Innovation, Technology, and Knowledge Management

Finbarr Murphy
Eamonn M. McAlea
Martin Mullins *Editors*

Managing Risk in Nanotechnology

Topics in Governance, Assurance and Transfer

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Innovation, Technology, and Knowledge Management

Series Editor:
Elias G. Carayannis
School of Business
George Washington University
Washington, DC, USA

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Editors
Finbarr Murphy
Department of Accounting and Finance
University of Limerick
Limerick, Ireland

Eamonn M. McAlea
University of Limerick
Limerick, Ireland

Martin Mullins
Department of Accounting and Finance
University of Limerick
Limerick, Ireland

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Series Foreword

The Springer book series *Innovation*, *Technology*, *and Knowledge Management* was launched in March 2008 as a forum and intellectual, scholarly "podium" for global/local, transdisciplinary, transsectoral, public–private, and leading/"bleeding" edge ideas, theories, and perspectives on these topics.

The book series is accompanied by the Springer *Journal of the Knowledge Economy*, which was launched in 2009 with the same editorial leadership.

The series showcases provocative views that diverge from the current "conventional wisdom" that are properly grounded in theory and practice, and that consider the concepts of ***robust competitiveness***,[1] ***sustainable entrepreneurship***,[2] and ***democratic capitalism***,[3] central to its philosophy and objectives. More specifically, the aim of this series is to highlight emerging research and practice at the dynamic intersection of these fields, where individuals, organizations, industries, regions, and nations are harnessing creativity and invention to achieve and sustain growth.

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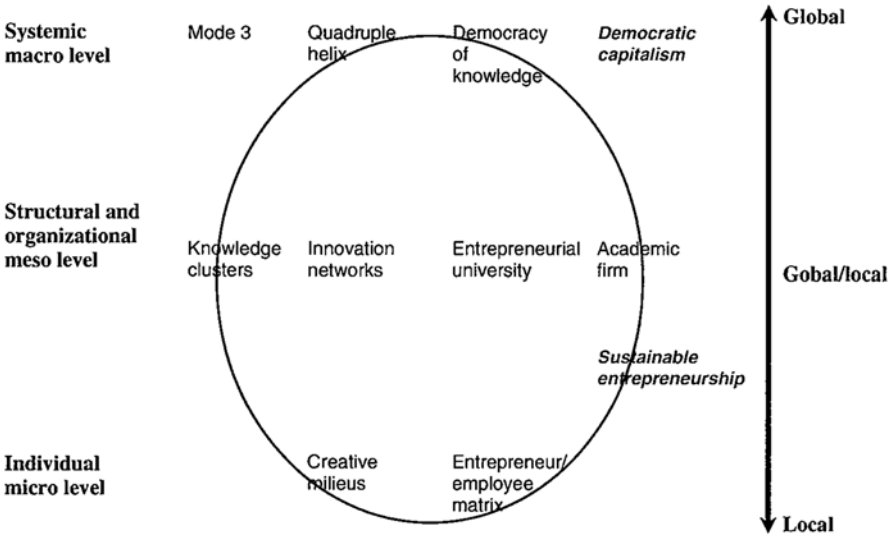
[1] We define *sustainable entrepreneurship* as the creation of viable, profitable, and scalable firms. Such firms engender the formation of self-replicating and mutually enhancing innovation networks and knowledge clusters (innovation ecosystems), leading toward robust competitiveness (E.G. Carayannis, *International Journal of Innovation and Regional Development* 1(3), 235–254, 2009).

[2] We understand *robust competitiveness* to be a state of economic being and becoming that avails systematic and defensible "unfair advantages" to the entities that are part of the economy. Such competitiveness is built on mutually complementary and reinforcing low-, medium-, and high-technology and public and private sector entities (government agencies, private firms, universities, and nongovernmental organizations) (E.G. Carayannis, *International Journal of Innovation and Regional Development* 1(3), 235–254, 2009).

[3] The concepts of *robust competitiveness and sustainable entrepreneurship* are pillars of a regime that we call "*democratic capitalism*" (as opposed to "popular or casino capitalism"), in which real opportunities for education and economic prosperity are available to all, especially—but not only—younger people. These are the direct derivatives of a collection of topdown policies as well as bottom-up initiatives (including strong research and development policies and funding, but going beyond these to include the development of innovation networks and knowledge clusters across regions and sectors) (E.G. Carayannis and A. Kaloudis, *Japan Economic Currents*, p. 6–10 January 2009).

Books that are part of the series explore the impact of innovation at the "macro" (economies, markets), "meso" (industries, firms), and "micro" levels (teams, individuals), drawing from such related disciplines as finance, organizational psychology, research and development, science policy, information systems, and strategy, with the underlying theme that for innovation to be useful it must involve the sharing and application of knowledge.

Some of the key anchoring concepts of the series are outlined in the figure below and the definitions that follow (all definitions are from E.G. Carayannis and D.F.J. Campbell, *International Journal of Technology Management*, 46, 3–4, 2009).



Conceptual profile of the series *Innovation*, *Technology*, and *Knowledge Management*

- The "Mode 3" Systems Approach for Knowledge Creation, Diffusion, and Use: "Mode 3" is a multilateral, multinodal, multimodal, and multilevel systems approach to the conceptualization, design, and management of real and virtual, "knowledge-stock" and "knowledge-flow," modalities that catalyze, accelerate, and support the creation, diffusion, sharing, absorption, and use of cospecialized knowledge assets. "Mode 3" is based on a system-theoretic perspective of socioeconomic, political, technological, and cultural trends and conditions that shape the coevolution of knowledge with the "knowledge-based and knowledge-driven, global/local economy and society."
- Quadruple Helix: Quadruple helix, in this context, means to add to the triple helix of government, university, and industry a "fourth helix" that we identify as the "media-based and culture-based public." This fourth helix associates with "media," "creative industries," "culture," "values," "life styles," "art," and perhaps also the notion of the "creative class."

- Innovation Networks: Innovation networks are real and virtual infrastructures and infratechnologies that serve to nurture creativity, trigger invention, and catalyze innovation in a public and/or private domain context (for instance, government–university–industry public–private research and technology development coopetitive partnerships).
- Knowledge Clusters: Knowledge clusters are agglomerations of cospecialized, mutually complementary, and reinforcing knowledge assets in the form of "knowledge stocks" and "knowledge flows" that exhibit self-organizing, learning-driven, dynamically adaptive competences, and trends in the context of an open systems perspective.
- Twenty-First Century Innovation Ecosystem: A twenty-first century innovation ecosystem is a multilevel, multimodal, multinodal, and multiagent system of systems. The constituent systems consist of innovation metanetworks (networks of innovation networks and knowledge clusters) and knowledge metaclusters (clusters of innovation networks and knowledge clusters) as building blocks and organized in a self-referential or chaotic fractal knowledge and innovation architecture,[4] which in turn constitute agglomerations of human, social, intellectual, and financial capital stocks and flows as well as cultural and technological artifacts and modalities, continually coevolving, cospecializing, and cooperating. These innovation networks and knowledge clusters also form, reform, and dissolve within diverse institutional, political, technological, and socioeconomic domains, including government, university, industry, and nongovernmental organizations and involving information and communication technologies, biotechnologies, advanced materials, nanotechnologies, and next-generation energy technologies.

Who is this book series published for? The book series addresses a diversity of audiences in different settings:

1. *Academic communities*: Academic communities worldwide represent a core group of readers. This follows from the theoretical/conceptual interest of the book series to influence academic discourses in the fields of knowledge, also carried by the claim of a certain saturation of academia with the current concepts and the postulate of a window of opportunity for new or at least additional concepts. Thus, it represents a key challenge for the series to exercise a certain impact on discourses in academia. In principle, all academic communities that are interested in knowledge (knowledge and innovation) could be tackled by the book series. The interdisciplinary (transdisciplinary) nature of the book series underscores that the scope of the book series is not limited a priori to a specific basket of disciplines. From a radical viewpoint, one could create the hypothesis that there is no discipline where knowledge is of no importance.
2. *Decision makers—private/academic entrepreneurs and public* (*governmental*, *subgovernmental*) actors: Two different groups of decision makers are being addressed simultaneously: (1) private entrepreneurs (firms, commercial firms,

[4] E.G. Carayannis, *Strategic Management of Technological Learning*, CRC Press, 2000.

academic firms) and academic entrepreneurs (universities), interested in optimizing knowledge management and in developing heterogeneously composed knowledge-based research networks; and (2) public (governmental, subgovernmental) actors that are interested in optimizing and further developing their policies and policy strategies that target knowledge and innovation. One purpose of public *knowledge and innovation policy* is to enhance the performance and competitiveness of advanced economies.

3. *Decision makers in general*: Decision makers are systematically being supplied with crucial information, for how to optimize knowledge-referring and knowledge-enhancing decision-making. The nature of this "crucial information" is conceptual as well as empirical (case-study-based). Empirical information highlights practical examples and points toward practical solutions (perhaps remedies); conceptual information offers the advantage of further driving and further-carrying tools of understanding. Different groups of addressed decision makers could be decision makers in private firms and multinational corporations, responsible for the knowledge portfolio of companies; knowledge and knowledge management consultants; globalization experts, focusing on the internationalization of research and development, science and technology, and innovation; experts in university/business research networks; and political scientists, economists, and business professionals.
4. *Interested global readership*: Finally, the Springer book series addresses a whole global readership, composed of members who are generally interested in knowledge and innovation. The global readership could partially coincide with the communities as described above ("academic communities," "decision makers"), but could also refer to other constituencies and groups.

Elias G. Carayannis

Contents

Chapter 1
Introduction

Eamonn M. McAlea, Finbarr Murphy, and Martin Mullins

1.1 Background

No single regulatory or governance strategy may be called upon that would singularly fulfill the actualization and promise of nanotechnology(ies) in terms of its universal societal adoption and acceptance. Instead, the obstacles and pitfalls that could derail its potential are scattered and varied, appearing in a multitude of disparate problem spaces and disciplines. The latter underlies the motivation behind this book. Acknowledging the multidisciplined character of nanotechnology, this book examines the core disciplines where the most troublesome issues are expected to appear (Part 1) and accordingly focuses on viable remedies (Part 2).

From a governance perspective, nanotechnology has to be holistically assessed in terms of a wide spectrum of technologies under their respective risk-benefit paradigms. Nanotechnology does not refer to a single instance of a technology. Instead, it is an umbrella term loosely encompassing a diverse range of technologies that are characterized by either nanoscale structures or behaviors that occur at the nanoscale. Technologies that are now being realized at these dimensions and technologies that are, by definition, based on nano-level processes (for instance, chemical engineering) sometimes describe themselves in nanotechnology terms. A vastly expanded definition of "nanotechnology" has prompted specialists from a wide diversity of fields to adopt the nanotechnology brand. Examples of where technologies have rebranded themselves to avail of nanotechnology-focused funding initiatives include nanoelectronics, more commonly known in the past as submicron electronics. In material science, the descriptor *nanostructured* commonly refers to ultrafine-grained materials. Nanobiotechnology is synonymous with molecular biology and

E.M. McAlea (✉) • F. Murphy • M. Mullins
Department of Accounting and Finance, Kemmy Business School, University of Limerick, Limerick, Ireland
e-mail: Eamonn.McAlea@ul.ie

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genetic engineering. Submicron mechanical devices have been popularized as nanomachines. In nonspecialist literature, the terms "nanotechnology," "nanomaterials," and "nanomachines" are oftentimes used interchangeably. This ambiguity has created much confusion, especially when discussing issues such as risk and regulation in association with nanotechnology. Misconceptions about the exact nature of nanotechnology can lead to false perceptions regarding its risks or unfairly tarnish the reputations of unrelated fields that may have been vaguely affiliated with the nanotechnology trend at one time or another.

1.2 Nanotechnology as the Exploitation of Engineered Nanomaterials

It can be argued that many classes of nanotechnology are inherently safe such as nanoelectronics in which the nanocomponents are securely embedded in solid structures and substrates. For those more unprecedented forms of nanotechnology that are commercially available, namely, unbound engineered nanomaterials (ENMs), there is an acute lack of regulatory oversight and comprehensive risk analysis frameworks. This problem is not unique to ENMs. In general, emerging technologies typically evade risk assessment and regulation for considerable periods after they first appear (Salsburg & Heath, 1981). ENMs can be considered foundational to many, but not all, technologies that regard themselves as "nanotechnology" in much the same way that the transistor is foundational to integrated circuits or carbon is foundational to organic chemistry. Thus, a more practical descriptor for nanotechnology as it currently exists is a technology based on the exploitation of properties that are unique to ENMs. It is this perspective of nanotechnology which the contributors to this work have largely adhered to, albeit implicitly in most cases.

So far, the evidence that ENMs may ultimately prove detrimental to human well-being is at best suggestive. There are presently no agreed standards for physicochemical characterization of ENMs or for testing their health impacts at the cellular, organism, or environmental level. This has made it difficult for regulators to prescribe safe exposure levels and for insurers to price the cost of liability risks for companies that use or produce ENMs. For instance, some insurers have pointed to potential employer liability claims as they see parallels between fibrous ENMs and asbestos fibers in terms of their experience with asbestos litigation that for many insurers is still a costly overhead. In the absence of actual long-term risk assessments, perceived risk may come to dominate the debate about whether ENMs pose any long-term threat to human health. In many cases, it is difficult for nanotechnology proponents to counter the "doomsday" scenarios presented by its detractors since objective risk assessments do not exist. A tenacious media campaign could conceivably sway public opinion to demand curtailment of the production and use of some classes of ENMs and undermine the dependent downstream industrial sectors.

Nanomaterials (NMs) are particles or fibers that are typically less than 100 nm in at least one dimension. Those that are engineered for specific industrial and scientific purposes (ENMs) currently represent only a fraction of the total. The majority are either naturally occurring or of anthropogenic origin, with atmospheric levels that are typically between 20,000 and 1,000,000 particles per cubic centimeter (Hussein, Hämeri, Aalto, Paatero, & Kulmala, 2005). They are by-products of ubiquitous chemical and manufacturing processes and natural processes such as rock weathering and volcanic eruptions. In urban regions, approximately 70 % of all atmospheric particles are nanoparticles, commonly known in this context as ultrafine particles (UFPs).[1]

There are several historical instances of where nanomaterials have been used. Although they did not understand why their techniques worked, medieval alchemists added color to stained glass by adding gold and silver nanoparticles, a technique that is still in use today. It is now understood from quantum mechanics that different gold and silver nanoparticle sizes and shapes produce different colors. Cranberry glass is known for its distinct cranberry-like coloring that is the result of the presence of gold nanoparticles, and the recipe for the mix is thought to go back to Roman times. Renaissance artists added gold and silver nanoparticles (colloidal gold and silver) to their paints which had the effect of enhancing the vitality of the paint pigments.

Unlike its medieval and Renaissance origins, modern science understands why ENMs have unique properties that are not always present in their bulk forms. This is primarily the result of the development of quantum mechanics that describes the behavior of very small objects (Roduner, 2006). This understanding enables the design of ENMs with specified physical characteristics and functionalities. In addition to solids, liquids, gasses, and plasmas, ENMs essentially represent a new state of matter with their own unique behavior and features not present in the parent materials. The atomic force microscope (AFM) and the scanning tunneling microscope (STM), both invented in the 1980s, can both image and manipulate individual atoms and molecules, thus enabling ENMs to be constructed, manipulated, and imaged. However, the cheaper and therefore more common method for ENM production is through chemical synthesis and electrospinning methods that can produce ENMs in bulk quantities. ENMs used as building blocks allow for the construction of mechanical and electronic structures at the nanoscale.

The present consumer focus for ENMs is in the areas of food additives, cosmetics, material science, energy, electronics, and medicine. For instance, titanium dioxide ENMs are added to some sun tan lotions as they are effective at blocking ultraviolet radiation. Although potential side effects are not definitively established, there is some evidence to suggest that titanium dioxide nanoparticles can penetrate broken skin and skin lesions. Carbon nanotubes (CNTs), when combined with conventional manufacturing processes, such as the production of ceramics and plastics, can imbue these materials with added strength and durability. CNTs are being used as connectors in the latest generation of integrated

[1] Ultrafine particles are less than 100 nm by definition.

circuits. Similar to the way in which asbestos fibers behave, CNTs once inhaled could remain in the lungs. Their fibrous nature renders the normal lung clearance mechanisms inefficient, possibly leading to pulmonary complications. It has been estimated the average person in the industrialized world consumes trillions of nanoparticles per day as they are contained in many processed foods to modify texture and color (Mahler et al., 2012). The long-term health effects of this are not known. There is some evidence, although not definitive, that suggests a link between Crohn's disease and the accumulation of nanoparticles in the lining of the intestine (Reijnders, 2007). Carbon buckyballs (fullerenes) can be adapted to target malignant tumors. They "piggyback" anticancer drugs and deploy them at tumor sites. This has the advantage of leaving healthy cells intact. Potential side effects of this form of cancer therapy are not known. Nanomaterials below about 10 nm in diameter, once inhaled, can easily pass through the lungs directly to the circulation system and other organs. Evidence suggests that smaller nanoparticles may persist for significantly longer periods than large particles (Han et al., 2015). For instance, one study has shown that 30 nm ceria nanoparticles were found to reside for up to 90 days in rats (Yokel et al., 2012). Recent research shows that nanoparticles less than 100 nm in diameter can enter cells, those with diameters below 40 nm can enter the cell nucleus, and those that are smaller than 35 nm can pass through the blood-brain barrier and enter the brain (Dawson, Salvati, & Lynch, 2009). Scientists are calling for a holistic and comprehensive nanotechnology life cycle assessment (LCA) in order to better manage these uncertainties (Klopffer et al., 2007).

