental exposure scenarios. (Adapted from ECHA, 2015).

To fulfil the ideal of collectively shaping innovation, a cultural shift needs to happen (Owen, 2014) in society as well as science, as scientists are part of the 'collective'. It also requires that responsibility be conceived more in an anticipatory or *ex ante* dimensions of care and responsiveness (Pellizzoni, 2004) rather than as accountability or liability. However, caring for (someone) or caring about (something) is a time consuming, demanding, exhausting, continuous and trying process. To walk the path of care is considered a misadventure in the individualistic society of advanced economies predominantly driven by self-interest. Moreover, in this globalised and cosmopolitan world where, in Bill Joy's (Joy, 2000) words, "....*We are aggressively pursuing the promises of these new technologies within the now-*

unchallenged system of global capitalism and its manifold financial incentives and competitive pressures", how can responsibility as care work remains to be seen.

6.6 Observations and Discussion

I generally avoided explaining what RI meant and encouraged the interviewees to share their thoughts. They took it in a spirited fashion and before expressing their understanding of the term, they voiced the assumption that the meaning of RI will be shared after they talk about it. When they were explained what the term RI means, or when their answers were validated, most of them expressed their enthusiasm, but some expressed cynical views. One expert said, ""…*This is responsible Kellogg, I think, isn't it? Meaning of responsibility?..... I mean that trying to lower the libido with his cornflakes that was his 'responsible innovation…."* (NMEn02). This was an important statement for me to reflect on the concept that responsibility can have plural meanings based on individual's perceptions, motivations, cultural context and worldviews. A few others were reluctant to answer and didn't want to venture into the discussion. Though Wynne (1991) and Ziman (1991) used 'public deficit' to make the point that public lacked scientific knowledge and hence needed to be educated in science, I take the liberty to extrapolate the term to 'expert deficit' when the experts were reluctant to answer or gave me 'don't know' answers and didn't want to pursue the discussion further. In other words, it could be due to lack of knowledge or interest beyond the expert's domains of expertise. The 'don't know' answers can also be inferred as uncertain knowledge (Engeman et al., 2012); scientists and

industry personnel are generally hesitant to provide responses unless they are certain or can give definitive answers.

6.6.1 Interpretive flexibility of RI

I evidenced a strong trend that the term RI can be framed on the current discourses on environmental sustainability, greening, corporate social responsibility, and health and safety and stakeholder engagement. This indicates the flexible way in which RI can be interpreted and hence using these already existing concepts and associated guidelines, protocols, voluntary initiatives and relevant instruments RI can be operationalised.

Even though some of the interviewees informed their lack of familiarity or unawareness of the RI as a concept or as a phrase, they associated the term with sustainable development, life cycle assessment, minimising negative impacts of research on the environment, cradle to grave approaches, responsible care – the voluntary initiative of the chemical industries. It could be due to 'preference construction' (Slovic, 1995) – i.e. when faced with unfamiliar questions, we tend to respond based on our values and beliefs and draw upon from a wider context. Can be a consequence of 'framing' [117](Entman, 1993) – my main aim of environmental consequences of nanomedicine was communicated to the experts while soliciting interviews. Interviewees used 'cognitive short-cuts or heuristics' to explain RI. They had general notions of the term and expressed their opinions based on the empirical

[117] Entman (1993) explains framing as: "Framing essentially involves selection and salience. To frame is to select some aspects of a perceived reality and make them more salient in a communicating text, in such a way as to promote a particular problem definition, causal interpretation, moral evaluation, and/or treatment recommendation for the item described."

knowledge gained from practice in their discipline and their understanding. To quote Schwandt (2000, p. 194) “understanding is interpretation”. Construction of ‘meaning’ is also influenced by values, beliefs, and worldviews of the participant. These underlying ideological orientations were expressed as being accountable to tax payer’s money and funders, sharing benefits, full disclosure of risks and uncertainties when conducting clinical trials, not wasting resources, optimally designing pre-clinical studies to reduce animal experiments, etc.

The interpretive flexibility of RI can be an opportunity for widespread cultural change and adoption. However, at the same time RI can risk being an oxymoron as has been the case with green economy and sustainable development. There is an apprehension that RI could become a simple check box exercise and experts (involved in the development of RI) were reluctant to make it very prescriptive. Interviewee SS04 mentioned the risk of RI evolving into fulfilling paper work requirements with the result that it could be followed more in letter than in spirit:

“I don’t want people using these things as tools so that they can say, “Okay, well, it says in this instruction manual that we should do X, Y, and Z.” I want them saying, “Okay, so this is how I should think about this case whether it’s nano medicine or geoengineering or whatever.”.... So, this can’t become a sort of... I’ve done two public engagements; therefore, I can tick that box and move on. That’s the danger.” [SS 04]

However, tick mark exercises could be helpful in bringing about cultural change because it forces us to think. For example, many nanomedicine scientists interviewed mentioned taking care of risks in the laboratory and informing potential risks to patients in clinical trials, which could be attributed to stronger and more pervasive health and safety regulations and the informed consent requirement for

subjects taking part in biomedical investigations (inspiration from the Nuremberg Code), respectively.

Bringing about a cultural shift (Owen, 2014), a change in thinking are what RI ultimately aims for; however, assessing adherence to a principle might be difficult if the principle itself is poorly defined. Nevertheless, the attempt to modulate and shape research and innovation can have public acceptance; studies have shown that the public trust scientists (Parkhill et al., 2013; Nature, 2015) although not in all countries (Bottini et al., 2011) and in some case even more than they trust policymakers (Eden, 2014).

Furthermore, disciplinary orientations of scientists (Gieryn, 1999) can challenge the success of RI as it aims to reconfigure the moral division of labour (Rip and Shelley-Egan, 2010). However, when an agenda of multidisciplinary collaboration is driven from the top management (Tsai-hsuan Ku, 2012), or funding body, then scientists from various disciplines can work together. The ERPSC's funding call for nanotechnology for healthcare in the UK was one such call where involvement of representatives from humanities was required. The advantages of such demands for involvement of researchers from different disciplines was expressed by one expert despite initial misgivings of being forced to involve a researcher from the social science field. The expert commented:

"*Well, when EPSRC put the requirement on us to have a social scientist, and I thought this is bizarre, why are they doing this, I don't know any social scientist, but I think we were quite lucky, one of my colleagues knew social scientists, who is into how to take technology into the market, from the social rather than the economic point of view, so we could see that there was, you know, once we found her, I was certainly a bit happy, I could see that she could actually make a useful contribution to the project"* [NMS 05].

While this kind of engagement adds value to research and its outcomes, it suffers from lack of sustainability of practice in the academic community. As telling as it is, the same expert later discussed the challenges of multidisciplinary research, of time taken to start a project and the dispersal of team members at the end of the funding duration:

"I think the EPSRC should encourage multidisciplinary research, which it does try to do, but there is a issue with multidisciplinary research, that of you do 3 years and it doesn't go anywhere the team breaks up and that is a big issue" [NMS 05]

Therefore, changing research and innovation funding requirements by funding agencies, as has been done by EPSRC, EU's ELSA programs can help to make the boundaries of science flexible and could promote reflexivity.

6.6.2 No mention of equitable access to medicines in the discussions

In an analysis of the 'value statements' of agencies tasked with communicating basic science research, Slade (2011) reported that the mention of the word 'equity' was lacking in these statements. The author analysed all modes of communication published by an agency that are available to the public freely, e.g. brochures, publications, websites. In my study, no interviewee mentioned about equity while responding to the question on RI, although during the interview when asked about the details of projects that the nanomedicine scientists were involved in, a few scientists developing medical devices mentioned cheap and easy to use devices. In contrast, distributional equity in health and access by poorer countries was mentioned by the public (Pidgeon et al., 2009). Woodson (2012) undertook a

bibliometric analysis of publications related to nanomedicine in the Web of Science and PubMed databases and found that 75% of nanomedicine research was on cancer, a major disease burden of high income countries. He found a 20 / 50 gap, [118] where less than 20% of nanomedicine research was for meant for diseases causing 50% of deaths globally.

The concept of 'evergreen' patenting is dominant in the pharmaceutical industry whereby small modifications to existing medical products can result in patent extension (Collier, 2013; Stanbrook, 2013). At the conferences related to nanomedicine which I attended, I noted the palpable enthusiasm in academics about the complexity of nanomedicine[119] and, as a consequence, the inability of generic industries to pose a competitive threat to the original innovators. I did not probe into the matters of distributional equity and access to medicines in this work, as it is widely known that the cost of medicines is profit oriented. Gilead Sciences Hepatitis C drug (tradename Sovaldi) was priced at $1,000 per day per patient resulting in a treatment cost from $84,000−$200,000 per patient; finally, after criticism from WHO and others, the company agreed to make the drug accessible in developing countries (Kessel, 2014). The cost of nanomedicines, such as Doxil® and Abraxane®, are 500 and 100 times (respectively) more than their generic counterparts, doxurbicin and paclitaxel (Goldberg et al., 2013). Moreover, the median survival time of cancer patients is reported to have increased by only a marginal amount by use of these

[118] In global health research, the gap is famously called the 10 / 90 gap, i.e., less than 10% of the worldwide expenditure on health research and development is towards health problems experience by 90% of the global population. STEVENS, P. 2004.*Diseases of poverty and the 10/90 Gap.* 16 pp. International Policy Network UK. Available: http://www.who.int/intellectualproperty/submissions/InternationalPolicyNetwork.pdf [Accessed 10 January 2015]

[119] One nanomedicine scientist explained the error in most published illustrations of liposomal nanomedicines and hence the cluelessness of generic companies to such nuances.

new nanomedicines[120] (Goldberg et al., 2013) even though toxicities such as cardiac toxicity have been shown to be reduced (Gaitanis and Staal, 2010).[121]

6.7 A concept for operationalisation of the RI framework

Nanotechnologies is a convergence of technologies, is highly interdisciplinary in nature (Islam and Miyazaki, 2010) and innovation and related intellectual property often occurs outside the typical boundary of an incumbent firm, e.g. in University labs, and spin-offs from Universities. The pharmaceutical industry has a distributed system of innovation where, typically, basic research and preclinical tests are done at Universities, and spin-offs or new SMEs and incumbent firms subsequently undertake the clinical trials and scale up (Mazzucuto, 2011; Demirel and Mazzucato, 2012). Moreover, public funding is important for the initial stages of drug development. Toole (2012) showed by the use of an econometrics approach that increased spending on basic research was correlated with increased translation of new molecular entities from the private sector, albeit after a long time gap – an integral characteristic of pharmaceutical innovation – thus reflecting the degree of connectedness between industrial R&D and public funding of basic research.

[120] For novel approved drugs, the non-significant increase in efficacy and serious adverse events has been discussed in depth. Refer NIRAULA, S., SERUGA, B., OCANA, A., SHAO, T., GOLDSTEIN, R., TANNOCK, I. F. & AMIR, E. 2012. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J Clin Oncol,* 30**,** 3012-9.and SOBRERO, A. & BRUZZI, P. 2009. Incremental advance or seismic shift? The need to raise the bar of efficacy for drug approval. Ibid.27**,** 5868-73.

[121] For example, median overall survival is 8.5 months for Abraxane® compared to 6.7 months for Gemcitabine, a conventional medicine (For a description of efficacy of Abraxane® compared to conventional cancer treatment strategies, see Rugo et al. (2015)). RUGO, H. S., BARRY, W. T., MORENO-ASPITIA, A., LYSS, A. P., CIRRINCIONE, C., LEUNG, E., MAYER, E. L., NAUGHTON, M., TOPPMEYER, D., CAREY, L. A., PEREZ, E. A., HUDIS, C. & WINER, E. P. 2015. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab as First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). *Journal of Clinical Oncology*.

It is common practise to cite the governance and regulatory framework existing in the pharmaceutical sector as best practice and is frequently suggested as an aspiration to attain for all other industrial and economic sectors. For example, in one of the special issues of the Journal of Research Policy, July 2007, Volume 36, the authors in the introduction to the Issue summarised the research questions raised by the contributors of the articles and wondered whether nanotechnology products could be deployed with stricter regulations as followed in the pharmaceutical sector. To quote the authors (Bozeman et al., 2007p, 811):

" *..... Will it push public authorities to intervene and, for instance, apply a "pharmaceutical-like" regulatory approach where each new product requires a legal approval before being commercialised?"*

The lack of strict regulation has been expressed also for the financial sector:

"Principles of testing and vigilance, such as ones put forward in the pharmaceutical industry, are still marginal in the financial sector." (Muniesa and Lenglet, 2013, p.185)

Surveys on risk perceptions have shown that both scientists and the public view risks from the use of nanomaterial in medicines or health care to be less when compared to the use of nanomaterial in other applications (e.g. food, sunscreens) and other technologies and products (like genetically modified organisms, cell phones and asbestos) (Siegrist et al., 2007; Capon et al., 2015). Similarly, scientists and policymakers see the application of nanotechnology in health care to be "especially beneficial" (Petersen and Anderson, 2007, p.249). Equally important is that the layperson also has positive perceptions of prescription drugs (Slovic et al., 1991)

although social justice and equity aspects of revolutionary drugs as a result of the use of nanotechnology have been aired (Pidgeon et al., 2009).

The questions thus arise: How do we shape innovations in such cases? Where do we begin? How to innovate responsibly, keeping in mind the values (cultural, ethical and moral) of a particular society? How to find equilibrium between opposing needs and requirements and establish the tradeoffs?

Several regulatory frameworks, standards, protocols and normative documents which prescribe specific actions and ways of monitoring and evaluation (e.g., the Global Reporting Initiative guidelines, OECD Principles of Good Laboratory Practices) related to the concepts of sustainable development, research ethics, and environmental sustainability exist. These diversified set of instruments and procedures can be used to arrive at a conceptual model for operationalising RI. Equally important is wide and targeted dissemination strategies to various stakeholders and institutions, because, as commented by an interviewee[122] and as I understood from the current literature in RI, it lacks a systematic approach to illustrating these guidelines or concepts except to mention them in the passing. Similarly, Weil (2013) in her survey of nanotechnology enterprises also found that only a few mention ISO guidelines regarding nanomaterials and none mentioned the OECD publications on nanotechnology indicating that cross sector communication linkages need to be strengthened.

[122] I asked this expert whether some linkages can be established with the current voluntary reporting guidelines for corporations,to which the expert answered " *Well, there's clearly a relationship and I don't know how many of the people who are working on responsible innovation are really immersed and familiar with all of those debates around corporate responsibility from years before, but you're quite right. Something like the GRI grappled with precisely these dimensions in relation to what did responsibility actually require of corporate practice and at what point is responsibility no longer enough and does need some sort of mandatory, regulated, legally enforced, standard, you know, in the case of the GRI, of transparency." [SS05]*

Keeping in mind that pharmaceutical innovation is a complex process with multiple feedback loops involving researchers in both University and industrial laboratories and with the early involvement of regulators, I present below (Figure 6.3) such a conceptualisation of RI, melding it with the existing discourses and initiatives, integrated in a continuum in the stage-gated model of medicine development where at each stage-gate, anticipation, reflective thinking, deliberation and responsiveness help arrive at the go/no-go/modify decisions. This conceptual framework of implementing and instilling the values that the concept of RI envisions, involves collaboration and coordination between various actors (e.g. patient advocacy groups and scientists) and across different institutions and within their structures and routines, operating under different incentives and voluntary norms. The Figure indicates where (physical space), who (the people who could be involved) and how (the exiting instruments, guidelines and academic propositions) RI can be operationalised. Before explicating the framework, I admit that presenting a complex interactional process with many feedforward and feedback loops, which also involves multiple actors at various stages, in a two-dimensional figure would have severe limitations such as which actors should be included at which stage and how to govern innovation and set the agenda for future research and development (basically how to trigger such a complex conceptualisation with competing agendas and motivations). The figure is presented with the aim to start a discussion regarding operationalising RI for nanomedicine and to thrash out or fine tune translation of RI into practice so that shared meanings could be encouraged and at the same time it could continue to be sensitive to the diversity of actors, sectors, motivations, ideals and values.

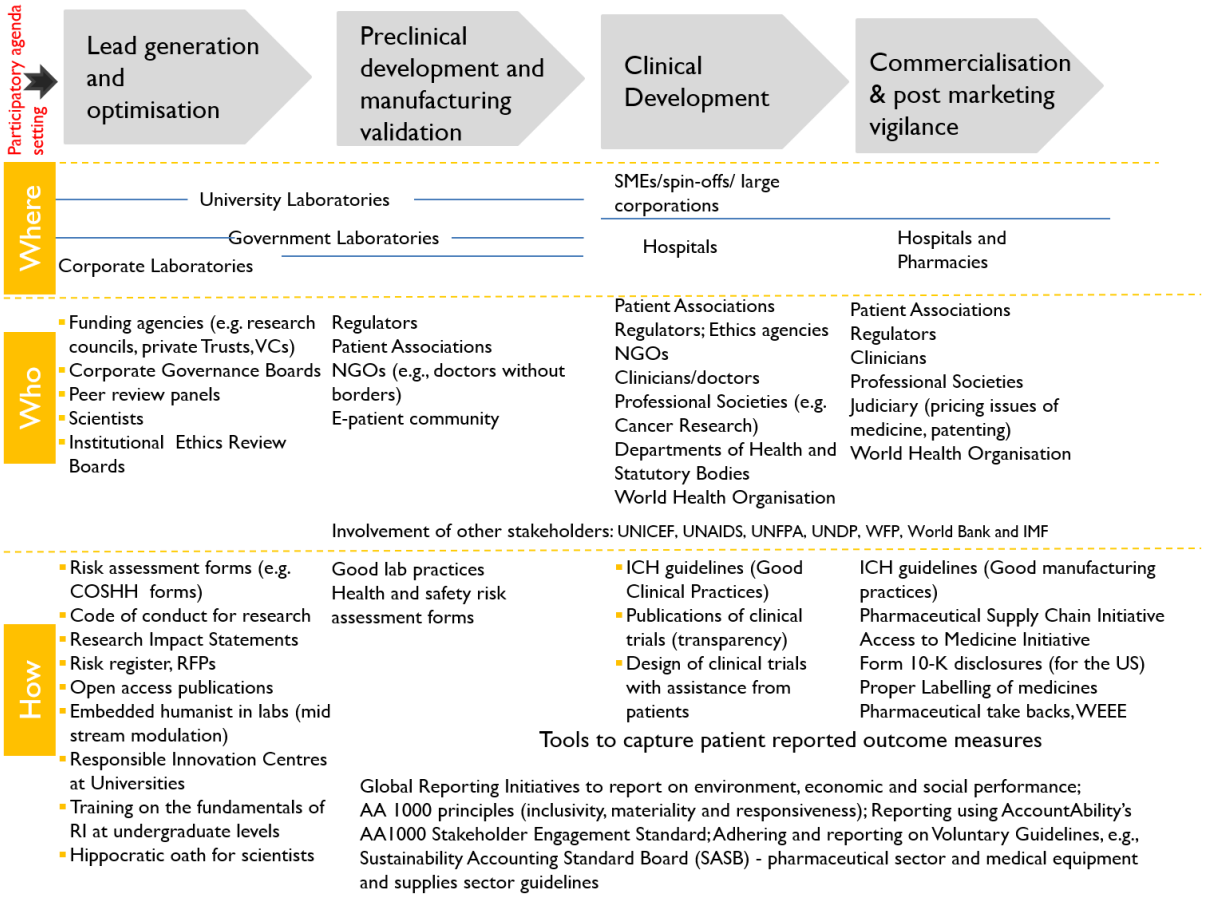


Figure 6.3: Operational framework for RI with suggestion of some implementable actions for the nanomedicine sector.

The different stages of medicine development (the stage-gates differ somewhat in case of medical devices) mapped against the dimensions of locations, actors and actions where existing instruments and guidelines could act as starting points for embedding the concept of RI. Some examples of additional actions which are not covered by existing instruments are also listed. Agenda setting in participatory manner is very important for new developments in nanomedicine. The figure shows embedding RI in everyday life requires innovation in the process of nanomedicine development and commercialisation along with innovation in medicine and medical devices.

The most important and first step to inculcate the values into everyday research, innovation, and R&D life that RI seeks to achieve is involving the affected

stakeholders (patients, their families and patient advocacy groups) and general practitioners or clinicians, in addition to scientists, social scientists, funding agencies and industrial institutions in setting biomedical research agendas. Rabeharisoa and Callon (2004), with their example of advancement of research in muscular dystrophy in France, have argued convincingly about the benefits of consulting patients and advocacy groups for setting research directions and priorities in biomedical research.

A cultural shift needs to happen (Owen, 2014) in society as well as in science to shape innovations collectively. To bring about the cultural shift to the proactive modes of responsibility – care and responsiveness – it is necessary that universities and schools have mandatory modules and courses, in all branches of studies, about responsibility, ethics, and relationships between science, technology and society, sustainable development, and concepts of responsible innovation. A full course on these aspects should be mandatory at PhD level. RI can be considered to be one of the components of sustainable development whereby, products and process innovation can be developed to achieve a future society which can be experienced and enjoyed by future generations. RI is about innovating in a manner that balances the need for economic prosperity and creating sustainable jobs with the foundation principles of human rights and equity, fairness and justice, and simultaneously takes care of the environment and conserves resources.

Therefore, to translate RI into practice, collective research agenda setting and opening up the disciplinary silos at the formative years when ideologies have not ossified is necessary. Similarly, it is important that the concept of RI be discussed with large pharmaceutical corporations, because larger established companies generally take up voluntary initiatives regarding non-financial performance and

communicate more openly about these initiatives both to their internal as well as external stakeholders (Kuzma and Kuzhabekova 2011) than smaller companies who have less access to the broader skill sets required to achieve this. The proposed approach to RI integration also recognises that larger enterprises are already practising some forms of the normative concepts, such as, sustainable development, thereby facilitating enterprise buy-in to the additional aspects.