1.3 Book Layout

The book is divided into two parts: Part 1, comprising Chaps. 2–7, essentially maps out and describes the dominant problem spaces, while Part 2 mostly explores a number of risk management and assessment methodologies.

Chapter 2 conducts a detailed exploration for a robust working definition of nanotechnology in terms of the activities of a group of European-based companies that describe themselves either in terms of pure nanotechnology or as having a nanotechnology component to their main activity. Chapter 3 lays out general governance principles and challenges, setting out a road map for ongoing and future regulatory and governance innovations in the context of the realization of benefits and the assessment and management of risks while being cognitive of social and ethical impacts. Chapter 4 explores the social impacts of nanotechnologies within a social LCA paradigm. A series of indicators are proposed that are then used in a quantitative scheme to measure social impacts in terms of risk and benefits. The global market for nanotechnology implies a need for international governance frameworks. This is the subject of Chap. 5 which compares the state of nano-safety and regulatory research cooperation between Latin-American countries with that of Europe and the United States, noting that in the case of Latin America, progress

is good but fragmented and lacks international visibility. Chapter 6 explores the mismatch between educational aspects of nanotechnology at the secondary and university levels and the needs of industry. Here, a model curriculum is proposed to help close the gap. Besides the provision of a technical competency for industry, it is remarked that the latter would tend to inculcate in a citizenry a sharper sense of the positive and negative impacts of nanotechnology while at the same time providing an appropriate paradigm for governance and regulatory specialist to draft regulation that fosters rather than impedes nanotechnology's adoption; an informed citizenry is less likely to reject a potentially beneficial technology out of fear, itself rooted in a lack of knowledge. Governance and regulatory specialists with a solid working knowledge of nanotechnology might arguably be more resistant to media hype and political posturing and other influences that would otherwise negatively impact the legislative process. Chapter 7 examines the potential legal challenges that nanotechnology may have to confront in the near future. A case is made that legal definitions of injury will change in order to keep pace with technological developments while simultaneously redressing potential grievances that currently would not have voice in the courts.

Chapter 8 details the workings of an existing commodities exchange that specializes in ENM trading and market making. Here, it is emphasized the advantages that the exchange model should bring in terms of ENM standardization, quality control, and transparency via trade reporting and collaborative compliance that eases the compliance burden on individual small ENM producers. It is argued that imbuing the ENM market with the aforementioned attributes will positively impact regulation and governance and risk management and assessment efforts; risk assessment of nanomaterials is especially hampered by the large heterogeneity inherent in supposedly similar ENMs from different producers.

Chapters 9–11 delve into the more technical and scientific aspects of ENMs in the context of regulation and risk assessment: Chap. 9 brings attention to the inherent transient nature of ENMs. That pristine isolated ENMs, by virtue of their affinity for other materials to lower their surface energies, do not remain pristine for very long presents a difficult challenge for their characterizations throughout their life cycles. Among a number of suggested approaches to address this issue is for regulators to borrow from regulatory models for pesticides and medicine which accommodate the transient chemical nature of these groups due to the metabolic transformations they typically undergo over their life cycles. Chapter 10 explores state-of-the-art research for designing ENMs that are inherently safe without compromising their intended industrial functionalities. In a sense, the complete realization of such techniques represents a holy grail for ENM safety efforts as the need for external safety controls would significantly reduce. Chapter 11 proposes a Bayesian regression framework for accommodating the heterogeneity present in ENM characterizations, both in the physicochemical and in vitro toxicological domains. It is claimed that in principle such an approach should extract optimum information from seemingly noisy and ambiguous characterization data, thereby providing dependable ENM characterization inputs for higher risk models for regulation and risk assessment.

Chapter 12 describes a certifiable risk management system for companies that use or produce ENMs. The system is highly comprehensive in its design, taking a "top-down" holistic approach that encompasses the functions of risk analysis, risk assessment, risk reduction, risk control, risk monitoring, risk treatment, and legal and regulatory requirements.

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Part I
Regulatory, Social and Legal Challenges

Chapter 2
Nanomaterial and Nanotechnology Firms: A Typology

Anthony Carroll, Martin Mullins, Finbarr Murphy, Eamonn M. McAlea, and Karena Hester

Abstract Despite many studies opening with ambitious forecasts of a rapidly evolving nanomaterial and nanotechnology industry, the industry's boundaries are not clearly delineated. This is problematic because, in order for regulators to regulate, insurers to underwrite risk, and capital providers to provide funding, they must first have an in-depth knowledge of the industry and the idiosyncratic risks of its constituents. In this study, 517 nanomaterial and nanotechnology firms were identified, then systematically categorized under six emergent themes: Analysis, Bioanalysis, Drug Delivery, Electronics, Energy, and Materials. Such a system of categorization thus provides the starting point for a risk assessment, whereby those belonging to a certain category inherently pose similar levels of occupational, consumer, and environmental risk. Data was also gathered on each firm's size, ownership structure, and source of funding. The majority of firms were found to have less than 50 employees and were privately held, many of which were funded by venture capital. This too has implications for industry stakeholders as their actions could potentially have an adverse impact on what is evidently still a nascent, emerging industry.

2.1 Introduction

As with many novel emerging technologies, much hype surrounds the growth of the industry and this hype is accompanied by impressive growth projections. For instance, it has been reported that governments, corporations, and private investors (venture capitalists) invested $18.5 billion in nanotechnology in 2012, that revenues from nano-enabled products grew from $339 billion in 2010 to $731 billion in 2012, and that the global value of nano-enabled products, nano-intermediates, and

A. Carroll • M. Mullins • F. Murphy • E.M. McAlea (✉) • K. Hester
Department of Accounting and Finance, Kemmy Business School, University of Limerick, Limerick, Ireland
e-mail: Eamonn.McAlea@ul.ie

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nanomaterials will reach $4.4 trillion by 2018 (Lux, 2012). Such precise figures presuppose the existence of an identifiable nanotechnology sector or industry grouping. Yet the Industry Classification Benchmark (ICB) uses a system of ten industries, which are subdivided into 19 supersectors, 41 sectors, and 114 subsectors, none of which contain the term "nano" (ICB, 2014). Perhaps the reason for this is that nanomaterials and nanotechnologies are prevalent across such a wide range of industries. Indeed, Mills (2013) posits that the biggest reason for the unique situation facing nanotechnology is that in no other field are so many distinct and diverse players involved in the development of a science, from medicine, biology, electronics, optics, and physics to materials engineering. For example, carbon nanotubes (CNTs) can be incorporated into a diverse range of commercial products from rechargeable batteries, automotive parts, water filters, and thin film coatings to microelectronics (De Volder, Tawfick, Baughman, & Hart, 2013). Quantum dots can be incorporated into a similarly wide range of applications from bioimaging to photovoltaic solar cells (Nozik et al., 2010; Zhu et al., 2011).

Hence, a sober analysis of the industry is required, particularly as there are potential risks associated with nanomaterial and nanotechnology firms that may require regulatory action (USEPA, 2007). We present such an analysis taking the unique approach of categorizing nanomaterial and nanotechnology firms according to their operations. Beforehand, however, the definitions of nanomaterials and nanotechnology deserve consideration. The US Environmental Protection Agency (EPA) uses the catchall term "nanotechnology" for both, defined as research and technology development at the atomic, molecular, or macromolecular levels using a length scale of approximately 1–100 nm in any dimension; the creation and use of structures, devices, and systems that have novel properties and functions because of their small size; and the ability to control and manipulate matter on a small scale (USEPA, 2007). Using such a definition, three very different firms, for example, one involved in electron microscopy, another involved in the manufacture of CNTs, and another involved in nanofluidics, could all be considered as nanotechnology firms even though their operations, and hence operational risk, are markedly different. For the remainder of this study, *all* such firms are referred to as nanotechnology firms.

Six dominant themes emerged: Analysis, Bioanalysis, Drug Delivery, Electronics, Energy, and Materials. Furthermore, three stakeholder groups were identified, which could benefit from such an "industry" typology: (1) regulators, who are tasked with regulating both an ever-increasing variety of nanotechnology firms (Maynard, 2007) and an ever-increasing number of nanomaterials across their entire life cycle (Helland et al., 2007; Linkov & Seager, 2011), (2) insurers seeking to profile the relative risk of different nanotechnology firms (Mullins, Murphy, Baublyte, McAlea, & Tofail, 2013), and (3) capital providers seeking to assess the market before making funding decisions.

Additionally, data was gathered on each firm with respect to size and ownership structure in response to Beaudrie and Kandlikar (2011), among others, who anecdotally observe that, like other new technological domains, nanotechnology innovations are often made by small companies and start-ups. Consequently, overly burdensome regulations risk increasing such firms' costs, thereby dampening the

pace of innovation. There have been previous attempts at characterizing nanotechnology firms, according to firm size at least: Schmid and Riediker (2008), in examining the use of nanoparticles in Swiss industry, find that out of 48 Swiss firms interviewed, 18 (38 %) had less than 50 employees; Helland, Kastenholz, and Siegrist (2008), in examining industrial perceptions of the human health and environmental impact of nanomaterials, find that out of 40 Swiss and German firms surveyed, 25 (63 %) had less than 100 employees; Conti et al. (2008), in examining health and safety practices in the nanomaterial workplace, find that out of the 82 international firms surveyed, 52 (63 %) were working with nanomaterials at either small or pilot scales.

All of the aforementioned studies use either interviews or surveys to elicit data directly from nanotechnology firms themselves, which can be biased as a result of either nonrespondents or self-reporting (Armstrong & Overton, 1977; Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Notwithstanding such biases, it is apparent that nanotechnology firms are predominantly small- to medium-sized enterprises (SMEs), defined as having less than 250 employees (EC, 2005). Moreover, researchers have suggested that nanotechnology is experiencing a shift from research to commercialization (Shapira, Youtie, & Kay, 2011) and that small, private firms form the primary site of large-scale nanomaterial use and production (Engeman et al., 2012). As an indication of how important a consideration the size profile of nanotechnology firms should be to regulators, Engeman et al. (2012), in examining international nanomaterial firms' risk perceptions and safety practices, find that these firms expressed a strong preference for autonomy from regulatory agencies, believing themselves to be better informed and sufficiently trustworthy to self-regulate. Similarly, Helland et al. (2007) find that smaller firms identified cost concerns as the biggest barrier to health and safety management, which suggests that smaller firms could be affected most by regulation. Indeed, in assessing the response of California-based producers and importers of CNTs to a mandatory call-in of information about, for example, monitoring methods used in the workplace, Beaudrie and Kandlikar (2011) suggest that the reason that half of the six private firms involved provided very brief responses is that they were likely small, venture capital-based firms lacking the resources to respond fully to questions.

In order to overcome these potential biases in this study, a larger, more comprehensive sample of nanotechnology firms was constructed. Moreover, rather than depend on anecdotal assumptions or surveys with their associated biases, data was instead manually compiled from online resources on each firm's main line of operations (Analysis, Bioanalysis, Electronics, etc.), firm size (proxied by a number of employees), ownership structure (whether privately or publicly held), and the identity of their capital providers (venture capitalists or otherwise). To our knowledge, this is the first study to investigate the size profile of a large sample (>100 firms) of nanotechnology firms. Furthermore, to our knowledge, this is the only study to examine either the ownership structure or the sources of funding for nanotechnology firms, with a large sample or otherwise. It is hoped that this first, clear typology of nanomaterial and nanotechnology firms will assist regulators, insurers, and capital providers in accurately assessing the relative risks of such a diverse sector.

2.2 The Sample

The sample consists of 517 European firms identified primarily from the Nanowerk database (Nanowerk, 2014). Engeman et al. (2012); Meyer, Curran, and Gonzalez (2009); and Musee (2011), among others, similarly use the Nanowerk database in their respective studies. Nonetheless, there are few suitable alternatives: the NanoVIP worldwide database used by Conti et al. (2008) is now defunct; the Consumer Products Inventory compiled by the Project on Emerging Nanotechnologies (PEN, 2014), whose reliability, from an academic point of view at least, has been questioned by Berube, Searson, Morton, and Cummings (2010), includes all downstream users of nanomaterials, from cosmetics firms to automobile manufacturers. Such firms could hardly be classified as nanotechnology firms and are thus excluded from the Nanowerk database. Likewise, in this study, we constructed a sample of firms that could feasibly be described as nanotechnology firms, i.e., their main line of operations, and hence operational risk, is nanotechnology related. Large cosmetics or auto manufacturers that benefit from nanotechnologies downstream, but whose operations do not largely depend on its sustained growth, were not considered to be nanotechnology firms.

The Nanowerk database, itself, is not ideal. Beaudrie and Kandlikar (2011) concede that it does not provide a means to check the accuracy of information provided nor should it, as it is intended as a business-to-business directory rather than an academic resource. Consequently, each firm's official website was double-checked to confirm that the nature of their activities was indeed nanotechnology related. Each firm was then characterized into one of the six categories: Analysis, Bioanalysis, Drug Delivery, Electronics, Energy, and Materials. These categories arose from recurring themes in the operations of firms in the sample. Further details on our rationale are given in the following section. Each firm was also classified as either publicly or privately held. Furthermore, if any of the privately held firms disclosed the identity of the venture capitalists that provide financing, this was recorded. Lastly, a proxy for firm size was sought. As we subsequently show, the majority of nanotechnology firms are privately held. As such, they are under no obligation to publish quarterly or annual financial results. Hence, in the absence of data on the more traditional measures of firm size (market capitalization, total revenues, or total assets), data was gathered on the number of employees in each firm. This information was most often contained in downloadable company brochures or the "About us" or "Meet the team" sections of the firms' websites.

2.3 Findings

Before presenting summary statistics, it is necessary to outline the criteria used for categorizing nanotechnology firms. Each firm's main line of operations was deciphered from their official websites and promotional literature. If not directly found

on a firm's home page, this information can usually be found in the "What we do," "Products," "Solutions," or "Applications" pages. Hence, for each firm in the sample, a single paragraph description (approximately 50 words) of their activities was recorded. Then, using a relational database management system (MySQL), the entire sample was examined for emergent themes and similar firms were grouped together. From this, each firm was given a short, one-line description (one to five words), from which they could then be characterized into six categories. Accordingly, there was no preconceived idea of how many categories there would be. Data was gathered between September and December 2014.

Table 2.1 provides a summary of the short, one-line descriptions of the firms in each category. It serves to highlight the diversity, not only within the sample but also within each category. The Analysis firms' activities predominantly include the various types of microscopy and spectroscopy. It is important to note that the activities are not mutually exclusive. For example, some firms' activities include both scanning electron microscopy (SEM) *and* transmission electron microscopy (TEM). Similarly, some firms active in nanopositioning are also active in the field of spectroscopy. As such, if a firm performs one or more of the activities listed in column 1, it is categorized as an Analysis firm.

Analysis firms are distinguishable from Bioanalysis firms because many of the latter's activities specifically relate to nanoscale metrology in the life sciences sector, for example, various types of assay development and fluidics that measure or manipulate cells rather than particles.

The Drug Delivery category includes firms who use nanotechnology and nanomaterials as a means to targeted drug delivery. For example, functionalization is one such method, whereby nanoparticles (or fullerenes, CNTs) can be conjugated with different biomaterials such as nucleic acids (DNA, RNA), enzymes, antibodies, carbohydrates, and peptides and delivered to specific areas of the body with the aid of, say, a magnetic field.

Electronics firms' activities include integrated circuit (IC), micro-electro-mechanical systems (MEMs) fabrication, and nano-electro-mechanical systems (NEMs) fabrication. This involves, among other processes, the deposition of thin film, nanomaterial layers onto a substrate (e.g., silicon wafers), onto which patterns are written using various types of lithography, the permutations of which make it impossible to discuss in appropriate detail here (Judy, 2001). Suffice to say that any firm involved at any stage in the production of ICs, MEMs, or NEMs is included under the Electronics heading. Furthermore, a separate Energy category was created because a sizable number of firms devote their operations exclusively to energy storage (photovoltaic cells, battery cells, supercapacitors), albeit using similar processes to Electronics firms.

Lastly, firms that manufacture nanomaterials were categorized under the Materials heading. These include the production and supply of nanoparticles, nanofibers, CNTs, fullerenes, quantum dots, and graphene. This category also includes firms who produce and then supply custom nanomaterials for specific applications, for example, nanofibers that can be used for filtration applications, nanoparticles for catalytic converters, CNTs for mechanical reinforcement of polymers and

Table 2.1 Categorization of nanotechnology firms

Analysis	Bioanalysis	Drug delivery	Electronics	Energy	Materials
3D holography	Assay development	Antibody-derived therapeutic proteins	Carbon nano tube transistors	Graphene supercapacitors	Advanced materials for adhesion promotion
3D tomography	Chemical separation assays	Biocompatible gold nanoparticles	CMOS technologies	Organic solar films	Alumina nanofibers
Cantilever sensors	Fluorescent and bioluminescent dye assays	High-hydrophilic nanoparticles	Conductive nano-scale carbon	Photovoltaic panels	Aluminium nanoparticles
Confocal 3D measurement systems	Immunoconjugates and immunoassays	In vivo magnetofection	Atomic layer deposition	Silicon based battery anodes	Binding agents for polymers
Dimensional metrology	Magneto-sensor assays	Magnetic hyperthermia	Atomic vapour deposition		Carbon nano tubes (CNTs)
Kelvin probe systems	Nucleic acid assays	Nano-sized drug delivery pumps	Chemical vapour deposition		Catalysts for particulate filtration
Magnetic field sensors	Resonance light scattering assays	Nanoparticulate encapsulation technology	Expitaxial layer deposition		Catalytic compounds for gas sensors and bio-sensors
Metallography	Biochips	Signal transduction	Plasma enhanced atomic layer deposition		Catalytic converters for the auto industry
Microarray products	Biomaterial testing	DNA transfection	Pulsed plasma deposition		Cellular metal for industrial strength applications
Atomic force microscopy	Bioreactors for cell cultures	Femtosecond laser transfection	Thin film deposition		Chemicals for paper/pulp
Ion-induced electron emission microscopy	Biosensors through surface plasmon resonance (SPR)		Dry processing for IC devices		CNTs for electronic packaging
Photoemisson electron microscopy	Cell imaging		Electron grafting		Diamond tools
Rapid probe microscopy	DNA sequencing		Electronic ink		Elastomers

Scanning electron microscopy	Genomics		Epitaxial synthesis of advanced nanowire structures		Ferrofluids
Scanning hall probe microscopy	Lab-on-a-chip		Flexible electronics		Filters for air purification
Scanning ion conductance microscopy	Magnetic separation		Focused ion beam nanofabrication		Fullerenes
Scanning probe microscopy	Micro- and nano-fluidics		Hydrophobic electronic coatings		Functionalized graphene
Transmission electron microscopy	Nucleic acid purification kits		Electron beam lithography		Glass coatings
Nano-forceps	Oligonucleotides		Extreme UV lithography		Glass polarizers
Nanoparticle counters and sizers	Opthalmic metrology		Ion beam lithography		Glass to metal seals
Nanopositioning systems	Pharma-toxicological research		Maskless lithography		Graphene
Piezoelectric actuators	Picodroplet technology		Nanolithography		Iron nanoparticles
Piezoelectric sensors	Proteomics		UV nanoimprint lithography		Magnetic and fluorescent nanoparticles
Piezoelectric transducers	Thermophoresis		X-ray lithography		Magnetic and fluorescent quantum dots
Powder and single crystal X-ray diffraction			Micro-electromechanical systems (MEMS)		Magnetic nanobeads
Scanning profilometry			Microlithography and photomask printing		Mesoporous and microporous structures
Optical spectroscopy			Molecular beam epitaxy		Metal nanopowders

(continued)

Table 2.1 (continued)

Analysis	Bioanalysis	Drug delivery	Electronics	Energy	Materials
Atomic spectrometry			Nano-electromechanical systems (NEMS)		Multilayered graphene
Mass spectroscopy			Nanowire light-emitting diodes (nLEDs)		Nanofibers for air and liquid filtration
UV spectroscopy			OLEDs (organic LEDs)		Nanofibers for fine dust filtration applications
Photon cross correlation spectroscopy			PCB (printed circuit board) protective plasma surface finish		Nano-membranes
Fluorescence correlation spectroscopy			PLEDs (polymer LEDs)		Optical coatings for high quality optics
Emission spectroscopy			Quantum Information Processing and Communication		Quantums dots
Absorption spectroscopy			Thermoelectronics		Silica nanoparticles
X-ray fluorescence spectrometry			Thin film field effect transistors		Silver nanoparticles
Surface plasmon resonance			Wafer bonding		Thermoplastics
Tribology					Thin film surface coatings
Ultrasonic homogenizing					Titanium nanoparticles
					Tungsten carbide nanopowders
					Zinc nanoparticles
					Zirconia nanopowders

This table describes the operations of six categories of nanotechnology firms: Analysis, Bioanalysis, Drug Delivery, Electronics, Energy, and Materials

Table 2.2 Country-wise and category-wise breakdown of European nanotechnology firms

	Analysis	Bioanalysis	Drug delivery	Electronics	Energy	Materials	Total
Austria	3			2		4	9
Belgium	1		1			8	10
Bulgaria	1						1
Cyprus						1	1
Czech Republic	1		1	1		4	7
Denmark	5	1	1		2	4	13
Estonia	1				1	1	3
Finland	2			7		5	14
France	15	3	5	8		7	38
Germany	64	17	6	17	4	62	170
Greece						2	2
Hungary	2						2
Ireland	1	3				1	5
Italy	4	3		2		5	14
Lithuania		1					1
Netherlands	7	2		6		6	21
Norway				3	1	3	7
Poland						1	1
Portugal						2	2
Spain	7	2	4	2		16	31
Sweden	1	5	2	7	1	5	21
Switzerland	13	4	2	6	2	7	34
Turkey						6	6
UK	39	14	5	15	4	27	104
Total	167	55	27	76	15	177	517

composites, quantum dots for flexible electronic displays, or magnetic and fluorescent nanoparticles for medical applications. Essentially, in providing the raw materials, these nanomaterial manufacturers form the first life cycle stage common to product manufacturing (Mohan, Trump, Bates, Monica, & Linkov, 2012).

Table 2.2 provides a country-wise breakdown of nanotechnology firms in Europe. Germany has the largest proportion with 170 out of 517 firms (33 %). The UK has the next largest with 104 firms (20 %), followed by France with 38 (7 %), Switzerland with 34 (7 %), and Spain with 31 (6 %). Table 2.2 also provides a category-wise breakdown of the same firms. The "Materials" category, i.e., nanomaterial manufacturers, has the largest proportion with 177 out of 517 firms (34 %), followed by "Analysis" with 167 (32 %), "Electronics" with 76 (15 %), "Bioanalysis" with 55 (11 %), "Drug Delivery" with 27 (5 %), and "Energy" with 15 (3 %).

Of the 517 nanotechnology firms in the sample, data was available on both the number of employees (our proxy for firm size) and ownership structure for 398 firms. As Table 2.3 Panel A shows, 121 (30 %) of these firms have less than ten

Table 2.3 Relationship between firm size and ownership structure

Panel A. Full sample									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	120	136	53	16	5	8	1	1	340
Publicly held	1	5	11	6	5	11	4	15	58
Total	121	141	64	22	10	19	5	16	398
Panel B. Analysis firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	31	52	28	1	3	4	0	0	119
Publicly held	0	2	0	2	3	3	0	0	10
Total	31	54	28	3	6	7	0	0	129
Panel C. Bioanalysis firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	14	22	4	0	0	0	0	0	40
Publicly held	1	2	1	1	0	2	1	0	8
Total	15	24	5	1	0	2	1	0	48
Panel D. Drug delivery firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	10	6	1	1	0	0	0	0	18
Publicly held	0	0	3	2	0	0	0	0	5
Total	10	6	4	3	0	0	0	0	23
Panel E. Electronics firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	16	12	9	8	1	0	0	0	46
Publicly held	0	0	3	1	2	3	1	5	15
Total	16	12	12	9	3	3	1	5	61

Panel F. Energy firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	3	5	3	0	0	1	0	0	12
Publicly held	0	0	1	0	0	1	0	0	2
Total	3	5	4	0	0	2	0	0	14
Panel G. Materials firms									
# Employees	1–10	11–50	51–200	201–500	501–1000	1001–5000	5001–10,000	10,000+	Total
Privately held	46	39	7	6	1	4	1	1	105
Publicly held	0	1	4	0	0	1	2	10	18
Total	46	40	11	6	1	5	3	11	123

This table describes the relationship between firm size (proxied by the number of employees) and ownership structure (publicly or privately held)

employees. Of these, all but one is privately held. A further 141 firms (35 %) have between 11 and 50 employees, of which all but five are privately held. Hence, 262 (66 %) of the firms in the sample have less than 50 employees, with the overwhelming majority being privately held. This trend continues: as the number of employees grows, the fewer nanotechnology firms we find, but a higher proportion of those found are publicly held. Of the 21 firms (5 %) with 5000+ employees, 19 are publicly held. In the following section, each of the six categories of nanotechnology firms is analyzed in greater detail with respect to composition, size, and ownership structure.

2.3.1 Analysis Firms

As alluded to in the previous section, there is a degree of overlap in the sample insofar as some firms are involved in a multitude of activities. This is particularly the case for Analysis firms. Nevertheless, in this section, their most popular activities are recounted, mindful that some firms perform more than one. Of the 167 Analysis firms, at least 18 are involved in scanning probe microscopy (SPM), 14 in atomic force microscopy (AFM), ten in SEM, eight in X-ray diffraction (XRD), and six in TEM. However, many firms do not specify the analytical instrumentation they use, instead listing "metrology," "tomography," "particle sizing," "metallography," "nanopositioning," "nanoprobing," "thin film characterization," "profilometry," "tribology," and "rheometry," among others, as their main activity. These firms could use SPM, AFM, SEM, etc., but do not explicitly state so. It is therefore difficult, if not impossible, to state that the numbers of firms using SPM, AFM, SEM, etc., are absolute. Table 2.3 Panel B shows that, of the 167 Analysis firms in the sample, data on both the number of employees and ownership structure was available for 129 firms. 119 (92 %) of these are privately owned and 85 (66 %) have less than 50 employees.

2.3.2 Bioanalysis Firms

Of the 55 Bioanalysis firms, at least ten are involved in microfluidics, nanofluidics, or lab-on-a-chip. However, a further 11 firms are involved in assay development, which may or may not include microfluidics. Other firms list their activities more generally as "biomaterial testing," "pharma-toxicological testing," "diagnostics," "genomics," "proteomics," or "cell processing." Consequently, as with Analysis firms, we can be confident of classifying firms correctly as Bioanalysis firms, but it is difficult to make a more precise classification than that. Table 2.3 Panel C shows that, of the 55 Bioanalysis firms in the full sample, data on both the number of employees and ownership structure was available for 48. Forty (83 %) of these are privately owned and 39 (81 %) have less than 50 employees.

2.3.3 Drug Delivery Firms

The Drug Delivery category is relatively straightforward insofar as these firms' operations are readily distinguishable. All 27 firms are involved in the targeted delivery of nanomaterials that are conjugated with active pharmaceutical ingredients. The applications range from oncology to Alzheimer's research. Table 2.3 Panel D shows that, of the 23 firms on which data on the number of employees and ownership structure was available, 18 (78 %) are privately owned and 16 (70 %) have less than 50 employees.

2.3.4 Electronics Firms

Of the 76 Electronics firms, at least 19 are involved in some form of lithography. This includes, but is not restricted to, electron beam lithography, ion beam lithography, focused ion beam (FIB) lithography, extreme UV lithography, maskless lithography, nanoimprint lithography, and X-ray lithography. At least another 16 are involved in some form of thin film deposition, which includes atomic layer deposition (ALD), chemical vapor deposition (CVD), physical vapor deposition (PVD), pulsed plasma deposition (PPD), molecular beam epitaxy (MBE), and electron grafting. The rest of the 76 Electronics firms are more general in the descriptions of their operations, using terms like "nanoelectronics," "CMOS technologies," "nanooptoelectronics," "MEMs," or "NEMs." Such firms could employ bespoke methods or similar lithographic and deposition techniques to those above but not to disclose it. Table 2.3 Panel E shows that, of the 61 firms on which data on the number of employees and ownership structure was available, 46 (75 %) are privately owned and 28 (46 %) have less than 50 employees.

2.3.5 Energy Firms

The Energy category is comprised of 15 firms, 11 of which are involved in the production of photovoltaics or, equivalently, solar films, organic solar films, or solar cells. Two firms are involved in the production of "ultra" or "super" capacitors, with the remaining two firms producing silicon anode technology for next-generation, high-energy batteries. Table 2.3 Panel F shows that data on the number of employees and ownership structure was available for 14 firms. Twelve (86 %) of these are privately owned and eight (53 %) have less than 50 employees.

2.3.6 Materials Firms

Of the 177 Materials firms, at least 11 manufacture CNTs. At least 21 firms produce nanoparticles including, but not restricted to, alumina, iron, silver, zinc, silica, nickel, zirconium, gold, platinum, and tungsten carbide. A further 12 firms produce nanofibers and 19 firms produce graphene. However, many other firms produce nanomaterials for a predefined application but do not disclose exactly what type of nanomaterial they use. For example, 68 firms produce nanomaterials specifically for coating applications. These include coatings that are heat, corrosion, UV, and scratch resistant, adhesion promoting, easy to clean, anti-fingerprint, antibacterial, hydrophobic, waterproof, and conductive. However, a further 18 firms produce nanomaterial composites that can be used to reinforce polymers or improve electrical conductivity (e.g., for airplane wings) *as well as* for coating applications. At least 11 firms produce nanofibrous filters and membranes for air, water, or dust purification or filtration. However, a further nine firms produce catalysts that can also be used for particulate filtration. Consequently, as with the other five categories above, we can be confident of correctly classifying firms as Materials firms, but it is difficult to make a more precise classification than that. Table 2.3 Panel G shows that data on the number of employees and ownership structure was available for 123 firms. 105 (85 %) of these are privately owned and 86 (70 %) have less than 50 employees.

2.3.7 Nanotechnology and Venture Capital

One hundred and thirty unique venture capital funds were identified that invest in European nanotechnology firms. Importantly, this is just the number of venture capital funds that are disclosed by the investee firms. Many privately held nanotechnology firms disclose receipt of several rounds of financing but do not identify the source. Some disclose that they are seeking further financing, while others might be in receipt of venture capital financing but simply choose not to disclose it. Furthermore, many venture capital funds have several offices around the world so do not necessarily restrict investments to firms in their home country. As Table 2.4 Panel A illustrates, funds from outside Europe (Hong Kong, Singapore, the USA) are actively investing in European nanotechnology firms. Within Europe, 40 (31 %) of the funds identified are from the UK, with France, Sweden, and Germany having 18 (14 %), 16 (12 %), and 15 (12 %), respectively. While care should be taken in interpreting these findings due to aforementioned nondisclosure, these figures are consistent with reports placing these four countries in the top ten countries of the world based on private equity and venture capital investment (Bain&CompanyInc, 2014; PwiceWaterhouseCooper, 2008). Of the 130 funds identified, 103 (79 %) have invested in firms with less than 50 employees. Intuitively, it would appear that venture capital funding is predominantly obtained by nanotechnology SMEs.