Health care innovations can take place at various spaces: Universities, research institutions supported by the government and the military, corporate labs and hospitals, clinics and pharmacies. In these locations, RI can be practiced in everyday lives by one or more of the following ways:

- Ensuring employees are sensitised to the concepts of responsible innovation and other normative goals
- Having an embedded humanist in the research project which can promote reflection and "socially accountable and resilient research" (Macnaghten et al., 2005,p. 278)
- Having a code of conduct for research (example, the European code of conduct for research integrity or adoption of the EU code of conduct for responsible nanosciences and nanotechnologies research)
- Having something like "The Universal Ethical Code of Scientists" at an institutional level since science can be misrepresented influenced by varied interests. Mandatory and regular trainings on these aspects.
- Having something like the Hippocratic Oath for Scientists (Garwood, 2016).

The extant instruments and mechanisms by which the principles of RI can be ingrained are many. Some key instruments and guidelines could be Institutional Ethics Boards (IEB), regular staff meetings or reflections on strategic issues, mandatory risk assessment forms (e.g. Control of Substances Hazardous to Health Regulations, i.e., COSHH assessment forms), quantitative risk assessments (where possible), Request for Proposals (RFPs) of funding agencies mandating inclusion of the dimensions of RI and public consultations. Effective and robust IEBs (and not an ethics board which lacks teeth and where scientists can get to do what they want to do without any uncomfortable questions asked), strategic meetings with employees or researchers to discuss the motivation and goal of the innovation, societal and environmental risks and benefits, possible alternatives could help RI to become a part of everyday life of researchers. Similarly, tools such as risk assessment forms and practices such as mandatory and regular training on filling up these forms for new researchers, research impact statements describing the outcomes and broader impacts or relevance of the research (e.g., required by the UK RCs and national funding bodies of the US), in addition to the risk of project implementation could be other ways of implementing RI.

Promoting broader discussions on the concept or goal of research in nanomedicine should lead to discussions (i.e., second-order reflexivity) such as: does this goal (e.g., developing costly nanomedicines with marginal efficacy) need to be pursued? Would it be worthwhile to pursue this as a goal? What kind of issues might need to be addressed? Who has ownership of the data that would need to be generated for development of such medicines? What kind of additional requirements (companion diagnostics) would such an innovation entail? Who could access these? Also, wider

discussions on responsibility (extended from responsible business) could bring in the cultural change where it becomes a habit for members of society to reflect on deeper motivations of innovation.

Due to the triple helix, multisite and global nature of innovation in the pharmaceutical and medical device sector, we need to move to the site of SMEs and multinational corporations to detail how RI can be operationalised in these spaces. The concepts of corporate citizenship and responsible business have gained wide currency in business circles and many companies are reporting their performance on the three dimensions – economic performance, social performance and environmental performance. The extant guidelines, such as those promoted by GRI, Social Accountability Standards Board's (SASB) guidelines for pharmaceutical and medical equipment sector, AccountAbility's Stakeholder Engagement Standard (AA1000SES) and Accountability Principles Standard (AA1000APS) to prepare a triple bottom line communication, offer good starting points.

Reporting and communicating about corporations' or research institutions' sustainability performance including their approaches to innovation, using the existing voluntary guidelines, can help to engage the wider publics Reporting on the material issues using SASB's guidelines (which could either form part of the Annual Report or disclosed in Securities and Exchange Commission's Form 10-K in case of the US which is available to the public or a standalone report) for pharmaceutical sector would address wider issues of societal concern. Similarly, if an organisation chooses to report using accountability standards, they need to report on how the firm practises inclusivity, identifies and reports on material issues and how the corporations respond to stakeholder inputs or concerns. Including various

stakeholders such as patients, clinicians, regulators, international bodies, such as United Nations Children's Fund (UNICEF), United Nations Programme on HIV and AIDS (UNAIDS), United Nations Population Fund (UNFPA), United Nations Development Programme (UNDP), the World Bank and International Monetary Fund (these organisations either fund research on social determinants of health or loan money to help developing countries improve health of their populations) at different stages in the research and development of (nano)medicine could help fulfil the vision of RI.

Traditionally, the business sector has conducted stakeholder engagement or collaboration (Svendsen, 1998) to design, create and customise products and services; in the development sector participatory rural appraisal (Chambers, 1994) forms the foundation of intervening in communities (for example, finding solutions to energy availability in remote communities), and more recently public engagement has been promoted to sensitise scientists to listen to and value public opinion (UK House of Lords, 2000; Wilsdon and Willis, 2004). The rich literature in these areas and concepts such as anticipatory governance (Barben et al., 2007), midstream modulation (Fisher and Mahajan, 2006), and technology assessment in all its forms (Schot and Rip, 1997; Guston and Sarewitz, 2002), can be in used in different contexts, and at institutional levels and scales to practise RI.

6.8 Conclusions

This chapter presented the expert interviewees' imaginings of RI. It clearly demonstrates that RI can easily become a 'buzz word' (Bensaude Vincent, 2014) as

most interviewees were able to identify with the word and could relate it to their work. The involvement and engagement of most interviewees while discussing their views on RI indicates that there is the possibility of opening up spaces for dialogue on the topic (though one can assume a positive answer bias in the interview situation which may not be directly and easily transferable to researcher's daily life). Even if the interviewees were not aware of RI (i.e. in the interviews conducted in 2013[123]), experts looked up the term to answer the question on RI and wanted to understand more about it from the interviewer. One interviewee expressed their preliminary understanding from the information they accessed and aired their concern that RI could result in hampering of innovation was expressed:

"…..I like the idea of irresponsible stagnation as the alternative. That's all I came across, so I quite like it to be explained to me because I actually read a couple of things and I'm almost none the wiser." [Industry 08]

The feeling that RI could be compared with 'irresponsible stagnation', indicates that the debate on the environmental and societal implications of nanotechnology continue to have dual implications: slowing down the pace of innovation related to nanotechnology applications and related economic growth in the light of wider societal concerns. This has also been concluded by others (Kelty, 2009; McCarthy and Kelty, 2010). Company executives expressed that the excessive focus on preventing risks, and hence the reduced risk appetite, after the financial crisis is hampering business growth and creating stagnation. The thrust is now on taking risks and CEOs view excessive regulatory burdens as hampering business growth

[123] From late 2012, RI has become more visible, and documents explaining the concept could be found by interested individuals by browsing the Internet.

(CEB, 2014; HBR, 2015; KPMG, 2015). Moreover, irresponsibility generally means hampering innovation and economic growth and it does not mean reflecting on the issue of whether a particular kind of innovation and economic growth ought to be done or ought to happen.

With regard to the issue of 'risk', the interviewees were concise (as illustrated in Chapter 5) and mentioned practices that can reduce risk to humans as well as the environment, safe work practices in the laboratory, safety to patients, safe disposal of nanomaterials, adopting the best available technology for personal protection, and designing environmentally benign products. Importantly, the concept of risk got connected to regulations. However, the concept of responsibility in innovation elicited a more diverse set of reactions ranging from accountability to funding agencies through scientific excellence, and included patient safety and safety of the people involved in research and production of nanomaterials. This indicates the broader and higher level remit of responsible innovation although it also indicated that the meaning of RI can be interpreted flexibly based on discipline and work background of the experts. However, this finding cannot be generalised as Shelly-Egan and Davies (2013) report that 'responsible development' was articulated narrowly in terms of risks and health and safety by representatives of industries in the US.

Responsible innovation can help, in Niklas Luhmann's words, to "avoid the regret of regrettable decisions" (Luhmann, 1990p, 225). RI can provide an opportunity to broaden the existing paradigms of corporate responsibility, business citizenship, and ethical, legal, social aspects (ELSA) of research, and can usher in the concept of sustainable development in the laboratory. However, reduction (of complexity) also

needs to be implemented in order to create effective policies in a complex society; RI seems to make issues more elaborate. Furthermore, issues of power and politics (Bijker, 1997; Stirling, 2008) influence technology choices, while RI is silent on these aspects.

RI can suffer the same criticisms as have been the case with the Precautionary Principle, i.e., stifling innovation, vagueness and ambiguous definition and multiple interpretations. However, the responses of most interviewees while discussing their views on RI indicates that there is the possibility of reconfiguring science and research policy and that RI could well be an 'umbrella term' (Rip and Voß, 2013) which could finally bring about change in real life by bringing together disparate groups under common themes (though interview situations might influence responses to be more positive and politically suave). The interpretive flexibility of RI means that it could well be a 'plastic' word (see e.g., discussion on public engagement in stem cell research by Parry et al., 2012) whereby it could be translated and interpreted by diverse groups with varying expertise based on their needs and implemented diversely (however, it could also potentially weaken its capacity to drive the culture change that it seeks and can result in 'responsibility washing').

Despite all these challenges of integrating RI and its drawbacks, I conclude this section with quotes from two interviewees. When I asked one of the upstream scientists whether the expert was aware of the term RI, the response indicates that the concept has the potential to usher in change:

" *I am now! I like the term and think it would stretch more than, say, companies inventing things and producing products, but scientist too. Are we being responsible for what we say*

about our systems, are we being responsible and investigating thoroughly and not being satisfied with the fact that you've injected a system into a tumor bearing animal..... Do we ever talk about this…are our systems, our journals and so on and the rewards scientists get based on just a little bit of obfuscation? But I think concepts like that are relatively new to me in terms of phraseology, but I think terminology is extremely important. Once people start using that, they start thinking about it….." [NMS18]

A social scientist (whom I interviewed and with whom I could find similarity with my own thoughts) when asked about what RI meant to this expert, after sharing his/her thoughts on the existing methods, concepts and tools for governing technology and research, suggested: "*There are different ways of talking about this sort of stuff but as long as it captures the imagination and gets the enthusiasm and support of a diverse set of constituencies in policy, in business, in science to sort of gather around it and move things forward under that umbrella, I'm happy to support the effort"* (SS 05)

It is expected that the findings from this empirical research, and the melding of RI with existing concepts of business citizenship, green manufacturing, corporate responsibility, and codes of conduct can help stakeholders in the 'real-world' of University laboratories and corporations to implement (the concept) and practise RI, and could form a basis for funding decisions of national, bilateral and multilateral agencies.

Of course, the suggested framework to operationalise RI is open to debate, to be critiqued and to be customised based on individual contexts, or further improvised or rejected. It would be interesting, as future research and a first step to understand at what stages in the pharmaceutical (and medical device) innovation pathway the

dimensions of RI – reflexivity, anticipation, deliberation and responsiveness – are included and to what extent, since *prima facie* it seems the dimensions are present to a certain extent at various stages of the innovation process. Secondly, it would be of interest to check whether and/or how this broader idea of RI can be implemented in various organisations (as mentioned in Figure 6.3 above) as a pilot action-cum-research exercise. Thirdly, it would be informative to explore whether individuals trained in the concept of RI can make changes in the pharmaceutical and medical device industry with their formalised organisational configurations and approach of conducting business (and whether this could also impact other organisations associated in the drug development process), or whether some external 'motivators' are needed which can drive research in the health care sector to include the concept of RI both in letter and in spirit.

Chapter 7: Conclusions

"*Any philosophy, that in its quest for certainty ignores the reality of the uncertain in the ongoing processes of nature, denies the conditions out of which it arises*." John Dewey, The Quest for Certainty: A Study of the Relation of Knowledge and Action (1929)

7.1 Research objectives and findings

The possibility of future environmental impacts from nanomedicines has been largely ignored in the scholarly discussions on nanotechnology and its implications, the various products containing nanomaterials, and their health and environmental impacts. Discussions on the adequacy of the ERA framework for nano-therapeutics are very limited (notable exceptions are Baun and Hansen (2008), Mahapatra et al (2013)). Moreover, literature addressing the implementation or operationalisation of Responsible Innovation (the way it has been conceptualised by Owen et al.(2013a)) in organisations which thrive on innovation is also sparse (an exception is Asante et al. (2014)).

The work presented in this thesis is a first attempt at exploring the potential environmental concerns related to the likely future increase in the use of emerging nanomedicines. This thesis is also the first study which explores expert viewpoints on environment hazards and risks from nanomedicine across the nanomedicine innovation pathway. Another novel contribution of this thesis is the investigation of experts' (from across the nanomedicine innovation value chain) understanding of the evolving context of responsible innovation and how it can be implemented 'on the ground' for organisations and scientists working on nanomedicine to complement

existing pharmaceutical regulatory regimes. Chapter 1 established the purpose behind the study, the scope of the study and outlined the research objectives.

The research presented used a mixed methods approach that combines quantitative modelling to predict likely future environmental concentrations of nanomedicines, with qualitative interviews with stakeholders along the nanomedicine innovation pathway and the details are part of Chapter 3. Before providing a future outlook, I reflect here on the objectives of the research and summarise the key findings from each aspect and the limitations.

Objective 1 was to ascertain nanomedicine R&D trends, through critically reviewing the existing literature on pharmaceuticals and nanomaterials in the environment, the current scenario of regulation in medicine and medical devices, and thereby to identify any mismatch between innovation arising out of new and emerging technologies and the existing regulatory framework. The output here was a published article: Potential environmental implications of nano-enabled medical applications: critical review (Mahapatra et al., 2013) whose conclusions included the environmental fate and exposure of nanomaterials with the potential to be used in health care to date (i.e. 2012). Ecotoxicity studies with nano-enabled medical products is fairly limited (in comparison to studies done with other nanomaterials), although there are around 40 (Duncan and Gaspar, 2011) approved medical applications and a number in clinical trials. The knowledge and data gaps identified include measured and modelled environmental concentrations, environmental fate and behaviour, dynamic changes in physical and chemical properties both *in vitro* and *in vivo*, applicability of exposure assays, dose metrics for exposure assessment, biouptake and toxicity mechanisms and chronic or acute toxicity relationships. This

chapter concludes by giving tentative suggestions relating to possible environmental hotspots including surface water and sewage sludge.

Chapter 2, in addition to including the outputs of objective 1, sets the theoretical framework used to analyse empirical material collected for Objective 4.

Throughout the thesis I make the point that there is a flurry of activities ongoing in the nanomedicine field, and I highlight the interest and support of the regulators in this arena leading to the potential for the co-production of knowledge. I mention the increased investments of incumbent pharmaceutical companies in small nanomedicine firms and university spin-offs to indicate the importance of the application of nanotechnology in the health care sector, and the distributedness of innovation in the pharmaceutical sector. I also have made frequent mention that the existing uncertainty and lack of data regarding nanomaterial or nanomedicine health and environmental risk points to a need for strategies for governing innovation democratically rather than governing risks. Moreover, because the health care sector is considered to be tightly regulated and is distinct from other sectors, the concept of RI needs to be embedded within existing regulatory frameworks to be implementable for nanomedicine.

Building on the knowledge gaps identified under Objective 1, and in parallel to interviewing experts regarding their perceptions on environmental hazards and risks, a quantitative study was done to estimate environmental concentrations for nanomedicine in high release worst case scenario. Objective 2 was to estimate the prospective environmental concentrations of nanomedicine, using gold nanoparticles for nanomedicine as a case study. Probabilistic mass flow modelling (PMF) and

probabilistic species sensitivity distributions (pSSD) were used to assess environmental risks. This work has also resulted in a publication and is presented as Chapter 4 of this thesis: Probabilistic modelling of prospective environmental concentrations of gold nanoparticles from medical applications as a basis for risk assessment (Mahapatra et al., 2015). Using eighteen different medical applications of gold nanoparticles, in the market or in clinical trials or show high potential for translation, concentration of Au-NP in freshwater was found to be pg L^{-1} and in sludge was less (more than 100 µg Kg^{-1}) in comparison to the amount found for widely used antibiotics in dewatered municipal sludge (Gottschall et al., 2012). Hence, it was concluded that environmental risks from Au-NP used in nanomedicine would be unlikely in the near future. However, of all the Au-NP aquatic toxicity studies published between 2008 and 2014, only 12 related scientific papers could be used for the model since it was difficult to arrive at the effect concentrations (LOEC or NOEC) from the other published studies or the studies were not conducted with organisms relevant or recommended for environmental risk assessment studies. Only one published study for toxicity of Au-NP to soil organisms could be used for the purpose of the modelling exercise. There are data reporting errors across data bases of UK and EU regarding type of solid waste and solid waste management. Similarly, land area under crop cultivation, pasture, and other categories were inconsistent across US State Departments. Many environmental data could not be extracted from published literature, e.g., overflows from STP, combined sewer overflows, leakages from sewers, sludge amounts applied on land. Thus, currently, modelling approaches are hampered by data gaps beyond those related to environmental concentrations of the nanomaterials themselves, and cross-checking of data to parametrise models is

enormously time-consuming. The novel contribution of this chapter was building a bottom-up consumption model (amount of medicine consumed by patients), whereas the widely used mass flow model for predicting environmental concentration of nanomaterials relies on a top-down approach (production by industries).

Objective 3 then was to assess the broader stakeholder views on the potential environmental risks of nanomedicine and the adequacy of current risk governance frameworks to manage these risks. The 62 interviews (involving 66 interviewees) conducted with stakeholders along the value chain (nanomedicine researchers, research funders, industry and regulators and downstream researchers) and discussed in Chapter 5 built support to the findings in Chapter 4 that environmental risks are unlikely in the near future from the use of nanomedicines. However, a majority of the interviewees agreed that the possibility of hazards exists primarily because medicines are designed to have biological effects. An intriguing finding was that the pharmaceutical sector is distinct (in terms of its stringent regulatory framework) and other than the regulatory agencies, the knowledge that environment risk assessment is required for medicines was not widely known specifically amongst the academic community, suggesting a disconnect between academic and real-world research and development in nanomedicine.

The final objective was to explore the construction of the concept of RI by experts in the nanomedicine innovation chain. Thus, a question was added to the questionnaire or interview schedule and stakeholders were asked if they understood RI and who they felt should be responsible. While not all were aware of the discussions on RI during the period when the interviews were conducted, most were able to relate to it, and indeed many of the views expressed by interviewees could be

categorised under the dimensions of ‘anticipation’ and ‘deliberation’ of RI. The findings are discussed in Chapter 6. Interviewees mentioned toxicity assessment, thinking about future implications, engaging with various stakeholders, life cycle assessment as among their key ideas of RI. They likened RI with the concepts of responsible business and responsible care which indicated that the existing ethical principles, guidance, and laws, and regulations can provide an appropriate way through which to implement RI. A key outcome from this chapter is the conceptual model for operationalising RI (presented as Figure 6.3 in Chapter 6), melding it with the existing discourses and initiatives, integrated in a continuum in the stage-gated model of medicine development. The conceptual model maps to the phases of nanomedicine development and defines the stakeholder roles and responsibilities, as well as how existing guidelines and regulatory best practice can be incorporated and what new could be done. The idea to integrate RI with the existing concepts, wherever possible, was to avoid making this approach merely a tick-box exercise or an ‘add-on’ to already existing frameworks and approaches. The aim was to understand the existing routines and practices in the pharmaceutical (and medical devices) sector and the voluntary and legal guidelines that the sector subscribes to already, in order to know in which spaces interventions could be designed so that the concept of RI becomes the guiding principle of research and innovation.

7.2 Limitations and Reservations

The research for this thesis began with no firm idea on what would finally emerge, other than a desire to find a means to have a sustainable nanomedicine industry.

Furthermore, research studies like the study done in this thesis are likely to have many limitations. However, I outline here some of the most important issues in my perspective. My first reservation is that the breadth of the topics explored in the questionnaires did not allow sufficient time to understand the reasons or motivations behind the answers of the experts. My second reservation is my inability to inform regarding how the environment risk assessment guidelines of human pharmaceuticals could be adapted for the existing and likely nanomedicines in the near future (although this challenge has also occupied the EMA and others for a number of years, suggesting that there is no simple solution and the current decision is that they will be treated on a case by case basis). My third reservation is that the questions on RI did not go far enough to explore the meaning of responsibility as articulated by the experts in order to allow me to contribute to the evolving framework on RI by unpacking 'responsibility' in responsible innovation through the lens of the experts. It would have been an interesting exercise (though the current responses indicate that responsibility was defined more with responsibility associated with the role rather than responsibility of a person and in terms of accountability). My fourth reservation is that in the process of making a customised questionnaire for each expert with the aim to make the experts comfortable to respond to the questions, I have lost some insights specific to the health care sector.

With these limitations in mind, I revisit the current status with respect to environmental implications of nanomedicine and RI in nanomedicine (the two key objectives of the thesis as mentioned in Chapter 1)

7.3 Current status and forward outlook

Information about concentrations and effects of pharmaceuticals in the environment is widely accessible and covered in the news (McKie, 2012; Carrington, 2014; Milmo, 2014; Owens, 2015). The concern about pharmaceuticals in the environment is steadily growing and research studying concentration, fate and effect is on the increase (more than 5,000 papers were published in the last two years). The news report written by McKie (2012) about treatment costs to efficiently remove oestrogens from STPs had around 170 comments, which indicates the degree of interest of the citizens to engage with the topic. Recently, a few research papers were published studying the environmental fate and behaviour of nanomedicines (Zhang et al., 2013; Chen et al., 2015). The ETC group, which called for a moratorium on nanotechnology in 2002, recently reported (ETC group, 2015) the establishment of a technology assessment centre at the United Nations which will include intergovernmental meetings of various stakeholders to discuss various aspects of new and emerging technologies. Another important development has been the publication by Andrew Maynard (2015) suggesting that RI needs to be developed in a way that it is integrated into business practices and imbibed by entrepreneurs and that it should not "*exacerbate the dilemmas entrepreneurs face"* (p.200). Around 15 projects have been funded by the EC in the last 3 years to develop the responsible research and innovation (RRI) concept, such as developing criteria, governance frameworks, tools, and conducting public dialogue on nanotechnology. However, the word 'environment' is conspicuously absent in the RRI wordle in the EU's website, suggesting that there are still gaps, which this thesis has intended to go some way towards filling.