Table 2.4 Nanotechnology and venture capital (VC) funds

Panel A					
# Employees	1–10	11–50	51–200	201–500	Total
Belgium		2			2
Denmark	1	6	1		8
Estonia		1			1
France		18			18
Germany	8	1	6		15
Hong Kong				1	1
Ireland	5				5
Norway	2				2
Poland	1				1
Singapore		1			1
Spain	6	2			8
Sweden	2	12	2		16
Switzerland	3				3
Turkey	1				1
UK	12	15	7	6	40
US		4		4	8
Total	41	62	16	11	130

Panel B							
Category	Analysis	Bioanalysis	Drug delivery	Electronics	Energy	Materials	Total
Belgium						2	2
Denmark	3		1	1	1	2	8
Estonia					1		1
France		9	6	2			17
Germany	3			3	5	5	16
Hong Kong				1			1
Ireland		5					5
Norway				1		1	2
Poland						1	1
Singapore			1				1
Spain	1	2	1	1		3	8
Sweden	2	5		6	3		16
Switzerland		3					3
Turkey						1	1
UK	6	11	4	15		4	40
US				8			8
Total	15	35	13	38	10	19	130

Panel A describes the relationship between VC funds and the size profile of the nanotechnology firms in which they invest. The first column lists the countries of origin of the VC funds. Columns 2–5 describe the number of VC funds investing in differently sized nanotechnology firms. Panel B describes the relationship between VC funds and the categories of nanotechnology firms in which they invest. The first column lists the countries of origin of the VC funds. Columns 2–7 describe the number of VC funds investing in the different categories of nanotechnology firms. Many of the VC funds identified invest in more than one of the sample firms. Additionally, many firms receive funding from more than one VC

Lastly, as Table 2.4 Panel B shows, 38 (29 %) funds invested in Electronics firms with a further 35 (27 %) investing in Bioanalysis firms. So, while Materials and Analysis firms make up the majority of the sample (Table 2.2), our findings suggest that venture capital funding is disproportionately drawn toward the former two categories. This is perhaps due to Electronics and Bioanalysis firms' relatively superior potential for value added. For instance, by virtue of Electronics firms being at a more advanced stage of the product life cycle than, say, Materials firms, they could pose a more attractive prospect for a near-term initial public offering (IPO) or private acquisition—the most attractive exit strategies for venture capitalists, in that order (Hellmann, 2006).

2.4 Discussion

There is growing evidence that nanotechnology firms are becoming recognized as a new industry or sector. As nanotechnology becomes even more pervasive in society, an ever-widening range of firms will therefore comprise the industry. The danger with such a situation is that certain stakeholder groups fail to recognize the myriad of activities within. Consequently, broad-ranging decisions by regulators, insurers, or capital providers could be of detriment. This study finds that European nanotechnology firms are operationally diverse but can be divided into at least six categories. This classification has significance because, from an operational risk point of view, each category should be perceived differently. It would be unfitting of regulators, for example, to generate blanket regulation on the production or use of quantum dots, titanium dioxide nanoparticles, CNTs, and various other nanomaterials. Rather, regulation needs to be nuanced to reflect the context in which these nanomaterials are being produced and used. As such, Table 2.5 presents a simplified risk assessment of each of the six categories from the point of view of occupational exposure, consumer exposure, and environmental exposure to hazardous materials.

Table 2.5 Risk assessment of nanotechnology firms

	Occupational	Consumer	Environmental
Analysis	Low	Nil	Nil
Bioanalysis	Mod	Nil	Nil
Drug delivery	Mod	High	Nil
Electronics	Low	Nil	Low
Energy	Low	Nil	Mod
Marterials	High	Mod	Low

This table provides a means to assess the relative risk of nanotechnology firms, from the point of view of exposure to potentially hazardous nanomaterials. Columns 2, 3, and 4 list each category's risk assessment in relation to occupational exposure, consumer exposure, and environmental exposure, respectively. "Nil" signifies no exposure, "Low" signifies low exposure, "Mod" signifies moderate exposure, and "High" signifies high exposure

As exhibited in Table 2.1, Analysis firms' primary activity is nanoscale metrology. Consequently, there is no risk that consumers could be exposed to hazardous materials. Similarly, as there is no product per se to dispose of, there is no risk of end-of-life, environmental exposure. Workers could be exposed to hazardous nanomaterials, but because Analysis firms are more instrumentation orientated than materials orientated, occupational exposure is likely to be quite low.

A key attribute of Table 2.5 is its malleability. Different stakeholders can add extra layers or drill down to a desired level of detail. For example, an insurer, looking to underwrite an Analysis firm for potential occupational exposure to hazardous materials, can see that its "initial" rating is low risk. Accordingly, the onus would be on the Analysis firm to prove that either relevant health and safety procedures are being adhered to or the type and quantity of nanomaterial being analyzed are sufficiently safe not to trigger a moderate- or high-risk rating. Similarly, a venture capitalist, looking to invest in an Analysis firm, can discard the potential of any consumer or environmental litigation and factor in only the low probability of worker litigation into investment decisions (Metrick & Yasuda, 2007)—from a venture capital point of view, the lower the risk, the lower the cost of venture capital and the higher a firm's valuation (Metrick & Yasuda, 2007).

Bioanalysis firms' primary activity is assay development. At the risk of generalizing what is, of itself, a diverse field, these firms may be deemed to have a moderate risk of occupational exposure due to their handling of biomaterials, while again posing little to no risk of consumer of environmental exposure.

Drug Delivery firms arguably have a similar level of risk of occupational exposure to Bioanalysis firms, if not lower due to the likely smaller quantities of nanomaterials being handled. However, if the "consumers" in this case were patients receiving treatment, the in vivo nature of the treatment would place Drug Delivery firms on a moderate- to high-risk rating. Stakeholder groups, for example, regulators, can reference an increasing body of literature to assess whether the nanomaterial or process being used is deserving of a lower rating and, hence, less onerous regulations (Ghaderi, Ramesh, & Seifalian, 2011; Karmali & Simberg, 2011; Prabhakar et al., 2013). As with both Analysis and Bioanalysis firms, there is little to no risk of environmental exposure with Drug Delivery firms.

As exhibited in Table 2.1, both Electronics and Energy firms' primary activities involve the manufacture of conductive, nanomaterial thin films, mainly in fabrication laboratories. Due to their likely tightly controlled manufacturing environments, occupational exposure would therefore be low. However, similar to Analysis firms, the onus would be on Electronics and Energy firms to prove that relevant safeguards are in place so as to not trigger a moderate- to high-risk rating. From the point of view of consumer exposure, nanomaterials are inevitably encased safely within consumer electronics, nullifying any risk. Likewise, while one could argue that safe handling guidelines for photovoltaics should be mandatory, there is little to no risk of consumer exposure. From the point of view of environmental exposure, electronics goods and photovoltaics pose low and moderate risks, respectively. For instance, consumer electronics could pose a risk if not disposed of responsibly at the end of life. Disposal of photovoltaics poses a higher risk due to their size and shape.

Insurers, for example, might therefore demand that an Energy firm distributes safe disposal guidelines to lower the risk of downstream litigation.

Materials firms would likely have the highest risk of occupational exposure, given the quantities of nanomaterials being handled relative to the other categories. This risk would ladder down as the eventual nano-enabled product or technology moves through its life cycle. Indeed, Helland et al. (2008) find that firms perceive themselves as clearly responsible for potential impacts to human health and environment in the research, development, and production stages, but this responsibility is gradually externalized to others throughout the product life cycle. However, the impact of downstream litigation could be felt both directly by product liability and indirectly through various avenues such as the loss of customers or reputational damage. Regulators could therefore compel Materials firms to internalize a share of downstream, adverse eventualities. Insurers and capital providers should also consider the impact of such eventualities in making underwriting and funding decisions, respectively.

Table 2.5 therefore provides an initial screen for evaluating the relative risk of nanotechnology firms from the perspective of regulators, insurers, and capital providers. As such, it could be used as a precursor to either a multi-criteria decision analysis (MCDA) for selecting nanomanufacturing alternatives (Subramanian, Semenzin, Hristozov, Marcomini, & Linkov, 2014) or a control banding approach for assessing the risk of different nanomaterials (Mullins et al., 2013; Zalk, Paik, & Swuste, 2009). For both the MCDA and the control banding approaches, knowledge of the type of firm using the nanomaterials, and hence its application, is of as much importance as the nanomaterial's attributes (surface chemistry, toxicity, carcinogenicity, mutagenicity, etc.).

Stakeholder groups must fundamentally consider the diverse typology of nanotechnology firms before making decisions with broad-reaching consequences. Furthermore, both the size and ownership structure of nanotechnology firms need to be primary considerations as, based on this study's evidence, the majority are privately held SMEs, many of which are funded by venture capital. Any lack of cognizance of these attributes by regulators, for example, risks stifling, continued innovation in a burgeoning industry. Likewise, both insurers and venture capitalists require the means to categorize the risks associated with particular activities. This study takes a methodological approach and, to our knowledge, is the first to categorize the nanotechnology industry by subsector and to assign broad risk classes to these subsectors. In doing so, this study provides a nuanced approach to a better understanding of the industry for regulators, insurers, and venture capitalists.

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Chapter 3
Governance of Nanotechnology: Context, Principles and Challenges

Steven M. Hankin and Sheona A.K. Read

3.1 Background

Progress towards harnessing and utilising the unique properties of current generation nanomaterials in new commercial and industrial applications is developing across a broad range of areas. Despite the massive expectations of nanotechnologies and growth in its application, there is a widespread belief that the hopes of this emerging technology will only fully materialise if its development takes place responsibly. The extensive development of nanotechnologies and nano-enabled products has been accompanied by considerable concern regarding the possible risks for the environment, health and safety (EHS) and broader ethical, legal and social issues (ELSIs) associated with its application and use (or misuse). Research conducted to date has shown the potential risks of nanotechnologies to be associated with a high degree of complexity and uncertainty, with no clear-cut cause-and-effect relationships. As such, understanding and managing the EHS and ELSI implications of this emerging technology is considered to represent a global and trans-boundary task and may require a novel multidimensional approach to risk assessment and risk management within a governance framework (Mantovani, Porcari, Meili, & Widmer, 2009).

Governance of nanotechnology is considered to be essential for realising economic growth and societal benefits, protecting public health and the environment and supporting global collaboration and progress (Roco, Harthorn, Guston, & Shapira, 2011). Given the scientific uncertainty associated with nanomaterials and its multidisciplinary and cross-cutting nature, nanotechnology is seen to present new challenges for governance. An effective and integrated governance approach

S.M. Hankin (✉) • S.A.K. Read
Institute of Occupational Medicine, Edinburgh, UK
e-mail: Steve.Hankin@iom-world.org

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must facilitate the realisation of *benefits*, whilst at the same time limiting the potential *risks* posed and remaining *sensitive* to public *concerns* and *changes* nanotechnologies may induce (Widmer, Meili, Mantovani, & Porcari, 2010).

Over the past decade, an international policy debate has emerged concerning appropriate mechanisms for the governance and regulation of nanotechnologies, with options ranging from requirements for an extension of existing regulatory frameworks, to 'softer' approaches such as voluntary schemes which may serve as a stopgap in the absence of proper risk assessment and classical regulatory monitoring. Overall though, much greater recognition and specificity is being given to EHS and ELSI aspects in governance considerations (Roco et al., 2011). It is widely foreseen that effective governance will require a high level of *cooperation*, *coordination* and *communication* between various institutions and stakeholders, including those who develop, manufacture, market and regulate nano-enabled products, as well as representatives of civil society, in order to promote a *proactive* and *adaptive* process (Widmer et al., 2010).

3.1.1 Responsible Development

The various initiatives concerning nanotechnology governance have culminated in a discourse on *responsible development*, a term often invoked by both government and industry (BASF, 2008; EC, 2008). Many different stakeholders have called for the responsible development of nanosciences and nanotechnologies, including the European Commission in its communication aimed towards a European strategy for nanotechnology (EC, 2004), where it was stated that 'Nanotechnology must be developed in a safe and responsible manner'.

'Responsible development' is often understood as extending beyond the traditional regulatory remit of anticipating and mitigating adverse impacts of the new technologies (Rip, 2009). The US National Research Council defined the responsible development of nanotechnology as follows (NRC, 2006):

> Responsible development of nanotechnology can be characterised as the balancing of efforts to maximise the technology's positive contributions and minimise its negative consequences. Thus, responsible development involves an examination both of applications and of potential implications. 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 or unintended consequences.

As such, responsible development offers an overarching framing of the governance of nanotechnology as fundamentally defined by its capacity to 'enable' research and development whilst balancing any negative consequences (Kearnes & Rip, 2009). According to Roco (2006), responsible development includes respect of life and ethics, support for improving quality of work and quality of life, sustainable development and overall respect to common resources and respect for human dignity and physical integrity and implies addressing societal concerns in both the short term and long term.

The discourse of responsible development also aims to operate internationally as a tool for the development of global consensus and strategy (Kearnes & Rip, 2009). This sentiment is embodied in the European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research (EC, 2008), which 'aims at contributing to proper coordination between Member States with a view to optimise synergies between all nanosciences and nanotechnologies research stakeholders at European and international level'. Kearnes and Rip (2009) suggest that the emerging discourse of responsible development and its embodiment in various codes represents an observable trend towards *reflexive*, *responsible* and *socially robust* governance, not only for nanotechnology but for emerging technology in general.

Studies of nanotechnology governance have typically focussed on the management of *risk* (see, e.g., IRGC, 2006; RCEP, 2008; Read, Kass, Sutcliffe, & Hankin, 2015; SCENIHR, 2006; The Royal Society & Royal Academy of Engineering, 2004). It is only relatively recently that experts have started to consider how the regulatory and promotion aspects of *innovation* might be better integrated, such that the direction of innovation becomes a more explicit feature of nanotechnology governance. Rafols, van Zwanenberg, Morgan, Nightingale and Smith (2011) highlighted three main conclusions which have repeatedly emerged from studies on the governance of nanotechnology:

1. 'Nanotechnology' is a palette of disparate technologies at the nanoscale and does not necessarily constitute a useful category to discuss regulation or technology governance.
2. There is major uncertainty and ignorance regarding the potential impacts of many manufactured nanomaterials on health and the environment.
3. Public concerns about both the potential risks and benefits posed by nanotechnologies are fundamentally about the purposes and interests behind innovation itself, and thus, policy should be concerned more broadly with innovation governance rather than risk governance.

3.1.2 Risk Governance

Risk governance is traditionally concerned with minimising the risks of harmful effects of nanotechnologies and is thus a 'back-end' response to innovation. Conversely, innovation governance is aimed at purposefully influencing technological choices, such that innovation is directed to socially agreed purposes, benefits and priorities, whether these are concerned with competiveness, health, well-being, social justice or environmental sustainability (Rafols et al., 2011). Responsible innovation, for example, may seek to nudge innovation away from trajectories that appear more likely to involve health and environmental risk and may also encourage avoidance of applications likely to promote public concern or undermine public acceptance. Rafols et al. (2011) specifically note that, if the scope is broadened from risk governance to innovation governance, it follows logically that a variety of

structuring institutions and sites need to be taken into account. Managing the interplay between these economic, political, scientific and civil society actors is an important component and challenge facing nanotechnology governance.

It can be seen from the progression of previous technology debates (e.g. genetically modified organisms (GMO) or nuclear energy) that numerous factors can inhibit the successful and sustainable development of a new technology, including late identification of EHS risks and missing or delayed inclusion of affected stakeholders (Widmer et al., 2010). Given the high level of interest in nanotechnologies and awareness of their potential risks amongst a broad range of stakeholders (including industry, government, academia, non-governmental organisations (NGOs), insurers, etc.), it is anticipated that a single major negative incident with a relation to nanotechnologies anywhere in the world has the potential to result in international reactions that might not remain restricted to the specific application it originated from (Widmer et al., 2010). It is therefore widely considered that public acceptance of a new technology is of utmost importance and a necessary prerequisite for the sustainable development of nanotechnologies. Thus, there have been calls for an *inclusive* governance approach, which facilitates stakeholder dialogue and stakeholder involvement. Establishing the boundaries between intolerable and tolerable risks as well as tolerable and acceptable risks is one of the most difficult tasks of governance. Stakeholders can play an important role in defining *acceptability* and *tolerability* of nanotechnologies by considering, amongst other factors, the *balance between risk and benefits* and the probability of extreme events (IRGC, 2006).

However, to understand and engage with this domain, a symmetrical approach may be needed which also attends to ways in which historically many risks have been systematically underplayed and ignored. In the UK, rejection of GMO and assurances of its safety by public scientists followed hard on the heels of the bovine spongiform encephalopathy (BSE) crisis where government had been reluctant to accept the risk to human health.

3.1.3 The Lag Between Governance and Innovation Development

Over the last 5 years or so, the development and commercialisation of nano-enabled products have occurred at an increasingly rapid pace. However, *knowledge about* '*nanotechnology-induced change'* with respect to potential EHS and ELSI, and the development of governance approaches for nanotechnologies, appears to be *lagging behind* (IRGC, 2006; Widmer et al., 2010). Linkov, Satterstrom, Monica, Hansen and Davis (2009) suggested that this is partly related to the inherent challenges in the research underpinning EHS data generation for nanomaterials (e.g. the need for new analytical approaches, the requirement of standards for testing and the adaptation of existing test methods for nanomaterials) but also that there is currently a lag between the time EHS data is available and the time when regulatory agencies use this data due: (i) to limited resources and (ii) the time required to potentially adapt risk assessment procedures for application to nanomaterials.

Uncertainty regarding whether the established governance systems are actually capable of adequately handling nanotechnologies and nano-enabled products within their frameworks has been highlighted (Widmer et al., 2010), and the policies and governance approaches across various countries largely remain fragmented. It is feared that nanotechnologies may cause EHS impacts before appropriate strategies based on quantitative risk assessment can be implemented. This may explain calls for implementation of a precautionary approach to the regulation and governance of nanotechnologies, with the view to avoid such a situation and also prevent public backlash. In any case, numerous stakeholders have emphasised the need for governance approaches for nanotechnologies to be *flexible*, *adaptable* and *dynamic* in light of the anticipated emergence of new knowledge and understanding regarding the potential EHS and ELSI impacts of nanotechnologies.

3.2 The Purpose and Principles of Nanotechnology Governance

Put simply, the purpose of governance is to anticipate and realise future developments, ensure safety and sustainability and generate trust and confidence. More specifically, one of the key purposes of governance is to act as a *safeguard* in society, serving as a protection to enable people to live their lives as free from harm, abuse and neglect as possible, and to have their health, well-being and human rights protected, and to provide *opportunity* for the improvement in health and well-being and ensure human rights and the environment are protected.

As governance involves the consideration of many different views, interests, values and norms, creating a complex structure, some general *principles* have to be set up to support a governance process with outcomes that are accepted or at least tolerated (Aven & Renn, 2010). In 2001, the European Commission published a White Paper (EC, 2001) describing a number of principles which underpin good governance, summarised as follows:

- *Openness*: The institutions responsible for governance should work in an open manner. They should actively communicate to the affected and interested parties and the stakeholders about their tasks, lay open their structures and make clear what and how decisions are taken. This includes the use of a language that is accessible and understandable for the general public, in order to improve the confidence in complex structures and decisions.
- *Participation*: Inclusion of stakeholders and the affected and interested public is set as a crucial task of governance. Acceptance in decisions about the handling of risks and confidence in the outcomes of governance processes depend on the inclusion of the interested parties throughout the whole governance chain.
- *Accountability*: Roles and responsibilities of the different actors in the governance process have to be made clear. From a European point of view, it has to be made clear which institutions carry out which tasks and where they have

responsibility on national and international level. Additionally, the specific tasks of the involved parties in the different stages of the governance process have to be made clear.

- *Effectiveness*: Governance policies have to be effective and timely and have to deliver what is needed on the basis of clear objectives, an evaluation of future impact and, where available, of past experience. Time and effort have to be treated as spare resources. Measures have to follow the principles of proportionality and appropriateness.
- *Coherence*: Policies and actions have to be coherent and easily understood. As the range and complexity of institutions is constantly growing, interdependencies between different sectors are increasing, regional and local authorities are increasingly involved in European policies, etc. These tendencies require political leadership, including a strong responsibility from institutional side, to guarantee consistent procedures within this complexity.
- *Proportionality and Subsidiarity*: Throughout the whole governance process, the choice of the level at which the action is taken (from European to local level) and the selection of the instruments used must be considered in the proportion to the objectives pursued.

These principles may be seen as idealistic, and compliance may be difficult to achieve in practice by those who carry out the different steps of the governance process. It is possible that some principles may be incompatible depending on the context in which they are applied. For example, the principle of 'openness' may be incompatible within the context of national security or proprietary rights governance. One of the challenges remaining is to define more pragmatic principles of good governance and to find a balance between taking measures which are proportionate to achievable objectives.

Prerequisites of good governance have been discussed in the literature, for example, by Aven and Renn (2010) who highlight the following considerations (with reference to IRGC, 2005; Paquet, 2001):

- It is important to make sure that the governance process is informed by the *best available knowledge and practice*.
- Institutions and organisations should be strengthened so that they are *empowered* and have the resources to *perform their tasks* in the most possible effective, efficient and fair manner.
- To make sure that the responsible institutions and organisations are able to act in that way, the following categories can be used to assess institutional capacity:
  - *Assets*: The knowledge bases and structural conditions for effective risk management build the assets of the governance institutions. This category includes rules, norms and regulations, available resources, competencies and knowledge and the level of organisational integration.
  - *Skills*: The quality of the institutional and human performance in exploring, anticipating and dealing with existing and emerging risks. They should enable

political, economic and civic actors to use effectively, and enhance the impact of, the described assets. Skills include flexibility, vision and directivity.
  - *Capabilities*: To build the framework, in which assets and skills can be exploited for the development and exploitation of successful policies of risk governance. Such capabilities include relations, networks and regimes.

- As a prerequisite for the building and functioning of these three categories, education and training have to be seen as fundamental resources for making use of the 'human capital' in order to handle global, emerging and systemic risks from new technologies.
- Such education and training measures should aim at a broad and multidisciplinary knowledge base instead of specialised in-depth knowledge, to be able to deal with the challenges of interdependencies, complexity and uncertainty and ambiguities.

Given the anticipated increase in complexity and significant technical and social uncertainties of future generations of nanotechnologies, many stakeholders have highlighted the need for a more *anticipatory* approach to nanotechnology governance. Numerous explanations of an anticipatory approach to governance have been put forward. Mendoza and Gonzalez (2002), for example, write that:

> Anticipatory governance […] means foretelling the future and preparing for it. It highlights the need for public organisations to have a long-range view of the future since the consequences of public policies and management decisions to future generations.

Barben, Fisher, Selin and Guston (2007) suggest that an anticipatory governance approach would enable stakeholders 'to collectively imagine, critique and thereby shape the issues presented by emerging technologies before they become rectified in particular ways' and summarise the requirements of an anticipatory governance approach into three components: *Foresight*, *Engagement* and *Integration*. Such an approach would act to *anticipate* and *realise future developments*, whilst also *identifying* and *reacting* to potential *risks* (Schaper-Rinkel, 2013). It may also help to identify how more useful, safer and societally beneficial applications can be developed and ensure successful integration of these new technologies into society. Related to the idea of anticipatory governance, Fedrigo and Senjen (2010) propose that a sustainable oversight system would need to include an 'early warning system', able to scan the horizon for potential concerns from a multi-scientific/societal perspective and allow systematic identification of areas of uncertainty. However, an anticipatory approach to governance faces significant challenges, most notably in terms of the necessary scale and support, organisation and engagement of stakeholders required (Karinen & Guston, 2010).

Ensuring the *safe* and *sustainable development* of nanotechnologies is widely agreed to be essential (Widmer et al., 2010), and an effective governance approach would ideally enable a safe, sustainable and society-focussed technology to be developed, without stifling innovation. The concepts of safety and sustainability are part of the principles underlying the European Code of Conduct for Responsible Nanosciences and Nanotechnologies (N&N) Research (EC, 2008) where it is stated

that 'N&N research activities should be safe, ethical and contribute to sustainable development and should not harm people, animals, plants or the environment'. Incorporating anticipation into a governance approach is strongly linked to the idea of being able to actively *guide innovation* with a view to avoiding societally unacceptable applications based on EHS or ethical grounds (Fedrigo & Senjen, 2010). Given that development is at a relatively early stage and that nanomaterials and nanotechnologies form part of increasingly more complex technological applications, Grobe (2010) highlighted that there exists the opportunity to give priority to the pursuit of innovations in fields that society considers desirable. The aim of exerting influence in this way is twofold (Grobe, 2010): (i) to steer the development of nanotechnologies in the direction of sustainable applications (e.g. reducing pressures on the environment and protecting resources) and (ii) to foster sustainability in the design of the technologies themselves. Governance strategies should seek to ensure effective oversight mechanisms are in place to foster the responsible development of sustainable nanotechnologies. This presents a challenge, however, given the aforementioned lag time between the generation of knowledge on the potential environmental, health and safety risks of nanomaterials and the pace of commercialisation of nano-enabled products. The resulting uncertainties are considered to be a major barrier to the sustainable and responsible development of nanotechnologies in the long term (Widmer et al., 2010).

Building *trust* and *confidence* amongst all stakeholders, including the public, is considered to be essential to gain *acceptance* and *ensure continued development* of a new technology (Kjølberg & Wickson, 2007; Mantovani et al., 2009; Paddock, 2010; Widmer et al., 2010). Trust and confidence cannot be created at will, however, and are the result of stakeholder perceptions deriving from an effective governance system. *Open* and *transparent discussion* and *public involvement* is acknowledged as a vital part of the governance process (Mantovani et al., 2009), with the purpose of:

- Increasing public awareness of nanotechnologies to support the building of opinions and positions based more on facts than on speculative claims and help to distinguish between perceived and real risks
- Increasing the level of interface and confidence amongst those developing and regulating nanotechnology and the public (citizens and consumers using the technology), with a view to defining proper, acceptable, trade-offs of risks and benefits

There are numerous different methods and initiatives underway to promote interaction between institutions and the public, but what is stressed by most initiatives is that risk communication strategies should involve *early stage* or *upstream public engagement* which allow two-way communication and give the public the opportunity to inform and shape the direction of research and development (Gavelin, Wilson, & Doubleday, 2007; Mantovani et al., 2009). Early discussion of the ethical and social dimensions of a technology is considered to generate and maintain trust in multiple directions and thus support the responsible development of nanotechnologies (Kjølberg & Wickson, 2007). It is important to note, however, that stakeholder engagement will not necessarily deliver consensus, as has been demonstrated with the GMO case.

3.3 Challenges Facing Nanotechnology Governance

Key challenges facing nanotechnology governance include, but are not limited to: the pace of nanotechnology development; the diversity of materials and applications; knowledge uncertainties specifically in relation to environment, health and safety (EHS) concerns and ethical, legal and social issues (ELSIs); the adequacy of existing procedures; international harmonisation of approaches; and awareness and perception of nanotechnology along the value chain (Bergeson, 2011, 2013; Fedrigo & Senjen, 2010; IRGC, 2006; Mantovani et al., 2009; Paddock, 2010; Roco, 2006; Satterstrom et al., 2009; Widmer et al., 2010).

The development and commercialisation of nanotechnologies and nano-enabled products are occurring at an increasingly rapid pace, and product innovation and manufacturing processes are likely to change frequently. Keeping pace with the new scientific discoveries, products, applications and commercialisation of nanomaterials and nanotechnologies poses a significant challenge to governance and creates difficulties for traditional approaches. Adding to this complexity is the fact that the nature of the current nanotechnology market and its likely innovation trajectories are, as yet, uncertain (Kearnes & Rip, 2009; Stokes, 2013). As highlighted previously, there is a risk of effective governance lagging behind and a need for a flexible, adaptable and dynamic approach with the ability to keep abreast of the constantly changing field.

The diversity of materials and potential applications in the field of nanotechnologies also poses a significant challenge to governance and regulation. Many conventional substances can be produced in the nanosize range (e.g. titanium dioxide, silver, gold, etc.), and novel nanomaterials (e.g. carbon nanotubes, fullerenes, etc.) are constantly being developed. There is thus the potential for a huge number of engineered nanomaterials, each with unique physico-chemical properties, and numerous applications spread over a wide range of fields (e.g. medicine, food, textiles, cosmetics, coatings, etc.). To add further complexity, the risk associated with these nanomaterials and related nano-enabled products is dependent upon a range of factors and will vary according to the nature of use, such that risk assessment will be required to consider the entire product life cycle. Mantovani et al. (2009) note that 'Existing regulations, for materials as well as applications, have difficulty to cope with this diversity of materials and applications', with IRGC (2007) highlighting that 'in no country is there a single regulatory structure that covers food, chemicals, personal care products, medical devices, water quality and so on'.

The diverse nature of nanomaterials and nano-enabled applications means they cut across a number of regulatory jurisdictions. As well as gaps and inconsistencies between different regulatory regimes, overlapping coverage may create competition for regulatory authorities. This has been seen in other domains, for example, in biomedical regulatory regimes, where their very particular standards and methods may be considered to 'trump' other governance regimes.

It is also widely agreed that one of the key characteristics of nanotechnologies that will make governance challenging is uncertainty in relation to their environment, health and safety (EHS) risks. In 2004, The Royal Society and Royal Academy

of Engineering (2004) published, at the request of the UK government, a major review of the opportunities and uncertainties of nanotechnologies. This was one of the first reports to highlight the potential risks to health and the environment that may arise from exposure to nanomaterials, especially nanoparticles, nanotubes and other nano-objects. Since then, a large number of national and international reviews carried out by government departments, industry associations, insurance organisations and researchers have considered nanoparticle risk issues (see, e.g., Aitken, Bassan, et al., 2011; Aitken, Chaudhry, Boxall, & Hull, 2006; Aitken, Hankin, et al., 2011; Hankin et al., 2008; Stone et al., 2010; Tran et al., 2008). These reviews have provided a remarkably consistent view about the nature and the potential risks of nanoparticles, which may be summarised as follows:

- There are potential risks to human health and the environment from the manufacture and use of nanoparticles.
- There is a lack of knowledge about what these potential risks might be and how to deal with them.
- The lack of data makes it difficult for manufacturers, suppliers and users to have effective risk management processes and to comply with their regulatory duties.
- All stakeholders (regulators, companies, etc.) need to start to address these potential risks.

Over the last few years, there has been a significant increase in research activity in the UK and internationally, intended to fill these gaps. This activity continues to expand and is continuing to develop the evidence base around what could be considered to be the key issues that contribute to the potential for nanomaterials to demonstrate enhanced toxicity compared with their bulk counterparts. Falkner and Jaspers (2012) highlight that emerging technologies such as nanotechnology:

> … are problematic because of the persistent uncertainty that surrounds potential risks. This uncertainty—about whether, in what form and to what extent risks exist—makes it difficult, and often impossible, to apply routine decision-making procedures for risk assessment and management. It impedes the application of standard scientific approaches and pushes regulatory decision-making into a more political direction. As a result, differences in national priorities, societal values, domestic interest group dynamics and institutional contexts often stand in the way of deeper international cooperation and regulatory harmonisation.

The uncertainty surrounding the potential health and environmental effects of nanomaterials, accompanied by research indicating that some risks do exist, has led various groups to suggest that an effective governance approach should include an appropriate precautionary element (Paddock, 2010).

Another area of uncertainty which poses a significant challenge to governance of nanotechnologies is in relation to the ELSIs. Mantovani et al. (2009) note that, whilst there is no formal statement regarding what is commonly included under the scope of the term ‘ELSI’, it is possible to identify the following key elements based on an elaboration from various sources:

- *Risk management and regulatory issues*. Based on the available knowledge about EHS implications and risk assessment of nanotechnology, how (and who) should

manage and regulate these risks, what is the right trade-off between benefits and risks and the correct level of precaution in using nanotechnologies
- *Public perception and public engagement*. How the public perceives/accepts applications and risks of nanotechnology; how to engage the public in a proactive debate on risks and benefits of nanotechnology; the role of scientific and not scientific communication; how these elements can influence the governance of nanotechnology development
- *Commercialisation and governance issues*. Impact of nanotechnology on economy, trade and employment at regional/national or local level; rights to access to information (also in relation with the use intellectual property rights); non-discrimination in the access to the benefits of nanotechnology, including the questions of a nanotechnology divide versus the promises for a beneficial use of nanotech in the developing world
- *Application specific issues* (mainly in relationship with nanomedicine and security applications). Ethical and philosophical issues related to nontherapeutic human enhancement and novel applications exploring man-machine interactions; increased personal responsibility related to novel diagnostic tools providing predictive information on diseases; protection of personal data, privacy, limits to personal freedom, confidentiality issues raised by novel surveillance, military and medical applications of nanotechnology; use/misuse of novel applications in criminal or terrorist activities

ELSI aspects of nanotechnologies are gaining an increasing importance in the agenda of government and authorities worldwide. A wide range of initiatives are underway which look to assess ELSI and stimulate a societal dialogue to inform political decision-making. There is now widespread agreement that it is better to address the long-term EHS and ELSI related to nanotechnologies early with broad stakeholder input, rather than having to adjust and respond to developments after they have occurred (Roco et al., 2011). However, achieving this in practice poses a significant challenge.

Regulators face uncertainties about the adequacy and applicability of existing risk assessment and management frameworks for nanomaterials and indeed about the overarching regulatory frameworks themselves (Falkner & Jaspers, 2012). Many experts acknowledge that performing risk assessment for engineered nanomaterials is a challenging task, not only due to significant scientific uncertainty and lack of data but also due to the need to take into account a wide range of different materials and their diverse properties and applications (EASAC-JRC, 2011). Scientists and regulators use many tools, experimental tests and computational models to assess hazards and risks of chemicals, but applying these procedures to new substances or materials, such as nanomaterials, may be difficult (Linkov et al., 2009). Regulators and policy-makers have responded to uncertainty regarding nanomaterials and nanotechnologies in different ways, as summarised by Falkner and Jaspers (2012):

> At one end of the spectrum, regulatory authorities have followed a "wait-and-see" approach and delayed regulatory action until sufficient knowledge about risks has become available. Their main focus tends to be on promoting scientific research to reduce uncertainty and

facilitate science-based decision-making. At the other end, authorities have regulated new technologies and their products despite persistent uncertainty, particularly when potential harm is likely to be severe or irreversible. In this precautionary response, regulators typically seek to promote further research but simultaneously take regulatory action to limit or prevent potential harm from uncertain risks.