7.4 Environmental Implications of nanomedicine and RI in nanomedicine: A topic worth exploration

When I started my research in the autumn of 2010 there was only one scientific publication on environmental risks of nanomedicine (Baun and Hansen, 2008). However, the EMA had held a workshop where the methodological issues with regard to risk assessment were presented and it was no surprise that the presentation was done by a representative of the German Environment Agency (UBA). The UBA hosts the 'pharmaceuticals in the environment' website and created a large database. The current regulatory frameworks for medical devices and pharmaceuticals for human use have been elaborated in Chapter 2. In the case of EU, if the log K_{ow} (octanol-water partition coefficient) of a chemical is less than 4.5 the regulatory threshold limit for triggering an environment risk assessment is PEC of 0.01 µg L^{-1} in surface water. However, I discussed the challenges of assessing log K_{ow} of polymers and CNTs (in fact I also presented briefly that log K_{ow} is not the correct metric for pharmaceuticals due their ionic forms). I argued that bioavailable 'smart' nanomedicine may show effects below 0.01 µg L^{-1} by various modes of action (e.g., decreasing ATP levels in cells, modulating a particular signalling pathway) and as a consequence may have sub-lethal and chronic effects rather than acute effects. The experts interviewed unanimously agreed to the inappropriateness and inadequacy of the criteria. Furthermore, I discussed that the regulatory framework for medical devices do not go through any environmental risk assessment. Approval of a medicine is not dependent of environmental impact indicating the dominant ideologies of anthropocentrism and speciesism. With regard to perception of interviewees about the adequacy of the current regulatory framework for medicines for safeguarding the environment (Chapter 5), many interviewees were not aware of

the Guidelines for Environmental Risk Assessment for pharmaceuticals for human use. Some expressed satisfaction with the knowledge that the Guidelines and the associated test protocols existed. A few experts noted that with regard to occupational health and safety in the laboratory, they had to adapt the COSHH forms for their research. The challenges of assessing log K_{ow} for nanomedicine as well as conventional pharmaceuticals was discussed by some of the interviewees. It would be of interest to conduct an ERA of nanomedicines currently on the market or in clinical trials which is currently (to the best of my knowledge) non-existent in the scientific literature. Most interviewees indicated that environmental hazard could arise from nanomedicine (if they found their way into the environment) because medicines are bioactive in nature, however, some experts suggested that I compare them with conventional chemicals which are present in much larger amounts. Some interviewees also suggested that the importance of health benefits from nanomedicines might outweigh any potential environmental concerns. This echoes the work of Dohle et al. (2013) who found that environmental concerns can take a back seat depending on the severity of a disease; if the severity of the illness is less, people surveyed in the study showed willingness to use a medicine which was environmentally safer.

The concept of RI has already gained traction in EU research and innovation policy by way of the Horizon 2020 programme. As discussed in Chapter 2, it seems that the stage gating approach, suggested as an approach to govern innovation in the RI framework by Owen et al. (2013b), is integral to the pharmaceutical (and medical device) sector. Hence, it would be interesting to study to what extent the dimensions of RI - anticipation, reflectivity, deliberation and responsiveness - are already present

in the pharmaceutical (and medical device) industry. An ethnographic research study within a University laboratory and a private or corporate laboratory involved with research and development of nanomedicines would provide insights to understand what kind of trade-offs exist at each stage of nanomedicine development and allow comparison and contrast between laboratories. It would also be worth exploring how 'responsibility' is understood by upstream scientists and innovators. To be able to bring communities together to deliberate on the proposed conceptual model of RI for the nanomedicine sector, so that it can be refined and necessary strategies designed to work towards integrating the concept, would be a natural next step. Such an approach would aim to increase institutional reflexivity and innovation with the underlying principles of care and concern, thus working towards the broader context of sustainable development.

ANNEXE

Annexe to Chapter 2

Definitions of invention and innovation

Generally the business dictionaries define innovation as "*The process of translating an idea or invention into a good or service that creates value or for which customers will pay…....Innovation involves deliberate application of information, imagination and initiative in deriving greater or different values from resources, and includes all processes by which new ideas are generated and converted into useful products*".[124]

The definition of innovation (below) in the Encyclopaedia of Social and Behavioural Sciences emphasises the difference between invention and innovation but conforms to the old meaning which is etymologically derived) of introducing something new or something which alters established practices.[125]

"*Invention is the conception of a new artifact or process that is useful, original, and non-obvious.... Innovation, as defined by Richard Nelson (1993), is the processes by which firms master and get into practice product designs and manufacturing processes that are new to them…....' Thus, an invention does not become an innovation (and many never do) until the invention is successfully embodied in a product and introduced to the market*." (Branscomb, 2001).

An innovation in medical therapy, which can also command higher prices, has been termed as rewardable innovation by Aronson et al. and they propose the definition of

[124] http://www.businessdictionary.com/definition/innovation.html#ixzz3taR7Eeyh

[125] http://www.etymonline.com/index.php?term=innovate

rewardable innovation as "*a medicinal product that provides, through a step change, something novel, with the potential or proven ability to yield, for individuals and/or their society, a treatment not previously available or a clinically significant improvement in treatment, with large health gains and favourable benefit to harm balance, at an acceptable cost*." (Aronson et al., 2012, p 254)

Active moiety[126] means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Or more simply, as provided in the Drugs@FDA Glossary: "*A NME is an active ingredient that has never before been marketed in the United States in any form*".[127]

FDA regulations at 21 CFR 210.3(b)(7)(16) state:

"Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect".

The European Commission in Chapter 1 of Volume 2A of the Notice to Applicants (NtA) – Revision 4, issued in 2013, defines new active substance as (EC, 2013c):

[126] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.108
[127] http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

- “a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;

- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing significantly in properties with regard to safety and efficacy from that chemical substance previously authorised;

- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;

- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union”.

Table A1: Biodistribution studies of gold nanoparticles (Au-NP).

The studies reported in this table were published during 2008–2013.For a review of studies published before 2008, please refer to Balasubramanian et al. (2010)

Reference	**NP size, capping**	**Route of administration**	**Animal model**	**Dose**	***Time points*** **Instrument used to analyse Au in tissues**	**Biodistribution**	**Observations**
(Cho et al., 2009)	13 nm PEG-coated	Tail vein injection (single dose)	6-week old male BALB/c mice	0.17 mg/kg (1.76×10^{11} particles), 0.85 mg/kg (8.8×10^{11} particles) and 4.26 mg/kg (4.4×10^{12} particles) of body weight	5 min, 30 min, 4 hrs, 24 hrs, 7 days *ICP-MS to determine Au levels in organs and TEM to determine cellular concentrations of Au*	Liver and spleen had the highest concentration of Au-NPs	Pathological examination of liver tissues showed significant apostosis and inflammation of liver cells 7 days post injection with respect to control for the medium and high doses. PEGylated Au-NP were found in the Kupffer cells of the liver and spleen macrophages (in the cytoplasmic vesicles and lysosomes) and increased with time. No excretion of Au-NP for up to 7 days. **Blood half life - 28.50±4.09 h (for dose** 0.85 mg/kg) **and 32.65±11.64 h (for dose** 4.26 mg/kg)
(Cho et al., 2010)	4 & 13 nm (synthesized in	Tail vein injection	6-week old male BALB/c mice	0.85 mg/kg body weight.	30 min, 4 hrs, 24 hrs, 7	Au-NP (all sizes) observed in	All Au-NP remained in the liver, spleen

	house) 100 nm (commercial) PEG coating	(single dose)		The average injected numbers of particles per mouse were 4 nm: 3.04×10^{13}, 13 nm : 8.80×10^{11}, and 100 nm: 2.04×10^{9}	days, 1 month, 3 month and 6 months *ICP-MS to determine Au levels in organs and TEM to determine cellular concentrations of Au*	liver, spleen, and mesenteric lymph nodes (Amount of Au/ organ weight = spleen > liver, mesenteric lymph nodes > kidney > heart > testis > brain). No Au-NP found in the nucleus of the analysed organs.	and mesenteric lymph nodes six months post injection. The genes CYP1A1 and CYPB2 from the Cytochrome P540 oxidase enzyme groups (responsible for Phase I drug metabolism) were upregulated 7 days post injection of 4 nm Au-NP. CYPB2 was significantly upregulated 24 hrs and 7 days post injection of 14 nm Au-NPs. No histopathological lesions were observed Au-NPs found in brain and testis
(Sadauskas et al., 2009)	40 nm; citrate (commercial)	Tail vein injection	8-12 weeks old Adult female C57BL mice	0.5 mL	1 day, 1 month, 3 months and 6 months *Autometallographic technique to visualise Au-NPs;* *ICP-MS to measure total amount of Au in*	One day post injection, 60% of the Au-NPs found in the liver – Au-NPs primarily in lysosomes or phagosomes of Kupffer cells.	No pathomorphological change in the liver was noticed. No Au-NPs found in hepatocyte or endothelial cells of the liver. Decrease in number of Kupffer cells. The amount of Au-NP in the liver decreased only

					the liver		slightly over 6 months. Slow elimination rate (0.05% per day)
(Simpson et al., 2013)	1.2±0.9 nm; Glutathione (GSH)	Subcutaneous injection	BALBc/cAnNHsd mice, 5–6 weeks old female	10, 20,30, 40, 60 (uM) in PBS solution	1 day, 2 weeks, 4 weeks *ICP-MS to measure Au concentration in urine, blood, organs*	At 24 hrs, initial accumulation of Au-NP in kidneys and lungs and then at 4 weeks, Au-NP were found in the liver and spleen for all concentrations. Consistent levels of GSH-Au-NP found in alveolar tissues of lungs up to 4 weeks –> slow elimination from lungs.	2 % of the Au-NPs found in lungs (24 hrs post injection) 90% of the Au-NP was cleared from the body in 8 hrs. 100% cleared form the blood (mean residence time in the blood was 4 hours). No persistent change in red or white blood cell (RBC/WBC) counts.
(Sonavane et al., 2008)	15, 50, 100, 200 nm (suspended in sodium alginate)	Intravenous route	ddY mice of 6 to 8 weeks old	1g/kg of body weight (13 mg to 41 mg / mice) 15 nm: 2.80×10^{22} 50 nm: 7.27 X 10^{20} 100 nm: 9.09 X10^{19}	24 hours *ICP-MS to measure Au content in organs*	Organs where major concentrations of gold was found were: 15 nm: Liver, Lung, Kidney, Brain, Spleen 50 nm: Liver, Lung, Spleen, Brain, Kidney	Smaller size Au-NP of 15 nm and 50 nm were found in the blood after 24 hrs. 100 nm Au-NP was not detectable in blood and 200 nm Au-NP was present in trace amounts. Increased accumulation in

				200 nm: $1.02*10^{19}$		100 nm: Liver, Lung, Spleen 200 nm: Liver, Spleen, Lung, Kidney. Other organs (brain, heart, stomach) had trace amount s of Au	spleen with increased particle size. Less than 1% of the injected dose of NPs of all sizes was found in various organs (in liver = 0.09 to 0.4% of the injected dose)
(De Jong et al., 2008)	10, 50, 100, 250 nm (commercial)	Tail vein injection	Male WU Wistar-derived rats, 6 to 8 weeks old	77, 96, 89, 108 µg/mL $5.1*10^{12}$, $4*10^{10}$, $5*10^{9}$, $3.2*10^{8}$ particles/mL	24 hours *ICP-MS*	10 nm Au-NP was most widely distributed , in liver, spleen, brain, heart, kidneys, lungs, thymus, testis. The liver had highest concentrations of all sizes of Au-NP. The amount of 250 nm Au-NPs in the blood was comparatively lower when compared to other sizes of Au-NPs.	Blood and liver had the highest concentrations of Au (between 70 and 80% of injected dose).
(Zhang et al., 2011b)	5, 10, 30, 60 nm; PEG	Intraperitoneal injection	ICR mice , 11 weeks of age, male	4000 µg/kg	28 days	5 and 10 nm Au-NP: liver > spleen > kidney 30 and 60 nm Au-NP accumulated more in the	No statistically significant difference in body weight and macroscopic change in organs observed. *Haematology:* Statistically significant

						spleen when compared to liver and kidney.	decrease in WBC counts in animals injected with 5 and 30 nm Au-NP. Significant increase in WBC counts, haemoglobin and haematocrit in animals injected with 10 nm Au-NPs. RBCs increased in animals injected with 10 & 60 nm Au-NPs. Biochemical analysis indicated possible damage to both liver and kidney by 60 nm Au-NPs.
(Zhang et al., 2012c)	2.1 nm Au_{25} nanoclusters (NCs) coated with GSH; 8.2 nm Au_{25} nanoclusters (NCs) coated with BSA	Intraperitoneal injection	ICR female mice; 11 weeks of age; female	7550 µg/kg	24 hrs and 28 days *ICP MS*	At 24 hrs, GSH coated NCs accumulated more in the spleen whereas BSA coated NCs were found more in the liver. After 28 days, bioaccumulation of BSA coated NCs in liver, spleen, kidney and lung is more pronounced than GSH coated NCs. Both GSH and BSA coated NCs	After 28 days, maximum amount of Au was excreted in the urine for the GSH NCs , whereas BSA NCs were not excreted in the urine. BSA NCs negatively impacted the liver and kidney.

						also bio-accumulated in reproductive organs.	
(Lipka et al., 2010)	5nm (^{198}Au) Capping: 1. PEG 750 Da - **AuPEG 750** 2. PEG 10 KDa - **AuPEG10K** 3. bis (p sulfonatophenyl) phenylphosphine - **AuPhos**	Intravenous tail vein injection Intratracheal instillation (i.t.)	Wistar-Kyoto rats; 8 to10 weeks; female	**AuPEG 750:** 0.07 to 0.15 mg/kg **AuPEG10K:** 0.11 to 0.30 mg/kg **AuPhos:** 0.09 to 0.19 mg/kg	1 hr and 24 hrs *γ–spectroscopy NaI (Tl) scintillation detector*	After 24 hrs, 18% of total dose of **AuPEG10K** administered intravenously persisted in the blood compared to 0.4% AuPEG750 and 0.1% AuPhos in blood. 54% of AuPEG10K accumulated in the liver and spleen. 85% of AuPEG750 and 90% of AuPhos was found in liver & spleen. AuPEG750 was the most widely distributed of NPs in the organs analysed; it was found in lungs, liver& spleen, kidneys, heart, brain (AuPhos & AuPEG10k not detected in the brain), carcass, blood.	Intratracheal instillation: after 24 hrs more than 97% of all three types of Au-NP remained in the lungs with negligible translocation to the blood. Around 26% to 38.4% of the applied dose of all 3 types of Au-NP were cleared from the thoracic airways. <0.7% of **AuPhos** and <0.3% **of AuPEG 750** was excreted in urine and faeces within 24 hrs of i.v. injection. However, 6.5% of the injected dose of **AuPEG10K** was found in gastrointestinal tract and faeces after 24 hrs. In case of i.t., none of the Au-NPs studied were detected in the brain.

						Excretion: increase in concentration of AuPhos over time in urine (100 times). No increase of AuPEG750 in urine and faeces over time. Increase (from 0.4% to 6.5%) in concentration of AuPEG-10 K in faeces over time.	
(Terentyuk et al., 2009)	15, 50 nm; PEG 160 nm - Silica Au nanoshells (NS); PEG	Tail vein injection in rats and injection in vein saphena medialis of rabbits	Laboratory rats Rabbits	57 µg/ mL	24 hrs (rats) 72 hrs (rabbits)	15 nm Au-NP found in the liver, spleen, kidney, blood, brain & lung of both rats and rabbits. 50 nm Au-NP and 160 nm NS distributed to all organs examined in rats.	Histological changes observed in liver, spleen and kidney samples
(Arnida et al., 2011)	50 nm (commercial) 10 X 45 nm: rods PEG (MW: 5000 Da) (commercial)	Intravenous tail vein injection (single dose)	Non-metastatic orthotropic ovarian tumour bearing mice	Spherical: 60 µg Nanorods: 40 µg	30 min, 2 hrs, 6 hrs, 24 hrs, 1 week *ICP-MS*	After a week, ca. 10% of the injected dose of Au nanorods and Au-NP was found in liver and circa 10% of Au nanorods & 20% of Au-NPs	Plasma clearance of Au nanorods was slower thanAu spheres. Faeces had Au-NP (0.3% of injected dose) after 1 week

						found in spleen	
(Balasubramanian et al., 2010)	20 nm; citrate	Intravenous tail vein injection (single dose)	Adult male Wistar rats	0.01 µg Au/kg body wt	1 day, 1 week, 1 month, 2 months	23 organs were examined for presence of Au. All organs showed presence of Au. Maximum concentration of Au (normalised to organ weight) was found in liver, spleen and adrenal gland 1 day, 1 week and 1 month post injection whereas post 2 months, maximum concentration of Au was found in liver > spleen > kidney > olfactory bulb.	Microarray analysis of liver and spleen samples indicated significant upregulation of genes of the Cytochrome P540 family and genes encoding to regulate cellular lipid metabolic processes in the liver. In the spleen, genes belonging to the functional categories of genes which controlled response to external stimuli, wound healing, etc. were downregulated. Very small amounts of Au (zero to less than 2 ng/g) was found in faeces and urine at various time points.
(Balasubramanian et al., 2013)	7 and 20 nm	Inhalation exposure (6 hrs/day, 5 days /week, and 3 consecutive weeks)	Adult male Wistar rats	Air volume inhaled by rats = 66,000 cm^3/day and no. of particles = approx. $1*10^6$ / cm^3	1, 5, 7, 10, 12, 15 days *ICP-MS*	Au amounts in organs upon exposure to 7 nm Au-NP : Lungs > Blood > Kidney > Small intestine > Liver Au amounts in organs upon exposure to 7 nm Au-NP	Total Au deposited in lungs upon 15 day exposure was greatest for 7 nm particle. 7 nm Au-NP was more widely distributed (21 organs) than 20 nm Au-NP (18 organs). Au amount in urine was not detectable.

						normalised to organ weight (ng/g): Lungs > brain (olfactory bulb, hippocampus, striatum, frontal cortex, entorhinal cortex, septum, cerebellum) > aorta > kidneys Total Au amounts in organs upon exposure to 20 nm Au-NP: Lung > Skin > Liver > Kidney > spleen > aorta Au amounts in organs upon exposure to 20 nm nm Au-NP normalised to organ weight: lungs > olfactory bulb > aorta > septum > entorhinal cortex > hippocampus > frontal cortex > oesophagus > kidney > cerebellum	Faeces of rats exposed to 20 nm Au-NP had more Au than those exposed to 7 nm Au-NP. Gene expression profiling (131 genes) of the hippocampus of rats exposed to 7 nm Au-NP showed downregulation of most genes, especially genes related to receptor mediated endocytosis and immune responses.
(Chen et al.,	21 nm	Intraperitoneal	Male C57BL/6	7.85 µg Au-	1hr, 24 hrs, 72hrs	Au-NPs	Significantly lower fat

2013a)		injection	mouse; 8 weeks	NPs/per gram body weight	*SEM and LA-ICP MS*	accumulated in the connective tissue between adipocytes and inside Kupffer cells. Au-NP were not found in the other organs analysed in this study, viz. Brain, kidney, heart, spleen	mass when compared to control mouse. However, no significant decrease in body weight or energy intake was observed. No change in plasma Alanine Transferase level, indicating no damage to liver. No morphological damage to the kidney. No change in number of Adipose Tissue Macrophages. Downregulation of TNF-α and IL-6 mRNA expression.
(Wojnicki et al., 2013)	25±8 nm Poly Vinyl alcohol (PVA = 67 KDa) – suspended in L-ascorbic acid	Intravenous injection	Albino-Swiss mice; Male; adult	361.9 µg/Kg	24 hrs *ICP-MS*	Au-NP accumulated in the liver (approx. 13% of the given dose). Brain, heart, kidney, lungs were also examined and cumulatively they accumulated <1% of the total dose.	Of the analysed organs, heart had the second highest accumulation of Au-NPs (0.11% of the total dose)
(Keene et al., 2012)	10 nm (commercial) Four states:	Intravenous tail vein injection (single dose)	Female Balb/C mice; 8 weeks	8mg/kg	24 hrs and 8 days	All four forms of Au-NP were found in lung,	Amount in major organs below: PPs: circa 91% and

	1. Primary particles (PPs) – 5 to 8 nm 2. Aggregation of PPs (AGR PPs) – non reversible bonds – 30 to 200nm 3.Agglomeration of PPs (AGL PPs) – reversible interactions – 500 to 2000nm 4. Agglomerated AGRs (AGL AGR) - 40 to 2000nm				*NAA*	liver, kidney, spleen, uterus, stomach, carcass, skin, blood, muscles, sternum/marrow, Thymus, heart, brain. All four forms of Au-NPs were found in faeces. However, only PPs and AGR PPs were detected in urine.	61% of the dose/g tissue in liver and spleen respectively. AGL PPs: circa 95% and 42% of the dose/g tissue in the liver and kidney respectively. AGR PPs: circa 86%, 61% and 55% of dose/g tissue in liver, spleen and lung. AGL AGR: circa 96%, 36% and 31% dose/g tissue in liver, spleen and lung.
(Hirn et al., 2011)	1.4, 5, 18, 80, 200 nm: capping TPPMS (mono-sulfonated triphenylphosphine) –negative charge 2.8 nm : capping cysteamine (CA) – positive charge 2.8 nm: capping thioglycolic acid (TGA)- negative charge All Au-NPs were radioactively labelled with ^{198}Au	Intravenous tail vein injection	Female Wistar-Kyoto rats, 8 to 10 weeks old	1.4 nm = 3.1±0.6 µg 5 nm = 43.7±5.3 µg 18 nm = 2.9±1.5 µg 80 nm = 18.5±2.3 µg 200 nm = 19.8±1.7 µg TGA 2.8 nm = 1.6±0.2 µg CA 2.8 nm = 29.0±3.4 µg	24 hrs *γ-spectroscopy - NaI (Tl)* *scintillation detector*	Au-NPs were found in all organs analysed: Liver, lungs**,** spleen, kidneys, brain, heart, uterus, GIT, blood, carcass. 5, 18, 80, 200 nm TPPMS coated Au-NP = 91.9% to 96.9% accumulated in the liver, i.e., less than 10% were found in other organs. 51.3% of injected dose of 1.4 nm TPPMS AuNPs	Au-NPs1.4, 2.8 & 5 nm showed increased accumulation in blood with decrease in diameter. Except liver, accumulation of Au-NPs of sizes 18, 80 & 200 nm in other organs was size independent. Significantly higher accumulation of negatively charged TGA capped 2.8 nm in the liver vis-a-vis 2.8 nm positively charged CA capped Au-NP was observed. Negligible clearance in the urine for Au-NP sizes 18nm to 200

						accumulation in the liver. Accumulation of TGA and CA coated Au-NP in the liver were respectively 81.6% and 72%. The **carcass** (skin, skeleton, soft tissue excluding tail vein injection site) had the second highest percentage of injected dose of Au-NPs (highest is liver) **Spleen**: 2% of the TPPMs coated Au-NPs of all sizes found in the spleen. However, accumulation of both TGA and CA coated 2.8 nm Au-NP was higher by a factor of 4 or 5.	nm. Only 4.7% of the injected dose found in the urine for the smallest 1.4 nm Au-NP. A similar percentage cleared through the hepato-biliary clearance pathway for 1.4 nm Au-NP. Increasing size of Au-NP (2.8 nm CA to 200 nm TPPMS coated) resulted in less clearance via the hepato-biliary pathway. Clearance of positively charged CA Au-NP > negatively charged TGA Au-NP of 2.8 nm. 18, 80 & 200 nm Au-NPs were bound more to the blood cells than serum, whereas 5nm Au-NP was equivalently bound to blood cells and serum & 75% of the 1.4 nm Au-NP was bound to the serum.
(Liu et al., 2013)	2.5 nm luminescent NPs, Coatings: 1.Glutathione (GS)	Intravenous injection	Female Nude mice (6 to 8 weeks old)	7 mg /mL	1 hr & 12 hrs	GS-Au-NPs and BSA-Au-NPs observed in the	Highest GS-Au-NP amounts in the kidney and highest BSA-Au-