Whether to adopt a "wait-and-see" or precautionary approach is an essentially political question, as it involves decision-making under uncertainty and the weighing up of sometimes competing values, such as technology promotion versus harm prevention. Scientific risk assessment criteria alone cannot guide regulators and policy-makers in such situations. Instead, a wider range of factors enter the calculations that inform regulatory action, from political ideology and societal risk attitudes to national or sectoral economic interests. Unsurprisingly, therefore, attempts to build global risk governance for emerging technologies tend to be politicized where scientific uncertainty is high.

Nevertheless, it is broadly agreed that 'dynamic developments need a dynamic framework' (Widmer et al., 2010), and regulators increasingly need to anticipate future technological developments and establish frameworks that offer flexibility and adaptability to ensure long-term effectiveness (Davies, 2009; Falkner & Jaspers, 2012).

A number of recent regulatory and policy reviews (see, e.g., Breggin, Falkner, Jaspers, Pendergrass, & Porter, 2009; IRGC, 2007) have highlighted the need for greater international cooperation and harmonisation in addressing the aforementioned uncertainties and developing effective regulatory and governance approaches for nanomaterials. Given the rapid globalisation and expansion of international trade in nanomaterials, demand for cooperation and harmonisation looks set to increase (Falkner & Jaspers, 2012). A wide range of proposals for filling the global governance gap have been made, from the use of soft law approaches (e.g. codes of conduct) (Bowman & Hodge, 2009) to the creation of an international framework convention (Abbott, Marchant, & Sylvester, 2006). However, current regulatory efforts are primarily focused at the national and regional level; the international dimensions of nanotechnology governance are still poorly understood and rarely feature on the international agenda (Falkner & Jaspers, 2012). The International Risk Governance Council (IRGC, 2007), whilst emphasising the importance of international collaboration and harmonisation of risk governance approaches for nanotechnology, recognises that the risk governance process cannot itself be standardised, which relates to the view that is no 'one-size-fits-all' prescription (Linkov et al., 2009). IRGC considers that governance approaches required for nanotechnologies will change as the technology develops, proposing that first-generation nanotechnologies at minimum require a precautionary approach (e.g. no data—no market, labelling, etc.) whilst later generations may require a shift to wholly new ways of sustainable, precaution-based technology assessment and management (IRGC, 2006).

Lastly, the challenge relating to awareness and perception of nanotechnologies has the potential to impact on governance, future investment and development of the nanotechnology industry (Engeman et al., 2012). Significant uncertainties remain about the public acceptance of nanotechnologies. This is a complex issue, influ-

enced by the role of NGOs and civil society groups (Kearnes & Rip, 2009), and it has been noted that characterisations of public perception often fail to capture the full range of issues or concerns (Macnaghten, Kearnes, & Wynne, 2005; Stokes, 2013). As highlighted by Paddock (2010), the risk of public rejection is particularly acute in situations where there is significant scientific uncertainty and where interest groups are likely to stake out strongly held positions at an early stage in the process of development. The prospect of unfounded public rejection suggests that there is a need for improved knowledge and good risk management and communication, such that governance tools must be identified that create public confidence in the industry. The issue of awareness and perception extends beyond the general public. Engeman et al. (2012) note that knowledge of both industry practices and leaders' perceptions of risk is vital for understanding how companies will act to control potential EHS risks, yet few studies have investigated risk perception from within the nanotechnology industry itself.

3.4 Conclusion

Three elements—risk, benefit and social and ethical impacts—are a focus in governance of emerging technologies, including nanotechnologies. These elements are increasingly being considered, with varying degrees of emphasis, in relation to other areas of innovation such as information and communications technology (ICT), and biotechnology, and are grouped under the term 'Responsible Research and Innovation'.

Key features of the governance landscape in which nanotechnology operates are presented in the subsections below which group features into four themes: *context*, *purpose*, *challenges* and *desired attributes*.

3.4.1 Context

There has been much concern regarding the social amplification of risk, created by the interplay between values-driven NGOs and headline-hungry media. The pace and direction of technological development is such that its potential risks and opportunities cannot be foreseen fully or accurately in advance of the development and deployment of that technology. Thus, governance often lags behind technological development—the challenge being to narrow this gap as far as possible whilst recognising that it cannot be eliminated altogether, even with the best foresight. The interplay between economic, political, scientific and civil society actors needs to be considered when looking beyond governmental or corporate actions in relation to governance. An external factor which is influential to the core risk governance framework is the social climate, which includes such key

variables as the willingness to accept risk, the relative tolerability or acceptability of different levels of risk from different sources in different contexts and the extent to which the governance of science and technology is trusted by numerous publics. Governance as an overarching theory does include mandatory regulation, but as a term it is generally used to mean voluntary oversight initiatives developed usually by non-statutory bodies, such as NGOs, businesses or private commercial groups, but sometimes also by governments. The reflexivity created by the increasing awareness of technology as a source of risk (as well as a source of the solution to the risk) creates a strong political and social demand for *accountability* and *openness*. Many individual technologies (e.g. biotechnology, nanotechnology, ICT, genetics, robotics, etc.) have developed bespoke governance frameworks as their technologies have evolved. However, it is increasingly recognised that many of the principles underpinning these frameworks are common to all technologies and a desire to harmonise this thinking across technologies has resulted, quite recently, in the consideration of cross-technology governance—often called 'Responsible Innovation'.

3.4.2 Purpose

The key characteristic of anticipative governance approaches is the application of predicting, forecasting and fore-sighting techniques to gain some *insight* into what might be *expected to happen*. Governance in the context of emerging technologies describes the ways in which the research, development, application and use of a technology are steered and controlled. It is also being used to promote the involvement of society in this process and explore not just health and safety issues, but the potential longer-term social impacts of a technology in use. One of the key purposes of governance is to act as a safeguard in society, serving as a protection to enable people to live their lives as free from harm, abuse and neglect as possible, and to have their health, well-being and human rights protected, and to provide opportunity for the improvement in health and well-being and ensure human rights are protected. It is hoped that early discussion and deliberation of the ethical and societal dimensions of a new technology will maintain and generate trust (e.g. between scientists, the public, consumers and political institutions) and that this, in turn, may lead to the acceptance and continued innovation and development of an emerging technology. In addition, there appears to be widespread belief in the capacity to direct technological development in a socially robust direction if ELSIs are considered and stakeholders are engaged early in the process. One of the key objectives for long-term governance is to 'elaborate and set up a protection system lasting as long as possible including mechanisms for allowing its evolution in the future according to prevailing circumstances and the expectations of future generations'.

3.4.3 Challenges

It is idealistic to assume that societies have developed the institutional and organisational capacity that is needed to perform the tasks described in the core governance framework, and a number of challenges have been highlighted. Given the inherent complexities and impossibility of creating reliable 'evidence of the future', it is inevitable that uncertainties, ambiguities and ignorance are fundamentally part of any approach to governing new technologies. Thus, the challenge is to characterise as far as possible the uncertainties faced whilst recognising the existence of 'unknown unknowns'—things we do not know that we don't know. A need exists to define pragmatic principles of good governance and to find a balance between taking measures which are proportionate to achievable objectives which can be implemented by people. The precautionary principle is often required to be examined on a case-by-case basis and cannot necessarily be applied holistically to all products and procedures placed on the market. There are no strict rules about the determination of acceptability of risks. The process of delineating and justifying a judgement about the tolerability or acceptability of a given risk is one of the most controversial parts of dealing with risks. Acceptability and tolerability of risks vary with time and cultural influences; what was once acceptable in the past may not be acceptable in the future, and what may be acceptable in one country may be totally unacceptable in another. The risk governance process cannot necessarily be standardised due to the wider scope and scale of governance issues and the numerous external factors impacting on it, including high levels of complexity and scientific uncertainties. *Norms* and *values* vary across *different contexts*, both between cultures and between issues. *Governing governance* needs to recognise the complex system and use some of the thinking behind complexity to understand how the system might work, its dynamics, patterns and possible modes of behaviour, leading to emergent properties. *Framing* is a critical challenge in developing approaches to governing new technologies. In essence, *framing* a technology is a way to *describe how a technology* is *perceived* and *discussed*. It is necessary not only to understand these framings but also who is using them and why they are doing so. In many instances, it is a narrowness of framing (either of the technology or its governance) that creates contention and conflict. A key challenge around governance is the extent to which the various rules and institutions of governance align with each other, thus either mitigating or exacerbating conflicts between jurisdictions and traditions. A key aspect of this 'boundary spanning' is the role that *harmonisation* plays in seeking to ensure *compatibility* and *interoperability* between different governance systems in different contexts and at different scales. Harmonisation between jurisdictions, whilst still seeking to maximise utility and retain alignment amongst individual actors within each level of governance, is a major challenge and hence why the wheels of multilevel governance run slow.

3.4.4 Desirable Attributes

It is important to make sure that the governance process is informed by the best available knowledge and practice. Techniques such as horizon scanning, wild-card analysis and scenario planning can be used as a way of appreciating what might happen as a way of testing and challenging current world views and assumptions to build a more flexible approach that takes account of uncertainty rather than trying always to reduce or eliminate it. As a prerequisite for the building and functioning of a governance process, education and training have to be seen as fundamental resources for making use of the 'human capital' in order to handle global, emerging and systemic risks from new technologies. Whilst countries, and often regions within a country, may be expected to employ different mechanisms for handling risk, a governance framework established an international level, and with an international context, can provide harmonisation and incentives for all countries to participate. Where there is a reluctance to adopt governance and its protective measures, possible solutions include the implementation of government standards and regulations coupled with third-party inspections and insurance. For these means to be effective along the entire value chain, communication of international standards and best practices to both developing and developed countries in a reasonable timeframe is crucial. Ideally, a comprehensive governance framework would strive for a combination of approaches that are procedural (i.e. rule based), reflexive (i.e. context based) and substantive (i.e. value based). Underpinning the main rationales of governance is the notion that none of these is any 'better' or 'worse' than any other and that they are not mutually exclusive. It is entirely appropriate to combine two or more rationales. Stakeholder engagement provides opportunities to further align the development of new technologies with societal needs and expectations, helping to drive long-term sustainability and stakeholder value. General methods that are commonly used include: technological forecasting, impact assessment, scenario analysis, interventions, consensus conferences and reflective studies. These are intended to reduce the costs of failure through anticipation and response to broad social goals. This then helps to close off inefficient routes to innovation and helps establish legitimacy, thus helping to pave the way to socially beneficial innovation where investors have greater confidence that they can gain a social licence to operate. Good governance and risk management decisions are ones that (CRARM, 1997; Van-Leeuwen & Vermeire, 2007):

- Address a clearly articulated problem in its public health and ecological context
- Emerge from a decision-making process that elicits the views of those affected by the decision, so that differing technical assessments, public values, knowledge and perceptions are considered
- Are based on a careful analysis of the weight of evidence that supports conclusions about a problem's potential risks to human health and the environment
- Are made after examining a range of regulatory and non-regulatory risk management options

- Reduce or eliminate risks in ways that:
  - Are based on the best available scientific, economic and other technical information
  - Account for their multisource, multimedia, multi-chemical and multirisk contexts
  - Are feasible, with benefits reasonably related to their costs
  - Give priority to preventing risks, not just controlling them
  - Use alternatives to command-and-control regulation, where applicable
  - Are sensitive to political, social, legal and cultural considerations
  - Include incentives for innovation, evaluation and research
  - Can be implemented effectively, expeditiously, flexibly and with stakeholder support
  - Can be shown to have a significant impact on the risks of concern
  - Can be revised and changed when significant new information becomes available, whilst avoiding 'paralysis by analysis'

Governance of emerging technologies strives for collaboration amongst a complex network of national and transnational actors/agents, including politicians, regulators, industry/ business, NGOs, media and the public. A crucial prerequisite for sustainable governance of emerging technologies is reliable information about the network of agents that are involved in or affected by technological innovation and diffusion. In addition, to support sustainable governance, there is a clear need to develop and nurture relationships between members of the actor network to ensure effective governance and risk communication along the *value chain*.

As a point of reference for the requirements of organisational governance, the British Standard (13500:2013) (BSI, 2013) provides clarity on the fundamental requirements for delivering effective governance of organisational performance, albeit not specifically for emerging technologies. This includes a self-assessment checklist which identifies the main steps that organisations should follow in implementing a governance system and principles, reproduced in Table 3.1 below.

Table 3.1 Self-assessment checklist for implementing a governance system and principles

System and component principles	Steps to implementation
Governance system	1. Implement governance to ensure that the organisation's purposes are fulfilled in alignment with its values
	2. Ensure all aspects of governance are integrated into a single holistic system
	3. Ensure the system is fully and accurately documented in founding documents and policies
	4. Ensure information is held in a central repository where documentation is provided to and from the accountability, direction and control components

(continued)

Table 3.1 (continued)

System and component principles	Steps to implementation
Governance accountability	1. Identify, consult with and report to relevant stakeholders
	2. Exhibit leadership
	3. Determine the organisation's best long-term interests
	4. Sustain clarity on organisation's purpose and values
	5. Establish an effective governance culture
	6. Establish governance competence and capacity
	7. Recognise and respond to governance performance
	8. Demonstrate sufficient transparency for accountability
Governance direction	1. Understand and ensure integrity of founding documentation
	2. Understand the organisation's context
	3. Establish and regularly review governance policies
	4. Ensure governance policies set standards for all aspects of organisational governance
	5. Establish governance role clarity
	6. Uphold good delegation principles
	7. Ensure ownership of policies is clear
Governance control	1. Set out and embed governance controls
	2. Ensure governance policies are monitored
	3. Ensure appropriate response to monitoring results

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Chapter 4
Integrating the Social Impacts into Risk Governance of Nanotechnology

Vrishali Subramanian, Elena Semenzin, Alex Zabeo, Danail Hristozov, Ineke Malsch, Peter Saling, Toon Van Harmelen, Tom Ligthart, and Antonio Marcomini

Abstract Literature on the risk governance of nanotechnology places significant emphasis on the potential social impacts of nano-enabled products. However, there is limited information on which social impacts are relevant for nano-enabled products, and a methodology to monitor them to support risk governance is lacking. This chapter proposes a quantitative methodology based on Social Life Cycle Assessment (s-LCA) and Multi-Criteria Decision Analysis (MCDA) to assess the social impacts of nano-enabled products through their life cycle. The s-LCA conceptual scheme (i.e. impacts and indicators for different stakeholders) is developed through an appraisal of literature on social impacts of products and Ethical, Legal and Social Impacts (ELSI) of nanotechnology, which is used to select suitable indicators in statistical databases. Five indicators associated with impacts of nano-enabled products, with two impacts in Worker category (professional training and non-fatal accidents) and three impacts in Community category (education, employment, research and development expenditure), were identified as relevant to compare nano-enabled products with similar functionality or nano-enabled product with their conventional counterpart. The indicators are organized within a conceptual scheme comprising benefits (education, employment and professional training) and costs (research and development expenditure and non-fatal accidents). A quantitative MCDA methodology is

V. Subramanian • E. Semenzin • A. Zabeo • D. Hristozov • A. Marcomini (✉)
Department of Environmental Sciences, Informatics and Statistics,
Ca' Foscari University of Venice, Venice, Italy
e-mail: marcom@unive.it

I. Malsch
Malsch TechnoValuation, Utrecht, The Netherlands

P. Saling
BASF SE, Ludwigshafen, Germany

T. Van Harmelen • T. Ligthart
TNO, Utrecht, The Netherlands

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proposed and applied to a case study according to benefit-cost conceptual scheme. The gaps to be addressed to expand the future development of methodologies to assess social impacts of nano-enabled products are discussed.

4.1 Introduction

The value of risk governance approaches in supporting early stage nanotechnology development has been recognized (Macnaghten, 2014; Roco, Harthorn, Guston, & Shapira, 2011; Subramanian et al., 2016). Risk governance includes "the totality of actors, rules, conventions, processes, and mechanisms concerned with how relevant risk information is collected, analysed and communicated and management decisions are taken" (Renn & Roco, 2006). The International Risk Governance Council (IRGC) framework focused on social impacts as key "deficits" to be addressed within present and emerging nanotechnology risk frames (IRGC, 2006). Some social deficits that need to be addressed include basic human needs (e.g. clean water, food), adequacy of social and legal infrastructure to absorb innovation, reorganization of labour sectors, human development impacts, political and security risks, education and training needs, equity and cognitive biases affecting risk governance (IRGC, 2006). Appropriate methodologies to assess the social impacts of nanotechnology are required to better balance benefits with risks and costs.