	2.Bovine Serum Albumin (BSA)					analysed organs of liver, kidney, lung, spleen, heart.	NP amounts in the liver. GS Au-NP: After 1 hr, approx. 17 % of injected dose (I.D.) / g, and 12 hrs post injection, 5% of the injected dose (I.D.) / g observed in the kidney. BSA-Au-NP: After 1 hr, 70% of the I.D./ g and 12 hrs post injection, approx. 50% of the I.D./ g in the liver.
(Zhou et al., 2011)	circa 2 nm, Glutathione (GS) (luminescent) Au-NP 6 nm and 13 nm (non-luminescent) GS coated Au-NP	Tail vein intravenous injection	Balb/c mice ; male; 6-8 weeks old	9 mg/ mL	24 hrs *ICP MS (and CT to detect dynamic accumulation of Au-NP in bladder)*	Accumulation in various organs as % of injected dose: Kidney > Lung > Liver > Spleen	Approx. 50% of the GS-Au-NPs were detected in the urine within 24 hours post injection (p.i.) and up to 65% present in the urine 72 hours p.i.
(Roa et al., 2012)	a. 20 nm; Capping: 1. 6-fluoro-6-deoxy-D-glucose (FDG) 2. FDG+ PEG b. 10nm, 20nm, 50, 100, 250 nm ; Capping FDG	Tail vein intravenous injection	BALB/c nude mice; 4-5 weeks old (before tumour cell injection); female	5mg/kg	a. 24 hrs b. 2 hrs post injection *(bio-distribution of different sizes of FEG capped Au-NPs)*	PEG+FDG and FDG coated Au-NPs (20nm) showed maximum accumulation in liver, spleen and kidney 24 hrs p.i. 20% and 5% of total injected	Maximum Tolerated Dose > 120 mg Au/kg; one week observation time After 2 hrs, 20 nm FDG-Au-NP was negligible in the blood, showing fast plasma clearance

					ICP-MS	dose of 20 nm FDG-Au-NPs found in liver and kidney respectively. However, PEG-FDG-Au-NP accumulation in liver was approx. 4 times less than mass of FDG-Au-NP/g tissue weight	rate. 50, 100, 250 nm FDG-Au-NPs had negligible accumulation in the heart after 2 hrs.

Table A2: Concentrations of widely occurring pharmaceuticals in different environmental compartments in various regions. Adapted from Mahapatra et al. 2013.

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
Analgesics/ NSAIDs	Acetaminophen	1.89 µg/L (max.conc.)	Groundwater	US (California)	(Fram and Belitz, 2011)
		0.08 – 13.8 µg/L	Treated Effluents (5 STPs)	Spain	(Bueno et al., 2012)
		1.4 – 5.9 µg/L	Untreated Effluent from 2 Hospitals	Italy	(Verlicchi et al., 2012a)
		0.012 – 0.058 µg/L	STP effluent	Italy	(Verlicchi et al., 2012a)
	Diclofenac	0.052 – 1.76 µg/L	Effluents (12 Municipal STPs)	South Korea	(Sim et al., 2011)
		230 ng/L (median values)	STP Effluents	Spain (Galicia)	(Rodil et al., 2012)
		LOD =2.95 µg/L	Effluents (3 STPs)	Ireland (Dublin)	(Lacey et al., 2012)
		100 –131 ng/L	STP effluent	Taiwan	(Fang et al., 2012a)
		53.6 ng/L (max.conc.)	Coastal receiving area(6.6km offshore)	Taiwan	(Fang et al., 2012a)
	Mefenamic acid	LOD =1.73 µg/L	Effluents (3 STPs)	Ireland (Dublin)	(Lacey et al., 2012)
		44 – 392 ng/L	Effluents (5 STPs)	South Korea	(Behera et al., 2011)
	Ibuprofen	5 µg/L (max.mean conc.)	Effluents (5 STPs)	Spain	(Bueno et

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
					al., 2012)
		552 – 1600 ng/L	STP effluent	Taiwan	(Fang et al., 2012a)
		57.1ng/L (max.conc.)	Coastal receiving area (6.6km offshore)	Taiwan	(Fang et al., 2012a)
		<MDL - 26.6 ng/L	Treated drinking water	US	(Wang et al., 2011a)
		96.9 ng/L – 166624 ng/L	Landfill leachate and inlet of leachate treatment	Norway	(Eggen et al., 2010)
		120 ng/L (max. conc.)	River water	US.(Washington D.C.)	(Shala and Foster, 2010)
Beta- blockers	Propranolol	1– 24 ng/L	Estuary, Harbour	Belgium	(Wille et al., 2010)
		3.18 ng/L (max. conc.)	Estuary	Portugal	(Madureira et al., 2010)
		1.51 – 2.60 ng/g	Sediments of marshy areas	Valencia, Spain	(Vazquez-Roig et al., 2010)
		107.4 ± 36 µg/kg	Achieved biosolids (collected in year 2001) from 94 STPs	US	(Chari and Halden, 2012)
		118.7 ng g^{-1} dry weight	Dewatered municipal biosolid	Canada	(Gottschall et al., 2012)
	Atenolol	80 –293 ng/L	Estuary, Harbour	Belgium	(Wille et al., 2010)

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
		511 ng/L (median value)	STP Effluents	Galicia, Spain	(Rodil et al., 2012)
		1.1 – 15 µg/L	Effluents (5 STPs)	Spain	(Bueno et al., 2012)
		261– 5911 ng/l	Effluents (5 STPs)	South Korea	(Behera et al., 2011)
Blood lipid lowering agents	Fenofibrate	13.20 – 17.23 ng/g	Sediments of marshy areas	Valencia	(Vazquez-Roig et al., 2010)
		LOQ=2.5ng/g	Sludge (3 STPs)	Spain	(Jelic et al., 2011)
	Gemfibrozil	0.15 – 1.24 µg/L	Effluent water	Spain (Valencia)	(Gracia-Lor et al., 2012)
		0.08 – 19.4µg/L	Effluent water	US(Texas)	(Fang et al., 2012b)
		0.11 – 6.86 µg/L	Groundwater below Land application site	US (Texas)	(Fang et al., 2012b)
Estrogens	EE2 (17α-ethinylestradiol)	2 ng/L	Effluents (11 STPs)	United Kingdom	(Kumar et al., 2011)
	Levenogesterol	11 ng/L	Groundwater	France	(Vulliet et al., 2008)
Antibiotics	Ciprofloxacin	1.9 µg/L (max.conc.)	Effluents (5 STPs)	Spain	(Bueno et al., 2012)
	Norfloxacin	256 ± 64 ng/L	Secondary effluent (1	China (Beijing)	(Shen et al.,

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
			STP)		2012)
		7.23±0.22 mg/kg	Dewatered sludge (1 STP)	China (Beijing)	(Shen et al., 2012)
	Ofloxacin	8.95 – 12.03 ng/g	Sediments of marshy areas	Spain	(Vazquez-Roig et al., 2010)
		528 ± 89ng/L	Secondary Effluent (1 STP)	China (Beijing)	(Shen et al., 2012)
		2.8 µg/L(max.conc.)	Effluents (5 STPs)	Spain	(Bueno et al., 2012)
		7.79±0.55 mg/kg	Dewatered sludge (1 STP)	China (Beijing)	(Shen et al., 2012)
	Sulfamethoxazole	13 – 96 ng/L	Estuary, Harbour	Belgium	(Wille et al., 2010)
		9.14 – 53.3 ng/L	Estuary	Portugal	(Madureira et al., 2010)
		0.17 µg/L (max.conc.)	Groundwater	US (California)	(Fram and Belitz, 2011)
		0.047 – 0.397 µg/L	Effluents (12 Municipal STP)	South Korea	(Sim et al., 2011)
		4.2 – 485 ng/L	Yangtze Estuary	China	(Yang et al., 2011)
	Lincomycin	1.06 – 45.7 µg/L	Effluents (12 Municipal STP)	South Korea	(Sim et al., 2011)
		1437 – 21278 ng/l	Effluents (5 STPs)	South Korea	(Behera et al., 2011)

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
Antineoplastics	Ifosfamide	4 – 10647 ng/L (median, 151 ng/L)	Hospital effluent (21 Hospitals)	China	(Yin et al., 2010)
	Cyclophosphamide	6 – 2000 ng/L (median, 100 ng/L)	Hospital effluent (21 Hospitals)	China	(Yin et al., 2010)
	5 - Fluorouracil	27 ng/L (max. conc.)	Hospital effluent	Switzerland	(Kovalova et al., 2009)
		0.09 – 4 µg/L (max. mean concentration = 0.8 µg/L)	Monitoring Point where hospital effluent was discharged to the sewage network	France	(Mullot et al., 2009)
	Tamoxifen	102 ng/L (max. conc.) 26.5 ng/L (median conc.)	STP effluent	France	(Coetsier et al., 2009)
		11 ng/L (median conc.)	River	France	(Coetsier et al., 2009)
		120–127 ng/L	Yangtze Estuary	China	(Yang et al., 2011)
Psychiatric drugs	Fluoxetine	8 – 44 ng/L	5 main rivers (Madrid)	Spain	(González Alonso et al., 2010)
	*Norfluoxetine(metabolite of Fluoxetine)	41.6 ± 25.1µg/kg	Achieved biosolids (collected in year 2001)from 94 STPs	US	(Chari and Halden, 2012)
	Diazepam	Upto 80 ng/L	Effluents (5 STPs)	Spain	(Bueno et al., 2012)
	Pipamperone	1.4 – 17.3 ng/L	Surface water	Belgium	(Van De Steene et

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
					al., 2010)
	Sertraline	458 ± 168.3 µg/kg	Achieved biosolids (collected in year 2001)from 94 STPs	US	(Chari and Halden, 2012)
	Carbamazepine	4 – 321 ng/L	Estuary, Harbour, Sea	Belgium	(Wille et al., 2010)
		0.37 – 178 ng/L	Estuary	Portugal	(Madureira et al., 2010)
		1.43 – 5.77 ng/g	Soils of marshy areas	Valencia, Spain	(Vazquez-Roig et al., 2010)
		1.81 – 6.85 ng/g	Sediments of marshy areas	Valencia, Spain	(Vazquez-Roig et al., 2010)
		2 – 272 ng/L	River (Lopan)	Ukraine	(Vystavna et al., 2012)
		0.208 – 21 µg/L	Effluents (12 Municipal STPs)	South Korea	(Sim et al., 2011)
		3.6 µg/L(max.conc.)	Groundwater	U.K.	Cited in ref 160
		0.42 µg/L (max.conc.)	Groundwater	US (California)	(Fram and Belitz, 2011)
		Upto 6.8 ng/L	Treated drinking water	US	(Wang et al., 2011a)
		161ng/L (max.conc.)	Stormwater collection system (discharge outfalls)	Canada	(Sauvé et al., 2012)

Category	Pharmaceutical product	Concentration	Environmental Compartment	Region	Reference
Note: Max. Conc.: Maximum Concentration; LOQ: Limit of Quantification ; STP : Sewage Treatment Plant This table gives a very small number of the different types of pharmaceuticals monitored in the environment. It is meant to provide the reader an overview of measured concentrations from recently published studies (2009–2012) and the different environmental compartments and different regions of the world in which PPs have been found. Detailed reviews on occurrence, fate, and ecotoxicity of pharmaceuticals and their metabolites are provided by Santos et al. (2010)					

Table A3: Selected ecological studies of toxicity effects, uptake, and bioaccumulation of ENMs and nanocarriers that can be used in nanomedicine.

The 'nano' component in nanomedicine*	Short description of select ecological studies of toxicity effects, uptake and bioaccumulation for NMs and nanocarriers used in nanomedicine	References
Polyethyleneimine (PEI) polymer	For tadpole larva, *Xenopus laevis,* both PEI and PEI:DNA (polyplex) showed teratogenic effects at concentrations 0.1 µg/L. PEI also showed higher toxicity for the algae *Pseudokirchneriella subcapitata;* EC_{10} = 40.8µg/L. The polyplex was found to be less toxic than the free polymer.	(Robbens et al., 2010)
Dendrimers	Commercially available amine terminated G4 dendrimer showed sublethal toxicity in zebrafish embryos at 0.2µM concentrations, whereas COOH terminated G3.5 dendrimers did not exhibit toxicity even at concentrations of 200 µM. Dose and time dependant mortality was observed for G4 dendrimer, 100% mortality at dose 20 µM in 24 h post fertilisation.	(Heiden et al., 2007)
	Commercially available G4 cationic PAMAM dendrimers at 15 nM, 25 nM and 35 nM concentrations resulted in a linear increase in ROS level and photosynthetic oxygen levels in the algae, *Chlamydomonas reinhardtii*. Also, most of the transcripts encoding proteins involved in photosynthesis and antioxidant genes were down regulated except for the gene which encode light-harvesting polypeptide for PSII (this was upregulated). Measured size range: 90 nm in MQ water (this reflects aggregation of NPs in water due to their cationic surface charge). Exposure duration: 6, 24 h	(Petit et al., 2012)
	A dose-effect study of amine terminated G4 and G1 PAMAM dendrimers with ethylenediamine core was conducted for *Pseudokirchneriella subcapitata*. The amine-terminated G4 dendrimer was found to be comparatively more toxic than the amine terminated G1 dendrimer. The negatively charged hydroxyl terminated G4 dendrimer had least toxicity.	(Suarez et al., 2011)
SPIONs and USPIOs (<25 nm core) used for treatment and diagnostics	Pumpkin plants (*Cucurbita maxima*) when grown hydroponically could translocate and accumulate coated magnetite (Fe_3O_4) nanoparticles (20 nm). Strong magnetisation signals were observed in the leaves. Exposure concentration: 0.5 g/L; exposure period: ~ 20 days. Also, when pumpkin plants were grown in soil, no magnetisation signal was noticed in the plants but when grown in sand, the pumpkin	(Zhu et al., 2008)

The 'nano' component in nanomedicine*	Short description of select ecological studies of toxicity effects, uptake and bioaccumulation for NMs and nanocarriers used in nanomedicine	References
	plants accumulated the iron NPs. Lima bean plants didn't accumulate Fe_3O_4 NPs.	
	Higher amounts of the oxidative stress enzyme catalase was reported for PVP coated magnetite (Fe_3O_4) NPs (25 nm) and bulk iron oxide NPs in the shoots of both rye grass and pumpkin plants and roots of rye grass plants. Exposure concentrations: 30 mg/L, 100 mg/L of nano- (Fe_3O_4) and 30 mg/L and 100 mg/L of Fe_3O_4 bulk. Exposure duration was 18 days. Lipid peroxidation was also reported. No magnetism was observed in the shoots of both the plants, indicating that the iron NPs were not translocated. The oxidative stress enzyme superoxide dismutase was also found at increased levels in the roots of both plants for iron bulk and NPs at 30 mg/L concentration.	(Wang et al., 2011b)
	In the presence of sublethal concentrations of As(V) (to rule out the probability that environmental Arsenic is causing the toxicity), commercial nano-Fe_2O_3 (20-40 nm) was shown to have increased toxic effect on *C. Dubia*. It was established that nano-Fe_2O_3 and As(V) caused the toxic effect in a synergistic mode (nano-Fe_2O_3 alone didn't exhibit mortality at the concentrations used in the study). It was found that 48 hour mortality was dose dependant but 24 hr mortality was not. At 20 mg/L of nano-Fe_2O_3, the 48 hour mortality increased from 30% to 70%.and then the mortality rate remained nearly constant for higher exposure doses. Depuridation (up to 75%) occurred after an hour for solutions having algal feed. It was observed that maximum bioaccumulation occurred at neutral pH. Exposure concentrations: 1, 5, 10, 20, 50 mg/L.	(Hu et al., 2012)
Gold Nanoparticles (different sizes for different medical applications; general size range 5-30nm)	Decrease in colony forming units of soil microbial community after 15 days exposure to commercially available Au-NP. Higher shoot/root ratio of lettuce exposed to lower concentrations of Au-NP observed indicating that Au-NP acted as a growth promoter. Concentration: 0.013% w/w in soil. Exposure time in soil: 15 days	(Shah and Belozerova, 2009)
	Size selective uptake of citrate capped Au-NP by tobacco plants. 3.5 nm Au-NP were found in the leaves of the plants and 18 nm Au-NP remained agglomerated / aggregated at the root surface. Necrotic lesions in leaves and death of plants occurred after 30 days of exposure. Concentration: 3.5 nm – 48 ppm; 18 nm – 76 ppm. Exposure duration: 3 to 30 days	(Sabo-Attwood et al., 2012)

The 'nano' component in nanomedicine*	Short description of select ecological studies of toxicity effects, uptake and bioaccumulation for NMs and nanocarriers used in nanomedicine	References
	Mean Au concentrations in tobacco plants was found to be between 2.2 mg/kg to 53.5 mg/kg when hydroponically exposed to tannate and citrate coated 10, 30, 50 nm of Au-NP. In contrast, wheat plants when exposed to the same exposure concentrations didn't show any uptake. However, it was found that aggregation of Au-NP occurred more in the wheat than the tobacco plant suspensions. Exposure concentration: 30 mg/L Exposure time: 7 days for tobacco and 3 days for wheat.	(Judy et al., 2012)
	No obvious toxic effects to cucumber and lettuce seeds exposed to Au-NP of mean size 10 nm at 2.4 X 10^{12} NP/mL concentrations.	(Barrena et al., 2009)
	Polyvinyl alcohol (PVA) capped Au-NP [Size range: 15–35 nm (spherical shape)]. Exposure concentrations: 10, 25, 50, 75, and 100 µg/mL were used to study impacts on embryos of zebra fish. The embryos developed normally (similar to the controls) - eyes, tail, brain and otoliths. No change in blood flow or cardiovascular development was observed. Detectable Au-NP accumulation was observed in the body of treated embryos (25 and 50 µg/mL)	(Asharani et al., 2011)
	Zebrafish exposed to citrate stabilised Au NPs (12 and 50 nm) through feed. Daily dose 90 and 106 ng Au-NP for 12 and 50 nm. Exposure duration: 36 days. Daily dose 36 and 42 ng for 12 and 50 nm Au-NP respectively. Exposure duration: 60 days. Au-NP were found in brain, liver and skeletal muscles with highest concentration of 12 nm Au-NP in the brain. Up-regulation of DNA repair genes, increase in mutation and mitochondrial impairment was observed and was more for the 60 days exposure duration.	(Geffroy et al., 2012)
	Feed containing citrate capped 15 nm Au-NP fed to Daphina melanogaster. Max dose: 12 µg/g/day. Life span and fertility were negatively affected. Reproductive performance decreased with increasing Au-NP doses (from 1.9 pmol/L to 380 pmol/L). Overexpression of heat shock protein occurred reflective of ER stress. DNA fragmentation in the gastrointestinal tissue was observed. Feed containing citrate capped 15 nm Au-NP fed to Daphina melanogaster. Max dose: 3 µg/g/day. Mutagenic effects were observed and aberrant phenotypes were observed in subsequent (F1 and F2) generations.	1. (Pompa et al., 2011) 2. (Vecchio et al., 2012)
	Oxidative stress observed in *Mytilus edulis*, a marine bivalve mollusc, when exposed to 750 ppb Au-NP	(Tedesco et al.,

The 'nano' component in nanomedicine*	Short description of select ecological studies of toxicity effects, uptake and bioaccumulation for NMs and nanocarriers used in nanomedicine	References
	(5.3 nm) for 24 h. The study also showed that larger size Au-NP resulted in lower oxidative stress in the animal. It was found that the Au-NP accumulated mainly in the digestive gland	2010)
	Filter-feeding bivalve *Corbicula fluminea* (1 to 2 yrs of age) exposed to BSA coated Au-NP of sizes 7.5, 15 and 46 nm. Exposure concentration: 2mg/L. Total exposure time: 180 h. • Efficiency of removal of Au-NP from solution due to filtration by the bivalves was size dependant and removal efficiency increased with particle size. • When the bivalves were exposed to varying concentrations (2 mg/L, 4 mg/L and 8 mg/L) of 46nm BSA coated Au-NP, removal efficiencies from solution found to be positively correlated with concentration of BSA-Au-NP solution. • The Au-NPs were evident in the digestive gland and regions of the digestive tract and the mass concentration inside the body was more for the 15 nm BSA-Au-NP exposed bivalves • The bivalves exposed to 7.8 nm Au-NP didn't efficiently excrete it during the experimental period and it was found that Au-NP concentrations remained elevated in these bivalves. 15 and 46 nm BSA-Au-NP exposed bivalves excreted out the Au-NP more efficiently.	(Hull et al., 2011)
	Evaluation of toxigenomic response of *Caenorhabditis elegans* (soil nematode) exposed to 4 nm Au-NP (LC_{10} = 5.9 mg/L at 24 hrs) and same concentration used for the genetic response analysis to Au-NPs. Observations reported are: • Upregulation of genes related to clathrin-mediated endocytotic pathway • Upregulation of Ca^{2+} signalling and amyloid processing pathway (protein unfolding and denaturation) • Upregulation of heat shock protein genes (reflective of ER stress)	(Tsyusko et al., 2012)
Silicon oxide NP (Branchytherapy)	Commercially available Silica NP (50% were below 100nm; 40% were between 100 and 200 nm) at	(Christen and

The 'nano' component in nanomedicine*	Short description of select ecological studies of toxicity effects, uptake and bioaccumulation for NMs and nanocarriers used in nanomedicine	References
	concentrations of 0.825 mg/mL was shown to affect the Endoplasmic Reticulum (ER) function leading to ER stress response in a fish fibroblasts cell line.	Fent, 2012)
	Commercially available Silica NP of 10-20 nm diameter were found to be toxic to *S. obliquus* (a fresh water green algae) as a function of concentration (50, 100, 200 mg/L) and time (48, 72, 96 h) Contents of chlorophyll- a and b decreased by 86.4% and 94.8% respectively as compared to the control group, but the amount of caretonoids didn't decrease. Exposure duration: 96 h at 50 mg/mL.	(Wei et al., 2010)
	Silicon dioxide NP (commercially available) of 12.5 and 27 nm shown to be toxic to *P. subcapitata (*green algae). EC_{20} was found to be 20 ± 5 mg/L and 28.8 ±3.2 mg/L for 12.5 nm and 27 nm NPs respectively. Adsorption to the cell wall was seen but no cellular uptake was observed by the investigators. Exposure duration:72 h	(Van Hoecke et al., 2008)

Annexe to Chapter 3

Abridged Interview Questionnaire

The following questions are some of the questions which were asked while conducting the interview:

A. Nanomedicine scientists

1. Please elaborate on your current research projects based on nanotechnology applications for healthcare sector.

Definition

2. How do you define 'nano' for the nano-enabled medical applications field?
3. What is your opinion on the European Commission's recommendation on the definition of 'Nanomaterials'[128]? And, on the special case for pharmaceuticals?