It is widely agreed that the entire life cycle of nano-enabled products is the appropriate unit of analysis to manage the Nanotechnology Environmental Health and Safety and Sustainability (Grieger et al., 2012; Shatkin, 2008; Som et al., 2010; Sweet & Strohm, 2006), and social impacts of nano-enabled products should also cover the entire life cycle. Social Life Cycle Assessment (s-LCA), an approach to assess social impacts associated with the product life cycle on specific stakeholders (UNEP, 2009), is suitable for this purpose. The s-LCA framework comprises two hierarchical levels: impacts and indicators. Social impacts can be defined as the consequences of social relations or interactions in the context of the life cycle of an activity and/or by preventive or reinforcing actions taken by stakeholders (UNEP, 2009). They may be caused by specific behaviours and socioeconomic processes and are related to human, social and cultural capitals (UNEP, 2009). SIA impact categories (and subcategories) are assessed using specific indicators, which are qualitative, semi-quantitative or quantitative variables associated with measurement units (UNEP, 2009). Semi-quantitative and qualitative approaches, while informative about stakeholder intentions and judgement on social impacts, do not provide an assessment of actual social impacts that have occurred through the value chain. Indeed, a key purpose of risk governance is to align perception of impacts with actual measured impacts (NNI, 2015), and thus there is the need to incorporate for both factors in the implementation of risk governance.

s-LCA for products has been implemented within SEEBALANCE sustainability assessment tool (Schmidt et al., 2004), Social Hotspots Database (SHDB) scoping

assessments (Benoit-Norris, Cavan, & Norris, 2012) and LICARA NanoSCAN tool (Som et al., 2014), the last one being the only existing nano-specific tool. However, LICARA NanoSCAN compares the manufacturer's perception on social impacts of nano-enabled products and conventional products through semi-quantitative indicators (Som et al., 2014), and therefore, there is interest in developing a quantitative methodology to assess the social impact of nano-enabled products in order to support risk governance, in particular by offering salient indicators to be used for monitoring and a basis for stakeholder dialogue.

This chapter proposes a quantitative s-LCA methodology to be included in a decision support system (DSS) currently under development in the EU FP7 Sustainable Nanotechnologies (SUN, http://www.sun-fp7.eu/) project. SUN adopts tools risk management and sustainability assessment of nano-enabled products within an overarching conceptual decision framework and software (SUNDS) (Subramanian et al., 2016). SUNDS comprises of two tiers that differ in terms of analytical complexity and data requirements. While in Tier 1 sustainability evaluation is performed by LICARA NanoSCAN, Tier 2 will be based on a quantitative multi-criteria approach that compares the benefits (or positive externalities) with risks and costs (or negative externalities) of a nano-enabled product or conventional product (in absolute terms) along the life cycle and through the value chain (Subramanian et al., 2016). The Tier 2 environmental pillar includes occupational, consumer and ecological risk assessment. The Tier 2 economic pillar includes microeconomic impacts, as well as insurance cost evaluation. The Tier 2 social pillar aims to assess social impacts through the life cycle and is the focus of this chapter.

Specifically, in order to develop a quantitative s-LCA with social impacts that are likely to differ between two nano-enabled products or a nano-enabled product with its conventional counterpart, the following methodology was adopted. First, a list of social impacts that can be used for sustainability evaluation of products was developed from available sources, e.g. guidelines pertaining to industry/manufacturing and product s-LCA tools (Sect. 4.2). In the next step, we summarized the key social impacts relevant to nanotechnology based on a review of nanotechnology Ethical, Legal and Social Implications (ELSI) literature (Sect. 4.3). Then, statistical databases were reviewed to find available indicators that could be classified under the social impacts. Indicators that were likely to differ for nano-enabled and conventional products were retained in the s-LCA framework (Sect. 4.3). Finally, a Multi-Criteria Decision Analysis (MCDA) methodology was developed to integrate the selected indicators into a final social impact score (Sect. 4.5) and illustrated with a hypothetical case study (Sect. 4.6). Steps required to further improve the social impacts of nanotechnology through its life cycle are discussed (Sect. 4.7)

4.2 Impacts for Social Life Cycle Assessment of Products

This section aims to compile a list of social impacts of products to be utilized within an s-LCA framework. Sources which comprise social impacts of products and manufacturing contexts include (a) guidelines like Corporate Social Responsibility

(CSR) guideline (ISO 26000, 2010), Global Reporting Initiative (GRI) Sustainability Reporting guidelines (GRI, 2014), REACH Socioeconomic Analysis (SEA) Authorization guideline (ECHA, 2011) and SEA dossiers found by searching the ECHA website (http://echa.europa.eu/), European Commissions' (EC) Impact Assessment (IA) guideline (EC, 2009) and United Nations Environmental Programme (UNEP)-Society for Environmental Toxicology and Chemistry (SETAC) s-LCA guidelines (UNEP, 2009) and (b) tools for sustainability assessment of products (Benoit-Norris et al., 2012; Schmidt et al., 2004; Som et al., 2014), also including reviews of sustainable development literature to build these tools (Schmidt et al., 2004).

The selection of social impacts from these sources entailed harmonization due to several reasons. Firstly, in nearly all sources, social impacts do not have an explicitly defined terminology and decisions needed to be made whether to combine or keep as separate similar sounding terms. In accordance with this approach, the broadest category was adopted to define the impact. For example, child labour and forced labour could be considered as part of the broader category of *human rights*. Secondly, social impacts in these sources are at different levels of analysis (i.e. impacts and indicators) and classified as being relevant to different stakeholders (e.g. gender equality may be relevant to both workers and community). Furthermore, there are varying classifications of which impacts count as "social"; environmental and economic impacts also have important social dimensions. Examples include toxicity potential and foreign direct investment. Indeed, a strict division between environmental, economic and social dimensions may not be possible in some cases. The Round table of Product Social Metrics (2014) harmonizes the definitions of social impacts and served as a valuable guide to resolving these issues in this chapter.

Two relevant sources containing indicators (instead of impacts) were chosen: GRI metrics and REACH SEA dossiers. They were mapped under existing social impacts (e.g. the number of jobs that can be classified under employment), or new social impact categories were defined for them (e.g. the impact of critical supply losses in the value chain).

The subsections below briefly summarize the sources for social impacts for products/manufacturing reported in Table 4.1 and explain the rationale behind the selection of the nine impacts for workers, consumers and community and the six impacts for value chain actors.

4.2.1 Corporate Social Responsibility Guidelines and Global Reporting Initiative Metrics

The key guideline available for CSR is ISO 26000 Guidance on Social Responsibility, which defines this concept as follows:

> "Responsibility of an organization for the impacts of its decisions and activities on society and the environment, through transparent and ethical behaviour that contributes to sustainable

Table 4.1 Social impacts for products through their life cycle

Stakeholder category	Social impact	Reference
Workers	Freedom of association and collective bargaining	UNEP (2009), Schmidt et al. (2004), RPSM (2014), and Benoit-Norris et al. (2012)
	Education and training	GRI (2014), Seear et al. (2009), EC (2009), Schmidt et al. (2004), and RPSM (2014)
	Human rights (including child labour and forced labour)	UNEP (2009), GRI (2014), RPSM (2014), and Benoit-Norris et al. (2012)
	Wages	UNEP (2009), SEA submissions (ECHA website, 2015), Benoit-Norris et al. (2012), Schmidt et al. (2004), and RPSM (2014)
	Working hours	UNEP (2009) and RPSM (2014)
	Equal opportunity/discrimination (including gender and other social distinctions)	UNEP (2009), GRI (2014), and RPSM (2014)
	Occupational health and safety (occupational diseases, accidents, etc.)	UNEP (2009), GRI (2014), EC (2009), SEA submissions (ECHA website), Schmidt et al. (2004), and RPSM (2014)
	Social benefits/social security	UNEP (2009), Schmidt et al. (2004), and RPSM (2014)
	Employment type and quality	GRI (2014), Seear et al.(2009), SEA submissions (ECHA website), and RPSM (2014)
Consumer	Consumer health and safety	UNEP (2009), EC (2009), Schmidt et al. (2004), and RPSM (2014)
	Quality of health and safety labelling and other information on other risks	Social-LCA-Project-Group (2010), GRI (2014), and Schmidt et al. (2004)
	Consumer satisfaction	GRI (2014), SEA submissions, Social-LCA-Project-Group (2010), Schmidt et al. (2004), and RPSM (2014)
	Complaints and feedback mechanism	UNEP (2009) and Social-LCA-Project-Group (2010)
	Legal issues and compliance	GRI (2014)
	Consumer privacy	UNEP (2009) and GRI (2014)
	Ethical issues	GRI (2014), Seear et al. (2009), and EC (2009)
	Transparent marketing communications	UNEP (2009) and Social-LCA-Project-Group (2010)
	End of life responsibility	UNEP (2009)

(continued)

Table 4.1 (continued)

Stakeholder category	Social impact	Reference
Community	Local engagement	UNEP (2009), EC (2009), and RPSM (2014)
	Employment	UNEP (2009), EC (2009), Schmidt et al. (2004), ECHA (2011), RPSM (2014), and Benoit-Norris et al. (2012)
	Technology development	UNEP (2009) and Som et al. (2014)
	Crime and security	UNEP (2009) and EC (2009)
	Access to material resources	UNEP (2009) and RPSM (2014)
	Social diversity	UNEP (2009), EC (2009), ECHA (2011), and Benoit-Norris et al. (2012)
	Delocalization and migration	UNEP (2009) and EC (2009)
	Contribution to sustainable development goals	Som et al. (2014)
	Cultural heritage	UNEP (2009) and EC (2009)
Value chain	Fair treatment	UNEP (2009) and GRI (2014)
	Human rights enforcement through the supply chain	Schmidt et al. (2004) and GRI (2014)
	Respect of intellectual property rights	UNEP (2009)
	Collective governance	GRI (2014)
	Non-EU country impacts	EC (2009)
	Impact of critical supply losses	SEA submissions (ECHA website)

The column "stakeholder category" lists one of four categories: worker, consumer, community and value chain actor. The column "social impact" specifies a word or phrase to describe the social impact chosen from our review. The column "reference" provides the sources where the social impact is mentioned, as described in Sects. 4.2.1–4.2.4

development, including health and the welfare of society; takes into account the expectations of stakeholders; is in compliance with applicable law and consistent with international norms of behaviour; and is integrated throughout the organization and practiced in its relationships" (ISO 26000, 2010).

While ISO 26000 elucidates the general principles of social responsibility in organizational culture and processes, GRI Sustainability Reporting guidelines provide practical principles and indicators for companies to report on their implementation of ISO 26000 (GRI, 2014). GRI comprises two categories of indicators: general standard disclosures and specific standard disclosures. Specific standard disclosures are divided into the three sustainability dimensions. The social category among these is further divided into four subcategories for which metrics are proposed: labour practices and decent work, human rights, society and product responsibility. Table 4.1 covers social specific standard disclosures (impacts) covered under GRI.

4.2.2 Social Life Cycle Assessment

The UNEP-SETAC report, "Guidelines for Social Life Cycle Assessment of Products" (UNEP, 2009), the key report which contains guidelines to implement an s-LCA, contains a list of social and socioeconomic impacts for five categories of stakeholders: workers, local community, society, consumers and value chain actors. This list of social impacts has been compiled from various sources including international conventions and treaties, CSR initiatives and social impact assessment literature. A related s-LCA document contains a list of social impacts for consumers with respect to health and safety impacts across the life cycle (Social-LCA-Project-Group, 2010). Table 4.1 covers these lists of social impacts covered by UNEP (2009).

4.2.3 Social Impact Assessment Methodologies

Social impacts associated with product life cycles are also available in some relevant regulatory and technical guidelines. We focused upon the social impacts mentioned in two sources: SEA Authorization guideline (ECHA, 2011) and six SEA Authorization dossiers available by searching the ECHA website (http://echa.europa.eu/) and European Commission's guidelines for Impact Assessment (EC, 2009). SEA is a route to REACH Authorization that requires companies to demonstrate that the benefits of using a specific chemical in a manufacturing context significantly outweigh the costs (ECHA, 2011). The REACH SEA Authorization guideline emphasizes two social impacts, employment and social inclusion, and refers to the EC Impact Assessment (IA) guideline for additional impacts (ECHA, 2011). EC's IA guideline lists potential social impacts related to the following areas:

employment, job quality, social inclusion, gender equality, culture, public health and safety, crime and security, impacts on non-European countries, family life and privacy, governance and education (EC, 2009). Social impacts in these guidelines are not explicitly associated with specific stakeholders. Table 4.1 covers social impacts covered by the SEA Authorization guideline and IA guideline and indicators from SEA Authorization dossiers.

4.2.4 Social Impacts from Existing Product Sustainability Assessment Tools

The authors are aware of three tools that focus upon the social sustainability of products: SEEBALANCE, LICARA NanoSCAN and SHDB. BASF developed the SEEBALANCE tool to assess the sustainability footprint of products.[1] The social indicators included in SEEBALANCE were developed based on a review of 60 sustainable development documents from which 3200 social impacts were extracted and further narrowed down to 33 impacts for the chemical manufacturing sector (Schmidt et al., 2004). SEEBALANCE social profile is divided by impacts on five "stakeholders": employees, international community, future generations, consumers and local and national community. LICARA NanoSCAN uses social indicators like technological breakthrough, qualified labour force and global health or food situation (Som et al., 2014). SHDB contains country- and sector-specific indicators for the themes of human rights, labour rights and decent work, governance and access to community services (Benoit-Norris et al., 2012). Table 4.1 covers social impacts and indicators used in these tools.

4.3 Salient Social Impacts for Nano-enabled Products

In addition to extracting social impacts of products, the literature on social impacts of nanotechnology was also reviewed in order to understand which impacts were most relevant for nano-enabled products. The ELSI literature on nanotechnology is largely focused on risk perception, governance and ethical implications of nanotechnology, and only few publications focus on specific social impacts of nano-enabled products. While this is a large literature, Seear, Peterson and Bowman (2009) provide a comprehensive review of social and economic impacts of nanotechnology. This literature provides insight on social impacts that could be relevant to nano-enabled products.

[1] https://www.basf.com/us/en/company/sustainability/management-and instruments/quantifying-sustainability/seebalance.html

Nano-enabled products may have features such as novel functionality, greater efficacy and lower cost over their conventional counterparts. These features may be linked to the downstream end of the value chain and result in greater consumer satisfaction and provide solutions to pressing global problems (e.g. as operationalized in the sustainable development goals (SDG)) (Cozzens, Cortes, Soumonni, & Woodson, 2013; Salamanca-Buentello et al., 2005; Som et al., 2014). These issues could be captured by the social impacts mentioned under stakeholder categories of consumer (consumer satisfaction, ethical issues), community (contribution to SDG) and value chain (human rights enforcement through the supply chain, non-EU country impacts) in Table 4.1.

Proactive communication with workers, supply chain and consumers about nanosafety and other risks are emphasized by voluntary codes of conduct for nanotechnology (e.g. Responsible Code of Conduct (NIA 2009) and BASF's Nanotechnology Code of Conduct (http://www.nanotechnology.basf.com/group/corporate/nanotechnology/en/microsites/nanotechnology/safety/code-of-conduct). Due to the significant uncertainty associated with nano-enabled products, it is important that the latest information on occupational, consumer and environmental risks of ENMs are shared within the value chain in a timely manner. Key forums to communicate risks may include (a) direct communication with downstream value chain on ENM hazard and exposure and (b) informative consumer labels about the ENM used in the product and its known risks. These issues could be captured by social impacts mentioned under stakeholder category of consumer (consumer health and safety, quality of health and safety labelling and other information on other risks, complaints and feedback mechanism and transparent marketing communications) in Table 4.1.

Moreover, there may be more or different educational needs and in-house technical expertise involved in producing nano-enabled products than conventional products, and this expertise may need to be updated frequently (Malsch, 2014). These issues could be captured by the social impacts mentioned under stakeholder category of worker (education and training) in Table 4.1.

Finally, loss of privacy and ethical implications may be associated with specific nanotechnology applications, e.g. nanomedicine (Kuiken, 2011; Spagnolo & Daloiso, 2009). These issues could be captured by the social impacts mentioned under stakeholder categories of consumer (ethical issues, consumer privacy, end of life responsibility), community (social diversity, cultural heritage, access to material resources, delocalization and migration) and value chain (respect for intellectual property rights) in Table 4.1.

This appraisal of the nanotechnology ELSI literature, while not specific to nano-enabled products, enables us to pinpoint some social impact categories that could be relevant to nano-enabled products (Sect. 4.4).