Risk governance

4. Perspectives on potential environmental implications
   - What might be the potential environmental implications of mass production and use of nanomedicine(s)/nano-enabled medical applications?
   - In your opinion, is there a possibility of environmental hazards and risks of nanomedical applications? What might be the potential hazards and exposure scenario?
   - Are the existing environmental risk assessment guidelines[129] for pharmaceuticals fit-for-purpose for nano-enabled medical applications? Please elaborate on your response.
   - Do you think that specific consideration needs to be given for medical devices based on nanotechnology with respect to safeguarding environment?

Research governance

5. In your opinion, is it important to have dialogues between various communities - the scientists, nano-environment, nanotoxicity, regulators, etc.at the time of product conception and development? If so, how can it be achieved?

   Specific question on Responsible Innovation

6. Are you familiar with the term *responsible innovation*? What does it mean to you? What should be considered at the innovation stage so that it fulfils the criteria of 'responsible innovation'?

[128] Document attached with the mail

[129] Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). Attached with mail.

B. Ecotoxicologists

Definition

1. How would you define the term ‘nano’? Do you think it is important to define the term ‘nano’ for nanotechnology applications?

2. What is your opinion on the European Commission’s recommendation on the definition of ‘Nanomaterials’? And, in particular, the special case for pharmaceuticals[130]?

Risk governance

3. Is the existing risk assessment framework for pharmaceuticals adequate for nanomedicine? Please justify your response.

4. The focus of nanomedicine developers has been to design nanocarriers which can evade the biological barriers in the body and deliver a payload of drug to the target site

    a. In your opinion, is there a possibility of any environmental hazards and risks from such products?

    b. What might be the potential hazard and exposure scenarios?

    c. Are you aware of the existing environmental risk assessment guidelines[131] for pharmaceuticals?

If yes,

    i. Do the test methods and protocols mentioned therein, adequate for nanomedicines? What might be the limitations? How can they be improved?

    ii. More specifically, in your opinion, is octanol-water partition co-efficient (log K_{ow}) the right surrogate for bioaccumulation with respect to future sophisticated materials based on polymers?

If no,

    i. Are the existing risk assessment protocols fit for purpose for nanomaterials in general? What are the limitations? How can they be improved?

5. Do you think nano-enabled medical devices are likely to pose a threat to the environment? (e.g., AuNPs and SWCNT in devices to detect cancer from breath; silicon nanowires)

[130] See Point 17 in the EC Recommendation on the definition of Nanomaterials

[131] Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) Attached with the mail

Research governance

6. Is it important to have dialogues between various communities - the nanomedicine/product development community, nano-environment and nanotoxicity community, regulators, etc. at the early stages of product development? If so, how can it be achieved?

7. Are you familiar with the term *responsible innovation*? What does it mean to you? What should be considered at the innovation stage, and by whom, so that it fulfils the criteria of 'responsible innovation'?

C.Social scientists

Risk governance

1. Healthcare products are being designed with the aid of advanced (including nano) technologies to evade the biological barriers in the body

    a. In your opinion, would these products find their way into the environment?

    b. Do you think they might pose ecotoxicological hazards and risks, if they find their way into the environment?

    c. If yes, how can these risks be dealt with?

Research governance

2. What importance do you attach to commissioning social science research for medical applications of nanotechnology? What contributions can social scientists make to an applied science project on nano enabled medical applications?

3. Might it be advantageous for a social science requirement to be 'built-in' to research funding on nanomedicine?

4. Is it important to have dialogues between various communities - the nanomedicine development community, nano-environment and nanotoxicity community, regulators, etc. at the early stages of product development? If so, how can it be achieved?

5. Are you aware of the term 'Responsible Innovation'? If yes, what should be considered at the innovation stage, and by whom, so that it fulfils the criteria of responsible innovation?

D. Research Councils

Definition

1. What is the Council's opinion on the European Commission's definition of 'Nanomaterials'? And, on the current developments regarding 'nano' in REACH and medical regulations.

2. What is XX's view on stage-gating as an approach for funding innovation, especially in the Nanomedicine development area?

Risk governance

3. Perceptions on the Regulatory framework:

    3a. Does XX discuss projects which have high potential for translation with medical regulatory authorities?

    3b. Is the current regulatory framework for human medicines adequate for future therapeutics based on nanotechnology? If not, what might be the limitations?

    3c. Has XX considered the possibility of environmental hazards and risks of nano-enabled medical applications?

    3d. Do you think that the existing environmental risk assessment guidelines[132] for pharmaceuticals, the test methods and protocols mentioned therein, adequate for nanomedicines? What might be the limitations?

Research governance

4. Does coordination exist between various research councils to promote innovation with regard to nanotechnology-based applications (especially medical applications) in the UK? If not, why not?

5. Is information and knowledge shared effectively amongst the nanomedical community, the nano-environmental, the nanotoxicological community, industries and the regulatory bodies? If not, why not? How could this be overcome?

6. Are you familiar with the term 'Responsible Innovation'? If so, could you please elaborate on the concept of 'Responsible Innovation'?

[132] Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00)

E. Regulatory agencies

Definition

1. What is RA's definition of 'nano'?
2. How are 'nano' issues handled at RA? Does RA respond to the development of nanomedical products? If so, how?

Risk governance

3.a. Nanomedicines may be designed to evade the biological barriers like the blood brain barrier; do you think they might pose ecotoxicological hazards? In addition, should information on toxicity, side effects, etc. of nano-pharmaceutical products be used to gauge their potential ecological effects?

3.b. Assuming these went into mass production, what could be the possible exposure scenarios?

3.c. Which nanomedical products or categories, if any, might pose a risk to the environment?

4. Are current EC Directives regulating environmental risks posed by medicinal products adequate for next generation nanomedical products? What limitations might there be with respect to accommodating future nanomedical innovations?

5. Are the current test protocols and methods sufficient for evaluating impacts of future nanomedical products?

6. What existing knowledge gaps impact on the ability of regulators to protect the environment with regard to nanomedical products?

Research governance

7. Are you familiar with the term 'responsible innovation'? If so, what should be considered at the innovation stage, and by whom, to ensure that the criteria of responsible innovation is fulfilled?

F. Industry

1. What are your/AB's views on the potential of nanotechnology in medical applications? In your opinion, which types of nano-therapeutics and nano-diagnostic devices (in terms of disease indication areas, nanocarriers and nanomaterials) would have large scale use in the coming decades?

2. Are there 'nano' specific challenges with regard to product innovation? In other words, is 'nano' fundamentally different from their bulk/macro counterparts with regard to product innovation? Please elaborate on your response.

Risk governance

3. Healthcare products are being designed with the aid of advanced technologies to evade the biological barriers in the body
    - Do you think these products will find their way into the environment?
    - Do you think they might pose ecotoxicological hazards and risks, if they find their way into the environment?
4. Does specific consideration need to be given for medical devices based on nanotechnology with respect to safeguarding environment?
5. What risk assessment and management frameworks that the company has for considering HSE implications of their products?
6. Do you think that dialogue with the regulatory agencies at the time of project conception is useful? Please justify your answer.

Research governance

7. Are you aware of the term ‘Responsible Innovation’? If yes, how would you define ‘Responsible Innovation’?
8. Is it important to have dialogues between various communities - the nanomedicine/product development community, nano-environment and nanotoxicity community, etc. at the early stages of product development?

Annexe to Chapter 4

Number of figures: 4

Titles of figures:

- **Figure A1** PEC vs pSSD in water with sublethal end points
- **Figure A2** PEC vs pSSD for water and using lethal endpoints
- **Figure A3** PEC vs pSSD in soil with lethal endpoints
- **Figure A4** PEC vs pSSD in water with sublethal end points

Number of tables: 7

Titles of tables:

- **Table A4:** The probabilistic distribution functions of the input parameters used to create the probability mass flow model
- **Table A5:** Prospective per annum amount of Gold nanoparticles in select medical applications (worst case scenario)
- **Table A6.1:** Summary of volume or mass of environment compartment – air, water, sediment and soil – as input parameters for the probabilistic mass flow model
- **Table A6.2:** Summary of non hazardous household and hazardous healthcare and biological waste
- **Table A6.3:** Summary of parameters related to waste water
- **Table A7.1:** Data for aquatic toxicity
- **Table A7.2:** Data for terrestrial toxicity

Table A4: The probabilistic distribution functions of the input parameters used to create the probability mass flow model.

Parameters		Probabilistic Distribution Functions(PDFs)		Values	
		UK	US	UK	US
Estimation of Au-NP Consumption (in grams)	Lateral Flow Immunoassay to detect the presence of *Methicillin Resistant and Methicillin Sensitive Staphylococcus aureus* in blood	Triangular	Triangular	0.17-(0.34)-0.51	3-(6)-9
	Test kit for detection and genotyping Warfarin metabolism	Triangular	Triangular	0.18-(0.36)-0.54	1.5-(3)-4.5
	Test kit for detection of single nucleotide polymorphism to detect risk from venous thrombosis	Triangular	Triangular	0.5-(1)-1.5	1.5-(3)-4.5
	OTC test kits to detect pregnancy and ovulation	Uniform	Uniform	3 to 100	20 to 460
	Test kits for qualitative detection of antibodies to HIV-1 and HIV-2 in human serum, plasma and blood	Uniform	Uniform	2 to 80	20 to 830
	Home based in vitro HIV test kits	Triangular	Triangular	10-(20)-30	45-(90)-135
	Test kits to establish viral load In HIV patients	Triangular	Triangular	30-(60)-90	270-(540)-720
	Test kits to diagnose infectious diseases	Triangular	Triangular	35-(70)-105	175-(350)-525
	Nasal decolonization of *Staphylococcus aureus*	Uniform	Uniform	30 to 53300	110 to 164640
	Periodontal disease treatment	Uniform	Uniform	270 to 106560	940 to 365158
	Sensors for diagnosing diseases from breath samples	Uniform	Uniform	0.01 to 1590	0.03 to 4620
	Treatment modality for Cancer : TNF delivery (Can_T1)	Triangular	Triangular	70 -(480) -1100	310- (2020) – 4600
	Treatment modality for Cancer (last line) : TNF delivery (Can_T1_LS)	Triangular	Triangular	210-(420)-630	750-(1500)-2250
	Treatment modality for Cancer: Thermal ablation (Can_T2)	Uniform	Uniform	140290 to 233820	744750 to 1241260
	Treatment modality for Cancer (last line): Thermal ablation (Can T2_L2)	Uniform	Uniform	*104710 to 174520*	*468250 to 780410*
	Transbuccal insulin delivery platforms (Dia_T)	Triangular	Triangular	64125-(128250)-192375	420810-(841620)-1262430
treatment	Can_T1 to wastewater	Fixed data	fixed data	0.65	0.65

	Can_T1 remains in body	Fixed data	fixed data	0.35	0.35
	Can_T2 to wastewater	Fixed data	fixed data	0.15	0.15
	Can_T2 remains in body	Fixed data	fixed data	0.85	0.85
	Dia_T to wastewater	Fixed data	fixed data	1	1
	Can_T1_LS to body	Fixed data	fixed data	1	1
	Can_T2_LS to body	Fixed data	fixed data	1	1
	Body to crematorium	Triangular	Triangular	0.37-(0.74)-1.11	0.19-(0.38)-0.57
	Body to burial	Triangular	Triangular	0.13-(0.26)-0.39	0.31-(0.62)-0.93
From STP	Percentage of population not connected to Sewage Treatment Plant	Triangular	Triangular	0.02-(0.04)-0.06	0.13-(0.26)-0.39
	Overflows from STP	Log normal	Uniform	mean=0.161, SD=0.077	0.01 to 0.07
	Leakage from sewerage networks	Uniform	Uniform	0.03 to 0.05	0.05 to 0.06
	STP misconnection	Uniform	--	0.0026 to 0.018	--
	STP removal efficiency	Triangular	Triangular	0.98-(0.99)-1.0	0.98-(0.99)-1.0
	Sludge to Incinerators (WIP)	Triangular	Uniform	0.09-(0.18)-0.27	0.15 to 0.17
	Sludge to Landfill	Triangular	Uniform	0.005-(0.01)-0.015	0.29 to 0.30
	Sludge to soil	Dependent	Dependent		
Waste	Hazardous waste to HMCIW Incinerators	Triangular	Triangular	0.2-(0.4)-0.6	0.05-(0.1)-0.15
	Hazardous waste to landfill	Triangular	Triangular	0.3-(0.6)-0.9	0.45-(0.9)-1.35
	Non-hazardous waste to MWI	Triangular	Triangular	0.075-(0.15)-0.225	0.09-(0.18)-0.27
	Non-hazardous waste to landfill	Triangular	Triangular	0.425-(0.85)-1.275	0.41-(0.82)-1.23
From Waste Incinerator Plant	Stack emissions from MWI	Triangular	Triangular	0.095-(0.19)-0.285	0.095-(0.19)-0.285
	Bottom-ash from MWI	Triangular	Triangular	0.62-(0.81)-1.0	0.62-(0.81)-1.0
	MWI bottom-ash to landfill	fixed data	fixed data	1	1
	MWI Fly-ash to air	Triangular	Triangular	0.00005-(0.0001)-	0.00005-(0.0001)-0.00015

				0.00015	
	MWI Fly-ash to landfill	Triangular	Triangular	0.99-(0.9999)-1.0	0.99-(0.9999)-1.0
	Au-NP in HMCIWI	Uniform	Uniform	0 to 1	0 to 1
	Gold eliminated from HMCIWI	Uniform	Uniform	0 to 1	0 to 1
	Au-NP from HMCIWI to stack emissions	Fixed data	fixed data	0.19	0.19
	Au-NP from HMCIWI to bottom-ash	Triangular	Triangular	0.81	0.81
	Bottom ash from HMCIWI to landfill	fixed data	fixed data	1	1
	Stack emissions from HMCIWI to wet scrubber	Triangular	Triangular	0.25-(0.5)-0.75	0.25-(0.5)-0.75
	Stack emission from HMCIWI to Dry scrubber and Fabric Filter (APCD)	Triangular	Triangular	0.25-(0.5)-0.75	0.25-(0.5)-0.75
	APCD to landfill	Triangular	Triangular	0.99-(0.9999)-1.0	0.99-(0.9999)-1.0
	APCD to air	Triangular	Triangular	0.00005-(0.0001)-0.00015	0.00005-(0.0001)-0.00015
	HMCIWI wet scrubber to waste water	Uniform	Uniform	0 to 1	0 to 1
	HMCIWI wet scrubber to air	Uniform	Uniform	1 to 0	1 to 0
TCs between Eco systems	Air to soil	fixed data	fixed data	0.9866	0.9324
	Air to surface water	fixed data	fixed data	0.0134	0.0676
	Surface water to sediments(S2S)	Worst-case scenario	Worst-case scenario	0 or 1	0 or 1

Section 4A.1: Estimation of annual Au-NP consumption

To arrive at Au-NP consumption (worst case or high release) for selected nano-enabled medical applications, a four step approach was followed:

1. Maximal possible amount (or a range) of Au-NP in mass units was estimated where mass of gold is calculated based on particle size and multiplied by amount per test for *in vitro* medical diagnostic devices and amount per dose for therapeutics.
2. The number of times a particular medical device is likely to be used in a year or dose required in case of therapeutics to treat a disease was estimated.
3. The prospective affected population was arrived at by using disease incidence and prevalence data
4. Multiplied the affected population with the amount of gold arrived at in Steps 1 and 2

Table A5: Prospective per annum amount of Gold nanoparticles in select medical applications (worst case scenario).

Application	Description	Amount per test / intake (unit)	Number of Applications per patient	Possible Population (*UK* and **USA**)	Prospective consumption amount[133]	Refer pages 10 to 20 for specific assumptions to estimate Au amount	End of Life
Diagnostic devices for Pregnancy and Ovulation detection	Lateral flow assay kits to detect the presence of select biomarkers in urine	(2.5 to 8.52)*10^{-7}g	1/year	*12770000*	*3.19 to 10.85*	Refer to **Bullet A**.	Household waste
		(2.5 to 8.52)*10^{-7}g	1/year	**61601000**	**15.40 to 52.36**		
		(2.5 to 8.52)*10^{-7}g	6/year	*19557000*	*29.34 to 136.10*		
		(2.5 to 8.52)*10^{-7}g	6/year	**90732000**	**99.74 to 462.73**		
Diagnostic devices for HIV tests	Rapid Lab based test kits for HIV AIDS	8.52*$10^{-7}$to 3.75*10^{-5}g	Once/year	*2073700*	*1.77 to 77.76*	Refer to **Bullets B.1. and B.2.**	Medical waste
		8.52*$10^{-7}$to 3.75*10^{-5}g	Once/year	**22000000**	**18.74 to 825**		
	HIV *Oral test kits*	8.52*10^{-7}g	Once/year	*20853000*	*17.77*	Refer to **Bullet B.3.**	Household waste
		8.52*10^{-7}g	Once/year	**101777000**	**86.71**		
	Lab based test kits for HIV AIDS	0.000517g	2 times/year	*116000*[134]	*59.97*	Refer to **Bullet H.**	Medical waste
		0.000517g	2 times/year	**1050000**[135]	**542.85**		
Diagnostic device for MRSA/MSSA test	Test is conducted on a positive blood culture report to detect the presence of Methicillin Resistant and Methicillin Sensitive *Staphylococcus aureus* in blood	1.7*10^{-5}g	Once	*20000*	*0.34*	Refer to **Bullet C.** Refer to **Bullet C.**	Medical waste
		1.7*10^{-5}g	Once	**325000**	**5.25**		
Modality for Infection Prevention	Removal of *Staphylococcus aureus* in the nasal passages to prevent nosocomial infection	(1.36 to 5.12)*10^{-2}g	2	*439014*	*11976.29 to 44911.1*	Refer to **Bullet D.**	Medical waste
		(1.36 to5.12)*10^{-2}g	2	**1600000**	**43648 to 163680**		
		3.52*10^{-5} to 1.32*10^{-4}g	2	*439014*	*30.90 to 115.899*		
		3.52*10^{-5} to 1.32*10^{-4}g	2	**1600000**	**112.64 to 422.4**		

[133] Unless mentioned, reported unit is gram
[134] Total no. of tests per year
[135] Total no. of tests per year

Application	Description	Amount per test / intake (unit)	Number of Applications per patient	Possible Population (*UK* and **USA**)	Prospective consumption amount[133]	Refer pages 10 to 20 for specific assumptions to estimate Au amount	End of Life
Treatment of dental diseases	Treatment of chronic peridontitis, endodontitis, peri-implant diseases	$5.28*10^{-5}$g	1	*5208200*	*274.99*	Refer to **Bullet E.**	Waste water
		$5.28*10^{-5}$g	1	**17847400**	**942.34**		
		$2.05*10^{-2}$g	1	*5208200*	*106559.77*		
		$2.05*10^{-2}$g	1	**17847400**	**365151.80**		
Diagnostic test kits for detecting infectious diseases	Gram positive blood culture tests (Septicaemia)	$5.66*10^{-6}$g	1	*20000*	*0.11*	Refer Bullet G.1.1.	Medical waste
		$5.66*10^{-6}$g	1	**325000**	**1.84**		
	Gram negative blood culture tests	$5.66*10^{-6}$g	1	*75000*	*0.42*	Refer Bullet G.1.2.	
		$5.66*10^{-6}$g	1	**280000**	**1.58**		
	C. difficile test (gram positive bacteria)	$5.66*10^{-6}$g	1	*20851*	*0.12*	Refer Bullet G.1.3.	
		$5.66*10^{-6}$g	1	**370260**	**2.09**		
	Respiratory Virus test	$5.66*10^{-6}$g	1	*12636400*	*71.52*	Refer Bullet G1.4.	
		$5.66*10^{-6}$g	1	**60856000**	**344.44**		
Diagnostic test kit to evaluate hypercoaguable state	Detection of single nucleotide polymorphism (F2/F5) to establish risk from venous thrombosis (VTE)	$5.66*10^{-6}$g	1	*225000*	*1.27*	Refer Bullet G.2.	
		$5.66*10^{-6}$g	1	**550000**	**3.11**		
Diagnostic test kit for genotyping drug metabolism	Genotyping Warfarin metabolism	$5.66*10^{-6}$g	1	*64000*	*0.36*	Refer Bullet G.3.	
		$5.66*10^{-6}$g	1	**550000**	**3.11**		
Sensors for diagnosing diseases from breath samples	Diagnosing of lung, prostate, head and neck cancer, breast, colorectal cancer and Chronic Kidney disease	$2.21*10^{-3}$, $2.21*10^{-6}$, $1.43*10^{-8}$g	1	718401	*0.01 to 1588.71*	Refer Bullet **F.**	Medical waste
		$2.21*10^{-3}$, $2.21*10^{-6}$, $1.43*10^{-8}$g	1	**2087211**	**0.02 to 4615.77**		
Treatment for solid tumors (colorectal, pancreas, breast,	Treatment of cancer by delivery of hrTNF (tumor necrosis factor)	95.39% of (95 to 1432 µg)	8 doses for full treatment cycle	*100639*	*0.07-(0.48)-1.10 kg*	Refer **Bullet I.**	Waste water

Application	Description	Amount per test / intake (unit)	Number of Applications per patient	Possible Population (*UK* and **USA**)	Prospective consumption amount[133]	Refer pages 10 to 20 for specific assumptions to estimate Au amount	End of Life
ocular)	bound to gold nanoparticles	95.39% of (95 to 1432 µg)		**421610**	**0.3-(2.024)-4.61 kg**		
	Last line treatment	95.39% of 1432 µg		*36565*	*0.42 kg*		
	Last line treatment	95.39% of 1432 µg		**130640**	**1.50 kg**		Waste water + burial cremation
Treatment for patients diagnosed with head & neck and lung cancer	Photothermal ablation of head and neck cancer and Lung tumor	2793 to 4655 mg[136]	2 doses per treatment cycle	*50230*	*140 to 234 kg*	Refer **Bullet J.**	Waste waster
				266650	**744.75 to 1241.25 kg**		
	Last line treatment			*37490*	*104.7 to 174.52* kg		
	Last line treatment			**167650**	**468.246 to 780.41 kg**		Waste water + Burial/cremation
Diabetes Management	Transbuccal Insulin delivery Platform	0.366 mg	One dose every day*365 days	*960,000*	*128.35 kg*	Refer **Bullet K**.	Waste water
				6300000	**841.62 kg**		
UK (total)					*540 kg*		
US (total)					**2700 kg**		

[136] Includes two doses recommended per treatment cycle

A. Test kits to detect pregnancy and ovulation

Seven Pregnancy and ovulation test kits containing colloidal Gold approved by USFDA:

- Atlas Medical
- IND Diagnostics
- Polymed therapeutics
- NewScen Coast Bio-Pharmaceutical
- Tianjin New Bay Bioresearch Co., Ltd.
- Nantong EGENS Biotechnology Co., Ltd.
- Church and Dwight

Assumptions to estimate amount of Au per application

1. Au-NP size = 60-80 nm size (Nazareth et al., 2012)
2. Conjugate release pad's width is 15 mm (Wong and Tse, 2009)
3. 1µl/mm of conjugate (gold + anti hCG) is used (Zhou et al., 2004)
4. Mass of 60 nm Au-NP/ml = $5.68*10^{-5}$ g/ml (BBI Solutions)
5. Range: 5-15 µl of gold conjugate per test device (BioAssay Works LLC). Therefore, use 15 µl of conjugate solution per test device: mass of Au = **$8.52*10^{-7}$** g per test device
6. Amount of gold antibody conjugate = 0.03 to 0.25 µg /test device, i.e., $3*10^{-8}$ g per test device and **$2.5*10^{-7}$ g** per test device (Wong and Tse, 2009)

Therefore, we use two estimates of Au per test device for high emission worst case scenario:

1. $2.5*10^{-7}$ g/test device
2. $8.52*10^{-7}$ g/test device

Assumptions for annual total number of tests

- All women in the child bearing (15-44 yrs) age group conduct one pregnancy test per year. The age range of child bearing age has been taken from the reported age range of 15-44 yrs in Table 13 of the report Health, United States, 2011(National Centre for Health Statistics, 2012)
- 50% women of child bearing age group from (30-44 yrs) conduct 6 ovulation tests per year
- 20 million pregnancy and ovulation tests in the US per year (BIO-AMD, 2014)

  - Total female population, aged 15 to 44 yrs, for the US = 61606000 (U.S. Census Bureau, 2011)
  - Total female population, aged 30-44 yrs, for the US = 30244000 (U.S. Census Bureau, 2011)
  - Total female population, aged 15 to 44 yrs, for the U.K.= 12777000 (ONS, 2012)
  - Total female population, aged 30-44 yrs,, for the U.K. = 6519000 (ONS, 2012)

B. Test kits to diagnose HIV

B.1. Four *Rapid* HIV tests approved by USFDA based on colloidal gold

1. Clearview® COMPLETE HIV ½ (Alere)
2. Clearview® HIV 1/2 STAT-PAK (Alere)
3. Uni-Gold Recombigen (TRINITY BIOTECH)
4. OraQuick® ADVANCE Rapid HIV-1/2 (Orasure technologies)

CE marked (European Union)

1. Genie™ Fast HIV ½ (Bio-Rad)

Assumptions to estimate amount of Au per application

1. Particle size: 5-50 nm (Krutzik, 2003)
2. Mass of Au-NP/ml = $5.68*10^{-5}$ g/ml (BBI Solutions)
3. Gold conjugate solution = 10 µl/test strip (Rohrman et al., 2012)
4. Gold conjugate solution = 15 µl/test strip (BioAssay Works LLC)

We use 15 ul/test strip = $8.52*10^{-7}$ g Au/test strip

B.2. Colloidal Gold based laboratory based HIV tests (MedMira Laboratories Inc, 2003)

Assumptions to estimate amount of Au per application

1. Au-NP size = 80 nm (Nazareth et al., 2012)
2. 10 ml vial (MedMira Laboratories Inc, 2003)
3. Per vial caters to 15 tests (MedMira Laboratories Inc, 2003). So, amount of gold solution per test is 0.66 ml
4. Mass of Au/ml = $5.68*10^{-5}$ g/ml (BBI Solutions)
5. Mass concentration of Au (80 nm) per 0.66 ml or per test device = $3.75*10^{-5}$ g

Assumptions for annual total number of tests

Number of HIV tests conducted per year in the US= 16-22 millions (Centers for Disease Control and Prevention)

To estimate for high emission scenario, we use the higher value = 22 million tests for the US

For the UK

- All people who attended Sexual Health Clinics are tested for HIV AIDS in 2013 = 1373700 (Yin Z et al., 2014)
- Total no. of women tested under antenatal screening program in 2013 = 700000 (Yin Z et al., 2014)

Therefore, total number of HIV tests for the UK in 2013 = 2073700

B.3. Colloidal Gold based HIV home based test kits

Approved by US FDA on 3 July 2012 (OraSure Technologies Inc., 2015)
Assumptions to estimate amount of Au per application

1. Au-NP size = 60 nm (Nazareth et al., 2012)
2. 15 µl/test device = $8.52*10^{-7}$ g/test strip (BioAssay Works LLC)

Assumptions for annual total number of tests

Since this is a home based test based on oral fluids, we assume 50% of people **from age 15 to 64 years** conduct one home based HIV test per year, though legally the self-testing kit is to be sold to population aged 17 years or more, we have used 15-64 yrs because of the class intervals provided in the population tables.

- Population in the age group of 15 to 64 yrs for the US (Year 2010) = 203 554 000(U.S. Census Bureau, 2011)
- Population in the age group of 15 to 64 yrs for the UK (Year 2011) = 41 706 000(ONS, 2012)

C. Lateral flow Immunoassay test for detection of Methicillin Resistant and Methicillin Sensitive Staphylococcus aureus in blood

Assumptions to estimate amount of Au per application

1. Au-NP size = 80 nm (20-80 nm for Lateral Flow Devices and Conjugates)
2. Mass gold /ml = $5.69*10^{-5}$ g/ml (BBI Solutions)
3. 15 µl of gold conjugate solution per strip (BioAssay Works LLC)
4. **Two** test kits per test(Microphage Inc., 2013). Therefore, 30 µl of gold conjugate per test, i.e., 0.03ml = $1.7*10^{-5}$ g of Au per test device

Assumptions for annual total number of tests

US:

No. of discharges with septicaemia = 1665400. Around 15% (approx 250000) of the above discharges were diagnosed to be due to gram positive bacteria (Elixhauser et al., 2011)

50% of patients suffering from septicaemia, the bacteria is unspecified. And, 15% have bacteria present in blood, but without the response. Keeping these factors into consideration, assume 30% more tests to be done (Elixhauser et al., 2011).

Therefore**, total no. of tests** = 25000 + 30% of 250000. **ca.325000**

UK:

No. of MSSA and MRSA reports in England (above 2 years of age) year 2013 = ca. 10000 (PHE, 2014)

Population for England above 4 years is ca. 50 million(ONS, 2012).

Total population over 4 yrs for UK = ca. 60 million(ONS, 2012)

So, for the UK = estimated number of MRSA and MSSA cases is 12000 (above 4 years of age) approx. = assume 15000 for all age groups.

Therefore, **total no. of tests** = 15000 + 30% more tests = 15000 + 4500 = ca. 20000

D. Nasal decolonization of Staphylococcus aureus

Assumptions to estimate amount of Au per application

1. Au-NP size = 2 and 15 nm (Wilson et al., 2008)
2. One vial = 1.5 ml, 54 vials in a pack (MRSAid)
3. Two treatments per patient (MRSAid)
4. 2nm Au-NP has ca. 270 atoms (M_{Au} = 53000 Da) (Gibson et al., 2007)
5. Mass of one Au-NP of 2 nm = 53000 dalton = $8.8*10^{-20}$ g (Gibson et al., 2007)
6. Particle mass of 15 nm Au-NP= $3.41*10^{-17}$ g (BBI Solutions)
7. Total particles in 1 ml = ($1*10^{13}$ to $1 * 10^{15}$) (Wilson et al., 2008). Use: $1 * 10^{15}$ particles /ml. Therefore, no. of particles in 1.5 ml =$1.5*10^{15}$
8. 1 drop = approx. 0.05 ml
9. 8 drops per patient= 0.4 ml per patient. Therefore, no. of particles in 0.4 ml = $0.4*10^{15}$.

Therefore, we use two estimates of Au per treatment for high emission scenario based on assumed particle size of 2 nm and 15 nm and volume of 0.4 ml and 1.5 ml:

- Amount per treatment (2 nm size)= $3.52*10^{-5}$ g (0.4 ml) to $1.32*10^{-4}$ g (1.5 ml)
- Amount per treatment (15 nm size) = $1.36*10^{-2}$ g (0.4 ml) to $5.12 *10^{-2}$ g (1.5 ml)

Assumptions for annual total number of tests

10-40% of population as outpatients or upon admission have nasal colonisation of S. aureus(von Eiff et al., 2001)

ca. 2% - 5% is the rate of Surgical Site Infections (Deverick J. Anderson et al., 2008)

We assume screening/treatment of 10% of the all surgical procedures (inpatients), because people with surgical procedures are at risk of contracting MRSA

US – ca. 16 million surgical procedures conducted (2010) (short stay discharges with procedures from non federal hospitals)(CDC, 2012)

Therefore, 10% of 16 million gives are the prospective number of patients treated = 1600000 for the US

UK – Sum of Scotland, England, Wales and Northern Ireland =10% of (0.25 million + 3749225+0.25 million +0.18 million) = 439014 patients treated

i. **Scotland:** Total main procedures/operations and inpatients stay greater than zero days for year 2011-2012 is 242518 = ca. 0.25 million (NHS Scotland, 2012)

ii. **England:** Total main procedures (minus drug therapy and diagnostic) = 8520965 (2011-2012). Inpatients = ca. 44% of 8520965 = 3749225 (HSCIC, 2012)

iii. **Wales:** Total inpatients for the year 2011= 226911 = ca. 0.25 million(NHS Wales)

iv. **Northern Ireland:** Total main procedures for the year 2011 -12 = 350651(DHSSPS, 2012), 48.9% (Myers et al., 2012) were inpatients = 48.9% *350651 = 171,483 = ca. 0.18 million

E. Periodontal disease treatment

Assumptions to estimate amount of Au per application

1. Au-NP size = 2nm and 15 nm (Wilson et al., 2008)
2. Mass of 2 nm Au-NP = $8.8*10^{-20}$ g (BBI Solutions)
3. Mass of 15 nm Au-NP = $3.41*10^{-17}$ g (BBI Solutions)
4. Application dose = 0.2 ml of solution per pocket (Ondine Biomedical Inc.)
5. Total dose: 0.6 ml per patient (3 teeth treated per patient)
6. No. of Au-NPs/ml = ($1*10^{15}$) (Wilson et al., 2008)

Therefore, we use two estimates of amount of Au per patient based on particle size of 2nm and 15 nm:

- 2 nm Au-NP size = $5.28*10^{-5}$ g
- 15 nm Au-NP size = $2.05*10^{-2}$ g

Assumptions for annual total number of tests

Background data to arrive the assumption for total number of tests

US:

Definitions (Eke et al., 2012)

i. Severe periodontitis: Two or more interproximal (IP) sites in different teeth having>= 6 mm Attachment loss AND 1 or more IP site >= 5 mm pocket depth

ii. Moderate periodontitis: Two or more I.P. sites >= 4 mm attachment loss OR two or more I.P. sites >= 5 mm pocket depth

- 47.2% of adults over 30 yrs of age in the United States have some form of periodontal disease(Eke et al., 2012)
- 8.5% of the adult population (30 years or more) in the U.S suffer from severe periodontitis
- 30% of the adult U.S. Population suffer from moderate periodontitis

U.K.:

- 45% of all dentate (at least 1 teeth) adults, age 16 yrs or more, have pocketing depth of 4 mm or more (HSCIC, 2011)
- 8% of all dentate adults, greater than 16 yrs of age, pocket depth >6 mm (HSCIC, 2011)

- 8% of all dentate adults, greater than 16 yrs of age, loss of attachment > 5.5 mm and 5% of all dentate adults aged 16 yrs or more = Pocketing depths > 5.5 mm (Morris et al., 2001)
- Percentage of total finished admission episodes dealing with periodontitis and gingivitis = 9% (NHS England, 2014)

10-15% of world adult population (greater than 15 yrs of age) -severe periodontitis, i.e. Community Periodontal Index = 4, Pocket depth of >= 6 mm(Petersen and Ogawa, 2005)

Assumptions for annual total number of tests

- 10% of the population of the U.S. above 30 yrs of age will seek treatment for periodontitis
- 10% of the population of the U.K. above 15 yrs of age will seek per seek periodontitis treatment
- Total population of the US above 30 years = 178474000 (U.S. Census Bureau, 2011)
- Total Population of the UK above 15 years of age = 52082000 (ONS, 2012)

F. Sensors for diagnosing diseases from breath samples

Assumptions to estimate amount of Au per application

1. Au-NP Size = 5nm; an array of monolayer capped spherical Au-NP.
2. Mass of 5 nm Au-NP = $1.26*10^{-18}$ g (BBI Solutions)
3. One drop as 180 pl (Raguse et al., 2007)
4. Or , 1 drop as 0.05µl (Steinecker et al., 2011)
5. Or, 1 drop as 0.05 ml
6. 9 sensors with 9 different surface cappings (Haick et al., 2011)
7. The sensor consists of 10 pairs of circular interdigitated (IDE) gold electrodes of 3 mm diameter and 20 µm electrode width and 20 µm electrode gap (Peng et.al, 2009).
8. 10 drops per circular IDE (Chow et al., 2009; Raguse et al., 2009; Chow et al., 2010; Cooper et al., 2010)
9. Disposal of sensors array every 10 tests[137].

Therefore,

- 9 sensors*0.05 ml per drop *10 drops =4.5 ml/per sensor array
- 9 sensors*0.05µl per drop *10 drops= 4.5 µl/ = 0.0045ml
- 9 sensors*180 pl*10 drops =9*1.8*10^-6*10=0.000162 ml/sensor

25 ml of 31.5 mM $HAuCL_4$ solution = 0.0315 moles/litre of $HAuCL_4$ solution (Haick et al., 2011)

Moles of $HAuCL_4$ solution in 25 ml = $7.875*10^{-4}$ moles/L (Lewis et al., 2006)

No. of atoms in a 5 nm particle = (Radius of Au-NP divided by radius of one atom of Gold NP) = $(5/0.137)^3$ = 48612 atoms of Au per NP.

No of nanoparticles formed = 4.74*10^20 atoms of Au divided by No. of atoms of Au per NP

= 48612 = $9.75*10^{15}$ Au-NP

Therefore 25 ml of 31.5 mM of $HAuCl_4$ forms = $9.75*10^{15}$ Au-NP

10. Number and Mass of Au-NP in different volumes:

- Volume 4.5 ml = $1.76*10^{15}$ Au-NP; Mass of Au = $1.76*10^{15} * 1.26*10^{-18}$ = $2.21*10^{-3}$ g
- Volume 0.0045ml = $1.75*10^{12}$ Au-NP; Mass of Au =$1.75*10^{12}$ Au-NP * $1.26*10^{-18}$ g =$2.21*10^{-6}$ g
- Volume 0.000162 ml = $1.26*10^{8}$ Au-NP; Mass of Au = $1.26*10^{8}$ Au-NP * $1.26*10^{-18}$ g =$1.59*10^{-10}$ g

[137] Disposal of sensor after every 100 tests for asthma diagnosis http://www.niox.com/en/ordering/)

Assumptions for annual total number of tests

Type of cancer	US (estimated cases in 2014)(Howlader N et al., 2014)	UK (cases for 2011) http://www.cancerresearchuk.org/
Lung	224210	43463
Colorectal	136830	41581
Head and neck cancer	42440	6767
Prostate	233000	41736
Breast	235630	50285
Total	**872110**	**183832**

Chronic Kidney disease (CKD):

US = 20 million (Centers for Disease Control and Prevention)

UK = Range of CKD 44607 to 7291480 = ca 7 million (Roderick et al., 2011).

G. Tests To Diagnose Disease Conditions

G.1. Infectious Disease

Assumptions to estimate amount of Au per application

1. Au-NP size = 13-20 nm (Nanosphere Inc.); assume Au-NP size = 20 nm
2. Volume per test cartridge: 0.1 ml, i.e., ca. 2 drops
3. Mass of gold per ml = $5.66*10^{-5}$ g(BBI Solutions); mass of gold in 0.1 ml or mass of Au per application= $5.66*10^{-6}$ g

Assumptions for annual total number of tests

G.1.1. Septicaemia (Gram positive blood culture test)

Refer to details in Page 12 for assumptions for annual number of tests.
US = 325000
UK = 20000

G.1.2. Gram Negative Blood culture test

US **=** No. of discharges with septicaemia = 1665400 (Elixhauser et al., 2011)

No. of discharges with gram negative bacterial incidences = 215000 (Elixhauser et al., 2011)

Assume, 30% more tests are done. Total no. of tests = 215000 + 30% of 215000 = 280000

Total no. of E-coli infections in England = 33336 for year 2013 (PHE, 2014)

Assume 50000 for the UK for all gram negative infections

Assume, 30% more tests are done. Therefore, total no. of tests for the UK= 30% of 50000 +50000 = 75000.

G.1.3. *C*. difficile infections (CDI)

336, 600 hospitalizations that involved CDI in 2009 (Locado et al., 2012)

Assume 10% more diagnostic tests have been performed

So, no. of tests/year for the US = 10% of 336600 +336600 = 370260

For England, reported cases is 13756 for the year 2013 (PHE, 2014)

To estimate reported cases for CD infections for the UK, using the rate of 30 per 100000 of population = 18955 (PHE, 2014)

Assume 10% more tests conducted

No. of tests done per year for the UK = 20851

G.1.4. Respiratory Virus

USA = 5 to 20% of the population every year (Centers for Disease Control and Prevention)

Assume, all people having flu like symptoms are tested for respiratory virus.

Incidences of flu = 20% of total population of the US = 60856000

UK = Same assumption as that for the US, i.e. 20% of population

Flu season = October to May (Centers for Disease Control and Prevention)

G.2. Test kit for detection of single nucleotide polymorphism (F2/F5) to establish risk from venous thrombosis (VTE)

Assumptions to estimate amount of Au per application

1. Au-NP size = 13-20 nm (Nanosphere Inc.); assume Au-NP size = 20 nm
2. Volume per test cartridge: 0.1 ml, i.e., ca. 2 drops
3. Mass of gold per ml = $5.66*10^{-5}$ g (BBI Solutions); mass of gold in 0.1 ml or mass of Au per application = $5.66*10^{-6}$ g

Assumptions for annual total number of tests

1. Prevalence of Factor V Leiden in European Whites = 3-15% (Kujovich, 2011)
2. Prevalence of Factor V Leiden in UK = 8.8% (Kujovich, 2011)
3. Prevalence of Factor V Leiden in Unites States, white population = 5.2% (Kujovich, 2011)

Assume, 8% of the white population will carry Factor V gene mutation

US white population = 223553265[138] = 8% of 223553265 = 17884261

White population for England and Wales = 54809000 (ONS, 2011b) = 8% of 54809000 = 4384720 = approx. 4400000

Estimated annual average of hospitalizations with VTE (≥18 years in the United States) = 547596 among those aged ≥18 years in the United States (Centers for Disease Control and Prevention, 2012)

547596 hospitalisations shows 3% of the white population of the US who might carry one of the risk factors for VTE are hospitalised in a given year.

Therefore, we assume 5% of the white population of the US and UK gets the genetic test done.

5% of 4400000 for the UK = approx. 225000

G.3. Test kit for detection and genotyping Warfarin metabolism

Assumptions to estimate amount of Au per application

1. Au-NP size = 13-20 nm (Nanosphere Inc.); assume Au-NP size = 20 nm
2. Volume per test cartridge: 0.1 ml, i.e., ca. 2 drops
3. Mass of gold per ml = $5.66*10^{-5}$ g(BBI Solutions); mass of gold in 0.1 ml or mass of Au per application = $5.66*10^{-6}$ g

Assumptions for annual total number of tests

To establish Warfarin dosages in patients diagnosed with VTE, we assume all hospitalisations/diagnosis with VTE are advised the genetic test for Warfarin metabolism to establish sensitivity to Warfarin and rate of metabolism.

UK, 64000 Finished Consultant Episodes of VTE for the year 2004-05 (NICE)

For the US, VTE diagnosis = 547596 = approx. 550000 (Centers for Disease Control and Prevention, 2012)

H. Test To Establish Viral Load In HIV Patients

Assumptions to estimate amount of Au per application

1. Au-NP size = 80 nm (Hansen and Krauledat, 2004)
2. One polypropylene vial for 20 tests (Hansen et al., 2012)
3. Assume each vial is 2.5 ml. Therefore, 0.125 ml per test.
4. No. of particles per ml = $8*10^{11}$ (Hansen and Krauledat, 2004)
5. Mass of one gold NP of 80 nm size = $5.17*10^{-15}$ g (BBI Solutions)
6. Amount of Au in 0.125 ml = 0.000517 g. Therefore, amount of Au per test device = **0.000517 g**

[138] http://www.infoplease.com/us/statistics/us-population-by-race.html

The test is to manage disease progression (start ARV therapy or change drugs when the disease becomes drug resistant).

Population assumptions for annual total consumption

US:

- HIV prevalence (year end 2010) = 872990 (CDC, 2013)
- HIV incidence (new diagnosis) is = ca. 50000 every year (CDC, 2013)
- Stage 3 HIV prevalence = ca. 500000 (end of 2010) (CDC, 2013)
- 500,000/872,990 = ca. 60% of people are in Stage 3 of total people living with HIV/AIDS
- Assume people with Stage 3 HIV infection and are on regular Anti-retroviral therapy
- Assume device is used once every 6 months to check their CD4 count. Therefore, Total tests done for patients living with Stage 3 HIV per year =500000 * 2 = 1 million (AVERT)
- Total tests per year = Newly diagnosed + test for HIV stage 3 = 1 million + 50000 = **1050000**

UK:

- Newly diagnosed = 6000 (Yin Z et al., 2014)
- 107,800 people are living with ***known*** HIV infection. Assume 50% of the people living with known HIV infection are late stage = 53900 = approx. 55000 (Yin Z et al., 2014)
- Total tests done for patients living with Stage 3 HIV per year = 55000*2 = 0.11 million =**116000**
- Total tests = Newly diagnosed + test for HIV stage 3 = 0.11 million + 50000

I. Treatment modality for Cancer : TNF delivery

Assumptions to estimate amount of Au per application

1. Au-NP size = 30-34 nm (Paciotti et al., 2004)
2. Total dose range of CYT-6091 = 90 ± 5 to 1208 ± 214 µg; therefore, use dose = 95µg to 1432 µg (Libutti et al., 2010)
3. SH- PEG = 20 kDa (Paciotti and Tamarkin)
4. TNF monomer = 17 kDa. Assume = 20 kDa (Paciotti et al., 2004)
5. One Au-NP has 400 TNF molecules bound to it (Paciotti et al., 2004)
6. Since the available literature doesn't inform of the number of PEG on one Au-NP(Tsai et al., 2012). Assume, both SH-PEG and rhTNF are bound to the Au-NP and they do not cross-link with each other.
7. Mass of 1 Au-NP of size 30 nm = $2.73*10^{-16}$ g (BBI Solutions)
8. Mass of 400 TNFs = 400* 20 kDa = 400* $3.32*10^{-20}$ g = $1.32*10^{-17}$ g (Conversion from Da to grams)
9. Ratio=Au-NP: TNF = (2.73*10^-16 /$1.32*10^{-17}$) = 20.76 : 1. Thus, percentage weight of gold is (20.76/21.76)*100 = 95.39%
10. No. of doses per treatment cycle (high dose) = 8 ; 4 courses where 1 course = 2 doses)(Libutti et al., 2010)

Amount of Au per patient:

- Estimates of range of Au per patient: 95.39% of (95*8) µg to 95.39% of (1432*8) µg
- Estimate of average amount of Au per patient = 95.39% of (4801 ug)

Population assumptions for annual total consumption

Type of enrolled patients in clinical trial phase I (Libutti et al., 2010):

1. Ocular melanoma
2. Adenocarcinoma of the colon and pancreas
3. Ductal carcinoma of breast
4. Carcinoma of rectum

Combine adenocarcinoma of the colon and carcinoma of rectum as colorectal cancer or bowel cancer.

Type of cancer	**US**		**UK**	
	Estimated cases in 2014 (Howlader N et al., 2014)	*Estimated deaths for 2014 (Howlader N et al., 2014)*	*Diagnosed Cases for 2011*	*Deaths in 2012*
Colorectal	136830	50310	41581(Cancer Reasearch UK)	16187(Cancer Reasearch UK)
Pancreatic	46420	39590	8773(Cancer Reasearch UK)	8662(Cancer Reasearch UK)
Breast	235630	40430	50285(Cancer Reasearch UK)	11716(Cancer Reasearch UK)
Ocular	2730	310	No data	No data
Total	421610	100639	130640	36565

J. Treatment modality for Cancer: Thermal ablation

Assumptions to estimate amount of Au per application

1. Dosage= 21 to 35 mg/kg body (Gad et al., 2012)
2. Two infusions is the expected clinical dose (Gad et al., 2012)
3. Average body weight = 70 kg
4. 95% of the weight of Auroshells is gold weight (Gad et al., 2012) Auroshells: 155 nm in diameter (120 nm diameter is the silica core) with a coating of polyethylene glycol 5000.

Estimates of Amount of Au per patient

- 95% of (21*70*2) =2793mg
- 95% of (35*70*2) = 4655mg

Population assumptions for annual total consumption

Type of cancer	US		UK	
	Estimated cases in 2014 (Howlader N et al., 2014)	*Estimated deaths for 2014 (Howlader N et al., 2014)*	Diagnosed Cases for 2011	Deaths in 2012
Lung cancer[139]	224210	159260	43463 (Cancer Reasearch UK)	35371 (Cancer Reasearch UK)
Head and Neck Cancer	42440	8390	6767 (oral cancer) (Cancer Research UK)	2119 (oral cancer) (Cancer Research UK)
Total	**266650**	**167650**	**50230**	**37490**

K. Transbuccal Insulin Delivery Platforms

Assumptions to estimate amount of Au per application

1. Au-NP size = 3.5 nm = 102 atoms of Au (Williams et al.)
2. Mass of 3.5 nm Au-NP = 102 atoms *196.96 g/ mol = $3.33*10^{-20}$ g
3. 1 IU of insulin = 0.0385 mg (Joshi et al., 2007)
4. Average body weight = 70 kg
5. Total daily insulin intake dose = 0.55 IU/kg of body weight[140] (without giving consideration to insulin resistance, other oral medications, etc.) = 0.55*70 = 38.5
6. Molecular weight of insulin monomer = 5808 Da (Joshi et al., 2007) = ca 5808 g/mol
7. No. of Insulin monomer required per day = 38.5 * 0.0385 mg (Mass of Insulin) = 1.48mg of Insulin/day = $2.5*10^{-7}$ moles of Insulin = $1.5*10^{17}$ molecules of Insulin
8. Binding of Insulin to NP is in the ratio of 14:1 (14 insulin monomer) (Williams et al.)
9. No. of Au-NP required for binding $1.5*10^{17}$ molecules of Insulin = $1.07*10^{16}$
10. Gold concentration = 4.037 mg of Au/ml =1.21 X 10^{17} Au-NP/ml (Williams et al.)
11. Mass of $1.07X10^{16}$ Au-NP = 0.366 mg of Au.

Therefore, Amount of Au per day per patient = **0.366 mg**

Population assumptions for annual total consumption

- Total diagnosed diabetic population in the US of all age groups (all ages, 2012) =21 million (Centers for Disease Control and Prevention, 2014)
- Total diagnosed adults (greater than 18 years) take insulin = 6 million, i.e. 28% of the diagnosed adult population (Centers for Disease Control and Prevention, 2014)
- People with diagnosed diabetes (20 years and less) = 215000 (Centers for Disease Control and Prevention, 2014)

[139] http://www.nanospectra.com/clinicians/trialinfo.html: The clinical trials include metastatic lung cancer and refractory head and neck cancer

140 http://dtc.ucsf.edu/types-of-diabetes/type1/treatment-of-type-1-diabetes/medications-and-therapies/type-1-insulin-therapy/calculating-insulin-dose/

Therefore, assume 30% of the diagnosed population of all age groups take insulin = **6.3 million**

UK =3.2 million people have been diagnosed with diabetes (2013) (Diabetes UK, 2014)

Also, assume 30% of UK's diabetic patients will take insulin (as derived from the American numbers) = 30% of 3.2 million = **960000**

Table A6.1: Summary of volume or mass of environment compartment – air, water, sediment and soil – as input parameters for the probabilistic mass flow model.

The Comments column provides the values used to calculate the mass/volume. The mass of soil and sediment compartment has been arrived at by multiplying the area, the mixing depth and the density. The area of natural and urban soils has been calculated by subtracting the area occupied by agricultural soils and other soils. Littoral sediments (beaches and intertidal mud flats and salt marshes) have been included for the UK as it represents a key ecosystem of the UK.

Compartments	Countries	Formula/ Calculation	Mass/Volume	Unit	Comments
Sludge treated soils	UK	$1.65*10^9*0.2*1.5*10^3$	4.95E+11	kg	• $1.65*10^9$ m^2: total sludge treated agricultural land area in the UK (Water UK, 2010) • 0.2 m: the depth of agricultural soil (ECB, 2003) • 408,139,000 acres is the total cropland/arable land in the US[141]= ca.1.65*1012 m2 (Trading Economics; USDA, 2011) • Total area of sludge treated soil the US: 1%(UN-HABITAT, 2008) of arable land= $1.65*10^{10}$ m^2 • $1.5*10^3$ kg/m^3: the density of dry soil (ECHA, 2012; OECD, 2013b)
	US	$1.65*10^{10}*0.2*1.5*10^3$	4.95E+12	kg	
Surface water	UK	$3.25*10^9*3*1000$ *(365/40)	8.90E+13	litre	• $3.25*10^9$ m^2 : the total freshwater area in the UK (Morton et al., 2011) • 3 m: the mixing depth of surface water • 1000: the conversion from m^3 to litre • 86,409 sq. Miles: the area of Inland water (U.S. Census Bureau, 2013) • 59,959 sq. Miles: the area of Great Lakes (U.S. Census Bureau, 2013) • $2.59*10^6$: the conversion factor from sq. mile to m^2 • 40:ENM residence time in the system (Gottschalk et al., 2009) • 365 days: 1 year
	US	$(86409+59959)*2.59*10^{6*}$ $3*1000$ *(365/40)	1.04E+16	litre	
Surface water Sediments	UK	$(3.25+2.59)*10^9*0.03*0.82*10^3$	1.44E+11	kg	• $3.25*10^9$ m^2: the total freshwater area (Morton et al., 2011) • $2.59*10^9$ m^2: the total littoral sediment area (Morton et al., 2011) • 0.03 m: the depth of sediment • $0.82*10^3$ kg/m^3: the bulk density of dry sediments (ECHA, 2012; Dedeh et al., 2014) • 86,409+59,959 sq. Miles: the surface water area in the US (U.S.
	US	$(86409+59959)*2.59*10^{6*}$ 0.03	9.33E+12	kg	

[141] 1 acre = 0.004046 km^2

		*0.82*10^3			Census Bureau, 2013) • 2.59*10^6: the conversion factor from sq. mile to m^2
STP Effluent	UK	11*10^9*365	4.02E+12	litre	• 11 billion L: the amount of wastewater collected/day in the UK(DEFRA, 2012) • 365 days: 1 year • 3.09*10^8: US population (2010)(U.S. Census Bureau, 2011) • 165 US gallons wastewater is assumed per capita per day(USEPA, 2000) • 3.785: gallons to litres
	US	3.09*10^8*165*3.785*365	7.04E+13	litre	
STP sludge	UK		1.41E+09	kg	• 1.41*10^9 kg : STP sludge (dry weight) generated in the UK (DEFRA, 2012) • 7.18*10^9 tons: Biosolids[142] generated in the U.S. (NEBRA, 2007; UN-HABITAT, 2008) • 0.9072: Short Ton to metric Ton
	US		6.5 E+09	kg	

[142] In the US, treated sewage sludge is termed as biosolids.

Table A6.2 Summary of non hazardous household and hazardous healthcare and biological waste as input parameters for the probabilistic mass flow model

Compartments	Countries	Formula/ Calculation	Mass/ Volume	Unit	Comments
Hazardous healthcare and biological (H&B) waste treated by incineration	UK		$1.4*10^8$	kg	• 144,000 tonnes of H&B waste incinerated in year 2008,i.e., 40% of hazardous H&B waste generated (DEFRA, 2013a) • 146,502 tons: Estimated throughput of 54 medical waste incinerators in year 2011(RTI International, 2012)
	US	146502*0.9072	$1.1*10^8$	kg	
Hazardous H&B waste sent to landfill	UK	Total hazardous H&B waste generated – waste incinerated	$2.1*10^8$	kg	• 350,000 tonnes: Total hazardous H&B generated in the year 2008 (DEFRA, 2013a)
	US	Total hazardous H&B waste generated – waste incinerated	$1.2*10^9$	kg	• 5.9 million tons: Total H&B waste generated per year (Practice Greenhealth) • 24%(Kwakye et al., 2011) of 5.9 million tons: Total hazardous waste generated per year
Non hazardous household waste treated by incineration	UK	15%*19 million tonnes	$2.8*10^9$	kg	• 19,354,616 tonnes of household and similar waste generated in the year 2010 (Eurostat) • 15% of waste treated (2008)(Eurostat, 2013) • Assume waste generated = waste treated • 29 million tons: Incineration with energy recovery (USEPA, 2013)
	US		$2.6*10^{10}$	kg	
Non hazardous household waste sent to landfill	UK	85%*19 million tonnes	$1.6*10^{10}$	kg	• 85% of waste treated is landfilled (2008) • 134 million tons: Municipal waste Landfilled in Year 2011(USEPA, 2013)
	US		$1.2*10^{11}$	Kg	

Table A6.3 Summary of parameters related to waste water as input parameters for the probabilistic mass flow model

Parameters	Countries	Values	Comments
Connection rate to STP	UK	0.96	• 96%: Percentage of population connected to STP (DEFRA, 2012)
	US	0.74	• 74%: Percentage of population connected to centralised STP (USEPA, 2008)
Misconnection of STP pipes	UK	0.0026 to 0.018	• Range estimated from (ONS, 2011a and Personal communication with Bryan Ellis; Ellis, 2013). Please see explanation in Notes
	US	*No data available*	• None
Leakage of STP pipes	UK	0.03 to 0.05 of effluent collected	• Range estimated from (Ellis et al., 2004; Ellis et al., 2008; Rutsch et al., 2008; DEFRA, 2012). Please see explanation in Notes
	US	0.05 to 0.06 of effluent collected	• Range estimated from (Ellis et al., 2004; Jr. Sharp, 2010)
Overflows	UK	Mean= 0.161, Sd=0.079	• 16.1% of dry weather flow (std dev =7.9% with lognormal distribution) (Constantino Carlos of Atkins, 2014)
	US	0.01 to 0.07	• Range estimated from (USEPA, 2008; ASCE, 2013). Please see explanation in Notes

NOTES for Table A6.1, A6.2, A6.3

1. **Dry weather flow**

Dry weather flow = Population served * per capita water output + Infiltration + trade effluent

Total Population (2010) census = 63,182,000

Population served by STP = 96%

Population served = 96% * 6318200 = 60654720

Per capita waste water output = 0.15 m^3/ day (British Water, 2013)

Total population output = 60654720*0.15 m^3 * 365 days = 3.32 billion m^3

Per capita industrial output =0.028 m^3/day (Scott Wilson, 2010)

Infiltration = 25% of population WW load = 25% * 3.32E+09 = 8.30E+08 m^3 = 830 million m^3 (Ellis, 2001; Scott Wilson, 2010)

Trade flow per year = 0.028 m^3/day * 60654720 * 365 = 6.20E+08 m^3 = 620 million m^3

Total days in a year =365

DWF/year = 4.77E+09 m^3 = 4.77 billion m^3 (nearly same as waste water collected - 4.02 billion m^3)

Storm tank discharges = 16.1% of dry weather flow (personal communication with Constantino Carlos)

2. **Misconnections Volume (UK)**

- Total no. of unshared dwellings in 2011(whole house or bungalow) (ONS, 2011a) = 20514994
- Misconnection rate = 1 to 7% and national average = 3% (Ellis, 2013)
- 1% to 7% of 20514994 = 205150 to 1436050
- 138 litres WW per day per household discharged due to misconnections (Ellis, 2013) (personal communication with Bryan Ellis)
- Misconnection volume = 0.138*365*205150 to 0.138*365*1436050 =10333402 to 72333817 m^3
- Volume percentage of WW discharged due to misconnections= 10333402/4.02E+09 72333817/4.02E+09= 0.26% to 1.8 %

3. **Exfiltration/leakage for the UK**

- Exfiltration rate: 0.0014 l/s/km or 2.8% of DWF for the city of Dresden (cited in Rutsch et al., 2008)
- Exfiltration = 3% of total average annual flow for Thames region (Ellis et al., 2004)

- 5-20% leakage rate for gravity sewers above water table. 5% is the lower value used in various studies (mentioned in Ellis et al., 2004); Other studies give very high exfiltration rate (see Ellis et al., 2008; Rueedi et al., 2009) (see ref. 27 summary and ref. 35 for recent study for Doncaster, UK)
- Range used for our study = 3 to 5% of effluent volume
- Sewer length in the UK = 347,000 km (DEFRA, 2012)
- Effluent volume (2011)= 4.05 billion m^3 (DEFRA, 2012)

4. Overflows/intermittent discharges for the US

- Discharges from decentralized water treatment systems due to failures: 66 to 144 billion Gallons (USEPA, 2008)
- Discharges from sanitary sewerage = 900 billion gallons (ASCE, 2013)
- Total overflows = 144+900 = 1,044 billion gallons
- Total centralized + decentralized effluent= 5.21E+10 + 5.96E+09 = 5.81E+10 m^3
- Percentage = 3.95E+09 / 5.80E+10 = 6.8% = ca. 7% (higher estimate because the infrastructure report card rates the waste water treatment infrastructure status of US to be 'D', i.e., poor and at risk (ASCE, 2013)
- Conservative estimate from USEPA's Report to Congress (2008): 10 billion gallons from Sewer overflows and 160 billion gallons from Combined Sewer Overflows = 1.1% or ca. 1% of total effluent volume
- Range = 1 to 7%

5. Sludge distribution

UK – (DEFRA, 2012)

Total sludge generated/annum	1412836 (tonnes dry weight)	Percentage
Land application	0.791	79.10%
Incineration	0.184	18.40%
Landfill	0.006	0.60%
Other disposal	0.019	1.90%

US (NEBRA, 2007; National Biosolids Partnership, 2013)

Total biosolids from Treatment works treating domestic sewage	7180000 dry tons	S	**Range**
Conversion to metric tonnes	6513586.43		6.5 to 9.1 million tonnes
Agriculture /farmlands	2651029.68	41%	41% to 45%
Incineration	967267.59	15%	15% to 17%
Landfill+Monofill	1963846.31	30%	29% to 30%
Class A exceptional quality as biosolids or heat dried pellet fertilizer/Compost - silviculture, horticulture, gardens, etc.	788143.96	12%	9% to 14%
Forest land and reclamation, other beneficial uses	143298.90	2%	

6. **Cremation of bodies:**

   UK : Cremation – 74% for year 2012(Cremation Society of Great Britain)

   US: Cremation - 38% for year 2012(National Funeral Directors Association)

7. **Hospital waste estimates from various sources for the US:**

- More than 4 billion pounds of waste disposed in 2007(Kagoma et al., 2012)
  1 pound = 0.45 kg
  Year 2007 = 4*0.45*109 = **1.8 million metric tonnes**

- 2 million tons/year(Brennan, 2009) = 2 * 0.9072= 1.8 million tones (if 7000 tons of waste per day = 2.32 million tonnes of waste per year)
  1 ton = 0.9072 tonnes
  1 year = 365 days
  Hospital waste generation range = **1.8 to 2.32 million tonnes**

- 13-15 pounds of waste/patient/day = 5.85 to 6 kg/patient/day(Rutala and Mayhall, 1992)

  Use = 6 kg/patient/day

  Total waste = waste/patient/day * total no. of discharges in a year * average length of stay in a hospital

  Total no. of discharges (in non-federal, short stay hospital) in 2008-2009 = 35908000 (Table 104)(National Centre for Health Statistics, 2012)

  Average length of stay (both federal and non-federal hospitals) = 6.2 days (Table 108)(National Centre for Health Statistics, 2012)

  Total waste generated in year 2008 to 2009 =**1.34 million tonnes**

- World Health Organisation (WHO, 1999)
  Medical waste generation = 1.1 to 12.0 kg/capita
  Population of USA in 2010 = 304280000
  Hospital waste generation range = **0.3 million tonnes to 3.6 million tonnes**

- Hospital waste = 5.9 million tons = **5.35 million tonnes** (Practice Greenhealth)
- In 1994 , USA generated around 3.361 million tons of medical waste **= 3.05 million tonnes**(USEPA, 2010)

  The higher estimate of **5.35 million tonnes** has been used in the study:
  - Due the futuristic perspective of nanomedicine waste
  - Increasing stringency in regulations concerning hospital waste

Table A7.1 Data for aquatic toxicity.

Data extracted from 12 related scientific papers. Ecological effects selected to create probabilistic species distribution were mortality and malformation, growth inhibition, reproductive impairment and acute immobilisation. Twenty three toxicity endpoints spread across four different taxonomic groups- fish, algae, crustacean and bacteria- were used to construct the Species Sensitivity Distribution for the aquatic compartment. The term Highest Observed No Effect Concentration (HONEC) was used when a range of concentrations were tested and the effects reported at the highest concentration tested was not statistically different from the control for the selected endpoint. The term No Observed Effect Concentration (NOEC) was used when two or less than two concentrations were tested and the reported concentration was not statistically significantly different from the control treatment. The concentration which caused an adverse effect in 10% of the test organisms was termed as Lowest Observed Effect Concentration (LOEC). The lowest concentration which caused an adverse effect in x% of the test organisms has been termed as ECx or if x% of the test organisms died, it has been represented as LCx. We used Assessment Factors (AF) to account for chronic toxicity (AF time) and to extrapolate to no observed effect values (AF-no effect) for deriving the species sensitivity values. For short time or acute exposure studies, the factor used for AF time was 10. AF no-effect factor used was 1 for the concentration which showed no difference in comparison to the control treatment, AF no-effect factor used was 2, if $L(E)C_{10} \leq L(E)C_x < L(E)C_{50}$ and a factor of 10 was used to derive NOEC if $L(E)_{50} \leq L(E)C_x \leq L(E)C_{100}$. Various units of exposure concentrations reported in the studies were standardised to microgram/litre (µg L^{-1}).

Gold nanomaterial tested (particle size in nm and coating)	Test organism	Exposure concentrations	Toxic endpoint	Effect concentration (µg/L)	Type of toxicity test	AF time	AF no-effect	Species sensitivity values (µg/L)	Source
15-35 nm Capping: Poly vinyl alcohol	*Danio rerio*	10, 25, 50, 75, 100 µg/ml	Mortality	HONEC=100000	Acute toxicity test	10	1	10000	(Asharani et al., 2011)
0.8 nm Capping -TMAT (N,N,N-trimethylammonium ethane thiol)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	EC_{60}=2000 (p<0.01)	Acute toxicity test (120 hpf)	10	10	20	(Harper et al., 2011)
1.5 nm Capping–TMAT (N,N,N-trimethyl ammonium ethane thiol)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	EC_{40} = 80 (p<0.05)	Acute toxicity test (120 hpf)	10	2	4	(Harper et al., 2011)
15 nm Capping -TMAT (N,N,N-trimethyl ammonium ethane thiol)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	EC_{40}=50,000 (p<0.01)	Acute toxicity test(120 hpf)	10	2	2500	(Harper et al., 2011)

Gold nanomaterial tested (particle size in nm and coating)	Test organism	Exposure concentrations	Toxic endpoint	Effect concentration (µg/L)	Type of toxicity test	AF time	AF no-effect	Species sensitivity values (µg/L)	Source
0.8 nm Capping: 2-mercapto ethane sulfonic acid (MES)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	LOEC=50000 (p<0.01)	Acute toxicity test(120 hpf)	10	2	2500	(Harper et al., 2011)
1.5 nm Capping: 2-mercapto ethane sulfonic acid (MES)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	LOEC=2000 (p<0.01)	Acute toxicity test(120 hpf)	10	2	100	(Harper et al., 2011)
0.8 nm, 1.5nm, 15 nm capped with MEE (2,2 mercapto ethoxy ethanol) and MEEE (2-(2-(2-mercaptoethoxy)ethoxy) ethanol)	*Danio rerio*	(16, 80, 400 ppb), (2,10,50, 250) ppm	Mortality and malformation	HONEC=250000	Acute toxicity test(120 hpf)	10	1	25000	(Harper et al., 2011)
1.2 nm (3-mercaptopropionic acid-functionalized)	*Danio rerio*	0.08 to 50 µg/ml	Mortality and malformation	HONEC=50000	Acute toxicity test(120 hpf)	10	1	5000	(Truong et al., 2012)
3 nm (4-9 nm) Triphenylphosphine monosulfonate (TPPMS)-functionalised	*Danio rerio*	0.25,2.5,25,250 µM	Mortality, embryonic malformations	HONEC=49000	Acute toxicity test (120 hpf)	10	1	4900	(Bar-Ilan et al., 2009)
10 nm (14-21nm) TPPMS functionalised	*Danio rerio*	0.25,2.5,25,250 µM	Mortality, embryonic malformations	HONEC=49000	Acute toxicity test(120 hpf)	10	1	4900	(Bar-Ilan et al., 2009)
50 nm (31-60nm) TPPMS functionalised	*Danio rerio*	0.25,2.5,25,250 µM	Mortality, embryonic malformations	HONEC=49000	Acute toxicity test(120 hpf)	10	1	4900	(Bar-Ilan et al., 2009)
100 nm (75-115nm) TPPMS functionalised	*Danio rerio*	0.25,2.5,25,250 µM	Mortality, embryonic malformations	HONEC=49000	Acute toxicity test(120 hpf)	10	1	4900	(Bar-Ilan et al., 2009)
1.3 nm TMAT (N,N,N-trimethylammoniumethanethiol) functionalised	*Danio rerio*	0.08, 0.4, 2, 10, 20, 30, 40, and 50 mg/l	Mortality	LC50=30000	Acute toxicity test(120 hpf)	10	10	300	(Kim et al., 2013)
2 nm (alkane thiol-ethylene glycol and then functionalised A1-Hydrophilic positive charge	*Oryzias latipes (adult)*	20 nM of Au-NP (800-1000ppb of Au)	Mortality	NOEC = 973	Acute toxicity test (120 hrs)	10	1	97	(Zhu et al., 2010)

Gold nanomaterial tested (particle size in nm and coating)	Test organism	Exposure concentrations	Toxic endpoint	Effect concentration (µg/L)	Type of toxicity test	AF time	AF no-effect	Species sensitivity values (µg/L)	Source
2 nm (alkane thiol-ethylene glycol and then functionalised A2-Hydrophilic negative charge	*Oryzias latipes (adult)*	20 nM of Au-NP(800-1000ppb of Au)	Mortality	NOEC = 973	Acute toxicity test (120 hrs)	10	1	97	(Zhu et al., 2010)
2 nm (alkane thiol-ethylene glycol and then functionalised ; A3-Hydrophilic neutral)	*Oryzias latipes (adult)*	20 nM of Au-NP(800-1000ppb of Au)	Mortality	NOEC = 973	Acute toxicity test (120 hrs)	10	1	97	(Zhu et al., 2010)
2 nm (alkane thiol-ethylene glycol and then functionalised; A4-Hydrophobic positive charge)	*Oryzias latipes (adult)*	20 nM of Au-NP (800-1000ppb of Au)	Mortality	LC_{100} = 973	Acute toxicity test (24 hrs)	10	10	10	(Zhu et al., 2010)
20 nm (15-21 nm) Capping: citrate	*Daphnia magna*	Not clear from the study	Acute immobilisation and reproductive test	LC_{50}=70000	Acute toxicity test	10	10	700	(Li et al., 2010a)
4.6 nm Capping: Dodecanethiol coated with Amphiphilic Polymer (hydrophobic part -dodecylamine and a hydrophilic part, poly-sobutylene-alt-maleic anhydride).	*Pseudokirchneriella subcapitata*	0.0012 to 0.12 µM (0.46 to 46 mg/L)	Growth inhibition test	EC_{50} =7500	Acute toxicity test (24 and 48 hrs)	10	10	75	(Van Hoecke et al., 2013)
4.6 nm (4 to 5.5 nm) Capping: 10 kD PEG coating on the ampiphilic coating	*Pseudokirchneriella subcapitata*	0.0012 to 0.12 µM (0.46 to 46 mg/L)	Growth inhibition test	EC_{50} =39000	Acute toxicity test (24 and 48 hrs)	10	10	390	(Van Hoecke et al., 2013)
2 nm Capping: α-D-manno-pyranoside terminated PAMAM (polyamidoamine) dendrimer) G-0 generation	*Chlamydomonas reinhardtii*	6 and 12 ng/ml	Growth inhibition test	GI60 (48 hours) - 12 ug/L ($p<0.01$) or EC60 = 12 ug/L	Acute toxicity test (24 and 48 hrs)	10	10	0.12	(Perreault et al., 2012b)
4 nm (5-9 nm) Capping: Citrate	*Caenorhabditis elegans*	0, 2.5, 5.5, 7, 15, and 30 mg/L	LC 10	LC_{10} = 5900	Acute toxicity test (24 hrs)	10	2	295	(Tsyusko et al., 2012)
10 nm Capping: Citrate	*Photobacterium phosphoreum*	28 µg/ml	Decrease in bioluminescence	NOEC= 28000	Microtox test	10	1	2800	(Barrena et al., 2009)

Gold nanomaterial tested (particle size in nm and coating)	Test organism	Exposure concentrations	Toxic endpoint	Effect concentration (µg/L)	Type of toxicity test	AF time	AF no-effect	Species sensitivity values (µg/L)	Source
5.1 nm Capping: Bovine Serum Albumin	*Bacteria*	Not clear from the study	Toxicity test	EC_{50} = 2.68*10^6ug/L	Microtox test	10	10	26800	(Zheng et al., 2010)

Table A7.2 Data for terrestrial toxicity.

Data extracted from one paper. Ecotoxicity endpoint data transformed to species sensitivity values as explained in Table 9.1

Gold nanomaterial tested (particle size in nm and coating)	Test organism	Exposure concentrations	Toxic endpoint	Effect concentration	Type of test	AF time	AF no-effect	Species sensitivity value (µg/kg)	Source
20 nm (20.5±0.7 nm) Capping: Citrate	**Eisenia fetida (Adult and fully clitelate)**	5, 20, 50 mg Au/kg of dry mass soil	Reproductive performance	LOEC = 50 mg Au/kg	Long term test (56 days)	1	2	25	(Unrine et al., 2010)
55 nm (54.9±0.7 nm) Capping: Citrate	**Eisenia fetida (Adult and fully clitelate)**	5, 20, 50 mg Au/kg of dry mass soil	Reproductive performance	LOEC = 20 mg Au/kg	Long term test (56 days)	1	2	10	(Unrine et al., 2010)

Section 4A.2: Alternate Scenarios

4A.2 details the scenario and possibilities:

1. Where modelled PEC of Au-NP is arrived at by considering 100% excretion of the therapeutic in waste water and is named as Scenario 2 (worst case)
2. Where the environment risk is estimated by comparing this worst case PEC with lethal endpoints and sub-lethal endpoints for the aquatic compartment
3. Where the environment risk is estimated by comparing the realistic scenario 1 (with accumulation of therapeutics in the body) and pSSDs with sublethal endpoint

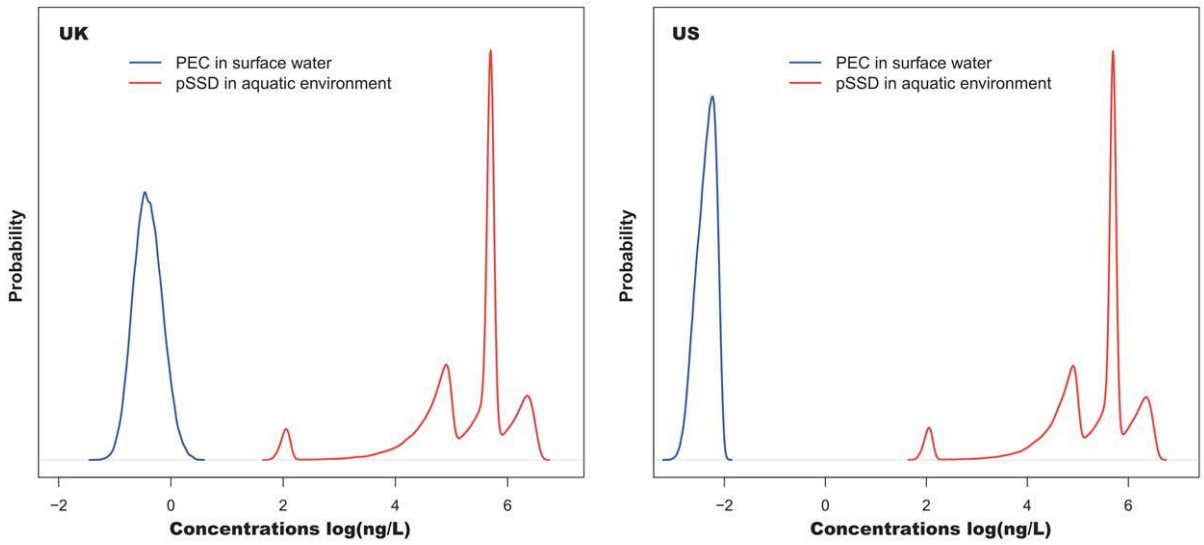
Scenario 2 (worst case): PEC of Au-NP without accumulation of Au-NP (from drugs) in body, i.e., 100% excretion. Black values designate concentrations; grey values designate yearly increases in concentrations. Au-NP concentrations in surface water and sediments represent no and complete sedimentation respectively. The results are expressed up to three significant digits.

		UK				US				Units
		Mean	Mode	Q_{15}	Q_{85}	Mean	Mode	Q_{15}	Q_{85}	
STP Effluent		**980**	**930**	500	1,460	**310**	**300**	170	460	pg/L
Surface water		**1,040**	**600**	500	1,600	**11**	**8.1**	6.3	16	pg/L
STP sludge		**280**	**290**	230	320	**330**	**330**	300	370	µg/kg
Sludge treated soil		**650**	**670**	540	760	**280**	**280**	250	320	ng/kg·y
Sediments		**640**	**370**	300	990	**12**	**9.0**	7.0	17	ng/kg·y
Hazardous waste		**77**	**27**	24	130	**65**	**44**	20	110	µg/kg
Medical WIP	Fly ash	**260**	**30**	36	520	**260**	**33**	37	520	µg/kg
	Bottom ash	**200**	**24**	27	390	**200**	**24**	27	400	µg/kg
Municipal WIP	Fly ash	**30**	**29**	24	37	**90**	**87**	76	100	µg/kg
	Bottom ash	**23**	**22**	17	29	**68**	**64**	55	82	µg/kg

Scenario 1: PEC vs pSSD (with the PEC considering accumulation of Au-NP in body)

PEC vs pSSD for water with sublethal end points: The graphs don't overlap and hence could indicate no risk **from Au-NP.**

Figure A1PEC vs pSSD in water with sublethal end points.



Scenario 2: PEC without accumulation of Au-NP in body and pSSD with lethal and sublethal endpoints

PEC vs pSSD for water and using lethal endpoints: The graphs don't overlap and hence could indicate no risk from Au-NP.

Figure A2 PEC vs pSSD for water and using lethal endpoints.

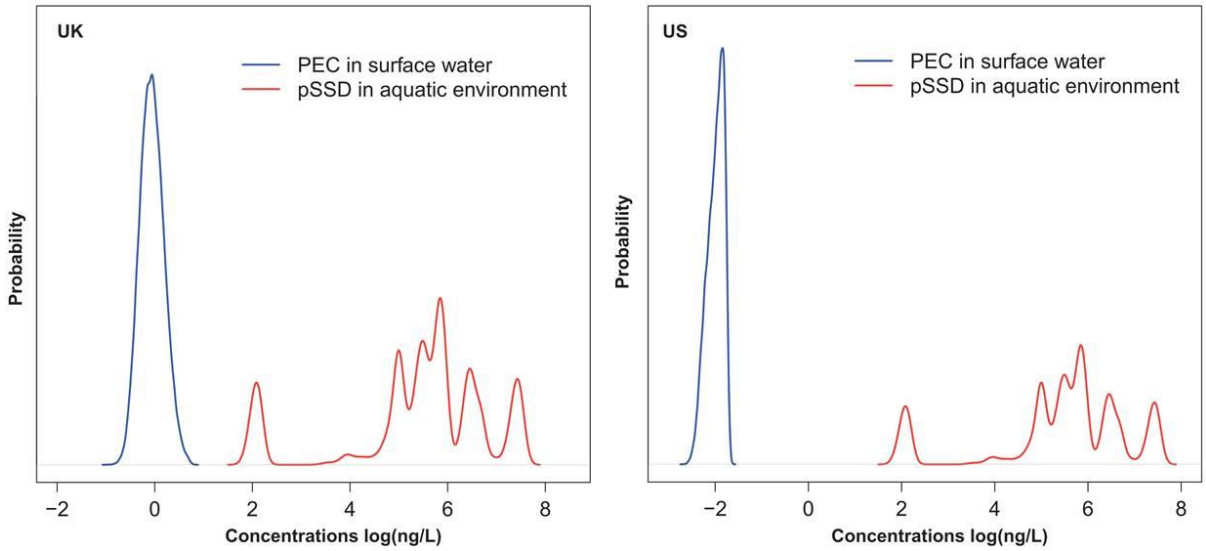
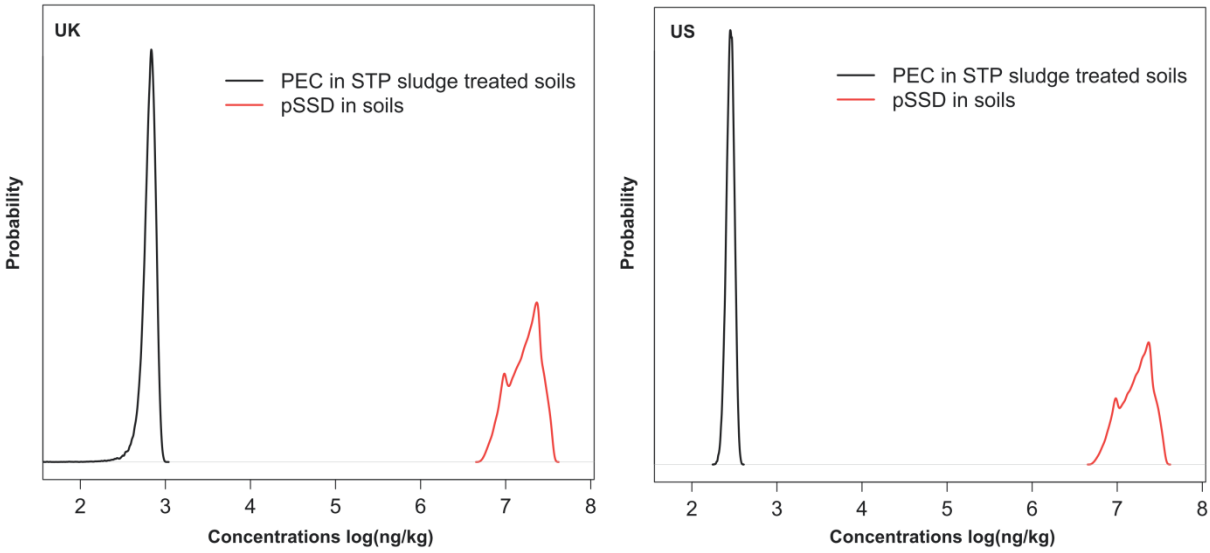
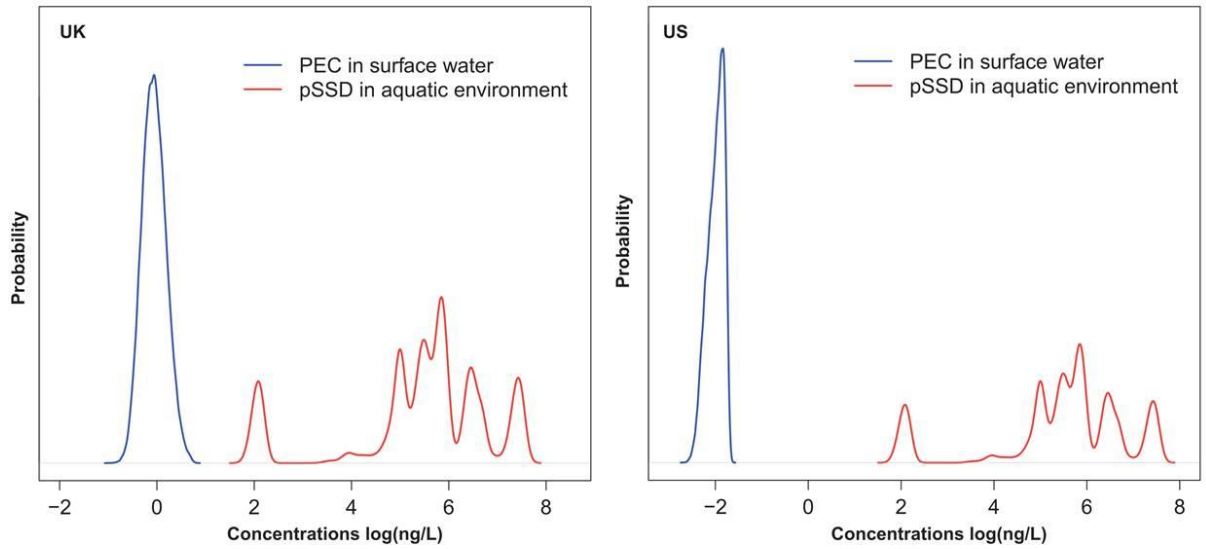


Figure A3 PEC vs pSSD in soil with lethal endpoints: The graphs don't overlap and hence could indicate no risk from Au-NP.



PEC vs pSSD for water using sublethal endpoints: The graphs don't overlap and hence could indicate no risk from Au-NP.

Figure A4 PEC vs pSSD in water with sublethal end points.



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