4.4 Selection of Quantitative Nano-specific Indicators

After compiling a list of social impacts for nano-enabled products (Table 4.1), the next step was to define indicators that could be used to build a quantitative methodology. One way to build a quantitative s-LCA methodology is to create scores for each indicator in which data at the level of production line or company level are normalized to the same data at region or country level (Schmidt et al., 2004). These scores are dimensionless and enable aggregation of social impacts with heterogeneous units to consider the overall social profile of the product. To find region- or country-level data that could be used to operationalize into indicators the social impacts listed in Table 4.1, the following sources were reviewed:

- OECD Science and Technology Indicators database (http://www.oecd-ilibrary.org/science-and-technology/data/oecd-science-technology-and-r-d-statistics/main-science-and-technology-indicators_data-00182-en)
- World Bank Database (http://databank.worldbank.org/data/databases.aspx)
- International Labour Organization (ILO) labour statistics database (http://www.ilo.org/inform/online-information-resources/databases/stats/lang--en/index.htm)
- United Nations Statistical Databases (http://unstats.un.org/unsd/databases.htm)
- World Health Organization (WHO) database (http://www.who.int/gho/publications/world_health_statistics/en/)
- Eurostat database (http://ec.europa.eu/eurostat/statistics-explained/index.php/Europe_in_figures_-_Eurostat_yearbook)
- Recent company annual reports containing data on social impacts

We found 16 indicators in these sources measured annually for countries for workers and community stakeholder categories. These indicators were further evaluated for their relevance to compare nano-enabled and conventional products using ELSI literature appraisal (Sect. 4.3) as well as expert judgement of the co-authors, narrowing down the list of indicators to 5:2 for worker and three for community stakeholders' categories. These findings are reported in Table 4.2.

4.5 MCDA Methodology

The five impacts chosen in Table 4.2 were then classified into benefits and costs and represented in the final s-LCA conceptual scheme in Fig. 4.1. Among the social impacts, training, employment and education were classified as benefits, while non-fatal accidents and R&D investment were classified as costs.

Subsequently, the s-LCA conceptual scheme was linked to an MCDA methodology to integrate the selected indicators into social impact scores for nano-enabled and conventional products. MCDA comprises a large class of methods for the evaluation of different alternatives based on relevant criteria (Giove, Brancia, Satterstrom, & Linkov, 2009). The methodology proposed in this chapter is based on the Multiple

Table 4.2 Social indicators relevant for nano-enabled products with statistical country-level data available to build quantitative methodology

S. no	Stakeholder category	Impact	Indicator	Indicator definition	Relevant to compare nano-enabled and conventional product?
1	Worker	Social benefits/social security	Social security	Four categories: health expenditure, public social protection expenditure, pension type, social protection coverage	No
					Not expected to be different for nano-enabled and conventional products
2	Worker	Social benefits/social security	Social protection and labour programmes	Total transfer amount received by the population participating in social insurance, social safety net, and unemployment benefits and active labour market programmes as a share of their total welfare	No
					Not expected to be different for nano-enabled and conventional products
3	Worker	Occupational health and safety (occupational diseases, accidents, etc.)	Accidents	Number of occupational injuries, fatal and non-fatal	Yes
					There are uncertain risks associated with nano-enabled products that may lead to accidents. Retain non-fatal injury impacts
4	Worker	Equal opportunity/ discrimination	Gender equality	Percentage of female share of employment in senior and middle management	No
				Percentage of gender wage gap by occupation	Not expected to be different for nano-enabled and conventional products
5	Worker	Freedom of association and collective bargaining	Collective bargaining	Collective bargaining coverage rate by economic activity as a percent of employees	No
					Not expected to be different for nano-enabled and conventional products
6	Worker	Freedom of association and collective bargaining	Trade union	Trade union density rate by economic activity—as a percent of employees	No
					Not expected to be different for nano-enabled and conventional products
7	Worker	Freedom of association and collective bargaining	Strikes and lockout	Days not worked due to strikes and lockout	No
					Not expected to be different for nano-enabled and conventional products
8	Worker	Education and training	Training	Data from company annual reports on total annual company expenditures for professional training	Yes
					Nanomanufacturing may require more trainings than conventional products

(continued)

Table 4.2 (continued)

S. no	Stakeholder category	Impact	Indicator	Indicator definition	Relevant to compare nano-enabled and conventional product?
9	Community	Education and training	Education	Number of labour force with tertiary education per thousand	Yes
					Nanomanufacturing may require specialized education as compared to conventional products
10	Community	Social diversity	Integration of handicapped persons	Employment rate of persons aged 15–64 who have long-standing health problem and/or a basic activity difficulty (such as sight, hearing, walking, communicating)	No
					Not expected to be different for nano-enabled and conventional products
11	Community	Social diversity	Social inclusion	Sum of persons who are at risk of poverty or severely materially deprived or living in households with very low work intensity	No
					Not expected to be different for nano-enabled and conventional products
12	Community	Technology development	Patent applications	Number of patent applications by residents and non-residents	No
					Social and human capital aspects represented by this indicator are covered by education and training
13	Community	Technology development	Researchers in R&D	Number of researchers in R&D per million people	No
					Social and human capital aspects represented by this indicator are covered by education and training
14	Community	Human rights (including child labour and forced labour)	Child labour	Percentage of children 5–14 years old involved in child labour	No
					This is an important consideration, but child labour data reporting tends to be poor (RPSM, 2014)
15	Community	Employment	Employment	Employment per thousand	Yes
					There may be differences in employment (less or more) between nano-enabled and conventional products
16	Community	Technology development	Research and development (R&D) expenditure	Business enterprise research and development in million euros for manufacturing and by business enterprise funding	Yes
					Represents potential technological development or initial investment

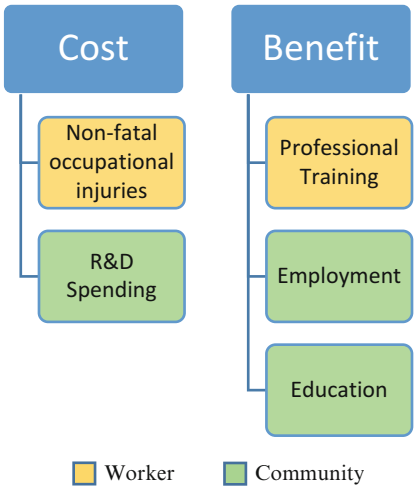

Fig. 4.1 s-LCA conceptual scheme to compare social impacts of nano-enabled product and conventional product

Attribute Value Theory (MAVT) technique under MCDA, in which a value function is specified for each criterion based on expert judgement (Giove et al., 2009). Value functions are used to normalize indicators from different domains into a final common domain representing their value according to expert's insights. The proposed value functions normalize indicators based on the proportion of this local impact to the national total figure. Normalized indicators are then aggregated into a final score by integrating user preferences using weighted sum.

The application of this MCDA methodology requires the following inputs for a specific case: (a) inputs for social indicators measured for a year in the relevant production line, (b) inputs for social indicators for the same time period at country level and (c) stakeholder preference for each social indicator within this context in terms of an importance weight within [0, 1]. These inputs are aggregated first into scores for each social indicator by multiplying weights to the contribution of the production line to the social indicator data measured at country level for the year. Social indicator scores are further aggregated in three ways:

1. Overall benefit and cost scores as per the conceptual scheme shown in Fig. 4.1 and overall net benefit score as the difference between benefit and cost scores.
2. Stakeholder-specific benefit and cost scores are calculated for stakeholder categories. For worker, benefit includes training and cost includes non-fatal accidents (shown in yellow in Fig. 4.1). For community, benefit includes employment and education and cost includes R&D expenditure (shown in green in Fig. 4.1). Stakeholder-specific net benefit score is the difference between benefit and cost scores for stakeholder of interest.
3. Stakeholder share for overall benefit and cost, i.e. stakeholder-specific benefit or cost scores expressed as a percentage of overall benefit or cost, respectively.

Social indicator scores, overall cost, benefit and net benefit scores, and stakeholder-specific cost and benefit and net benefit scores are graphically represented using a bar graph with benefit scores and cost scores represented to the left and right of the vertical axis, respectively. Stakeholder share of benefits and costs is represented as pie charts.

4.6 Case Study Illustration

We chose as a hypothetical case study two nano-enabled products used as disinfectant. The functional unit is to prepare nano-enabled products to disinfect a swimming pool for a year. The first product, called "Biocide", consists of a stable colloidal dispersion of nanoparticle X through the chemical reduction of its salts. The second product, called "Filter", consists of an activated carbon impregnated with nanoparticle X using wet dispersion techniques. This section illustrates the methodology of how a manufacturer located in Italy can assess the social impacts of product filter and product biocide using fictitious data at the company level.

The manufacturer obtains data for the production line of these two nano-enabled products calibrated to the functional unit and indicator specification (reported in columns 2 and 4 in Table 4.3). These data are normalized using annual statistical data available for Italy on the indicator (reported in column 6 in Table 4.3) to obtain indicator-specific scores. In this case, it is assumed that the manufacturer decides to assign the same weight (equal to 1) to each indicator. Social indicator scores for filter and biocide products are reported in Table 4.3 (columns 3 and 5, respectively). The social impact indicator scores for the two products are also graphically represented in Fig. 4.2.

The next step is to calculate overall and stakeholder-specific benefit, cost and net benefit for both products as per methodology described in Sect. 4.5 These scores are represented in Fig. 4.3.

Table 4.3 Social impact indicator scores for filter and biocide products using nanoparticle X

Social indicator	Annual data for production line of filter	Score for filter	Annual data for production line of biocide	Score for biocide	Country-level annual data (Italy)
Non-fatal accidents (total number)	93	0.002	201	0.0044	45,526
Training (in million euros)	5	0.033	2	0.0133	150
Education (total number)	211	0.0001	509	0.0001	4,513,500
Employment (total number)	23	0.0056	41	0.0099	4134
R&D expenditure (in million euros)	3	0.0004	0.5	0.0001	6834

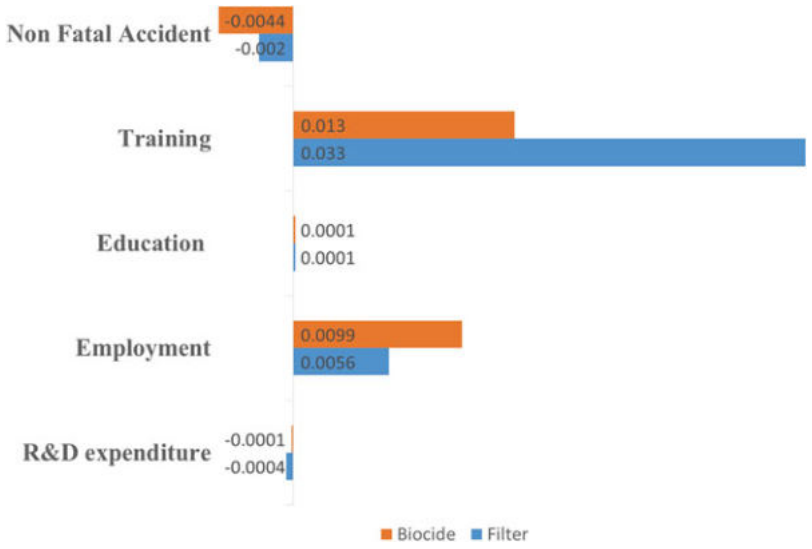

Fig. 4.2 Social impact indicator scores for products filter and biocide

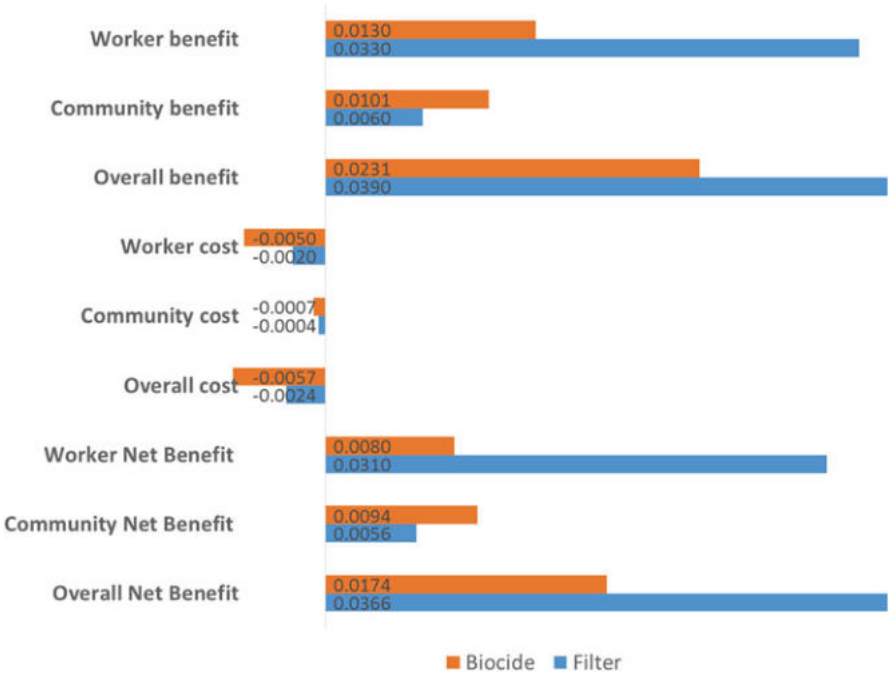

Fig. 4.3 Summary scores for products filter and biocide

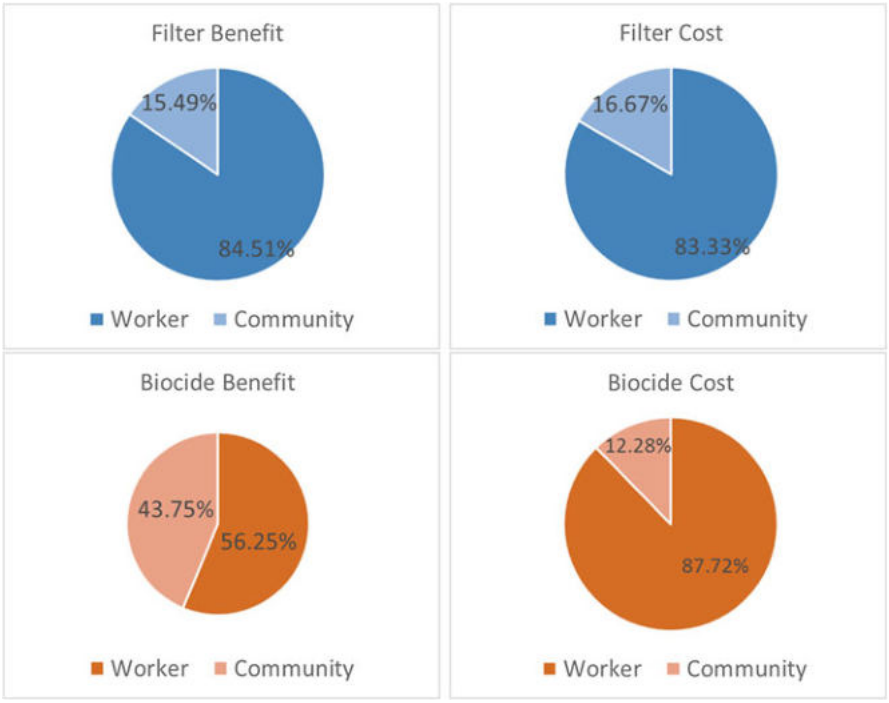

Fig. 4.4 Stakeholder share of benefits and costs for products filter and biocide

Stakeholder share of benefits and costs are calculated for workers and community for both products and represented in Fig. 4.4.

Our analysis shows that for the overall case and the worker, filter product has higher benefits and lower costs than biocide product (Fig. 4.3). However, benefit and net benefit for community is higher for biocide product (Fig. 4.3), apparently due to the substantially higher contribution of biocide to employment (Fig. 4.2). Workers and communities experience benefit of the same magnitude as they do cost for filter product, with worker impact over five times greater than community (Fig. 4.4). While in the case of biocide product, the benefit is almost equally distributed for both stakeholders, the cost for workers is five times that for community (Fig. 4.4) and is apparently caused by substantially higher accidents (Fig. 4.2). From the perspective of the manufacturer, all these results suggest that filter can be chosen.

4.7 Discussion

We found relatively few indicators associated with data required to develop a quantitative methodology (Table 4.2), particularly indicators that are suitable to assess social impacts of nano-enabled products through their life cycle (Sect. 4.3). Three categories of social impacts that are currently not possible to include in a quantitative methodology are described below: (a) sharing of the latest available information about nano-EHS risks in the value chain, (b) the contribution of the innovation to SDG and (c) social impacts with substantial ethical and cultural value dimensions.

Timely and adequate risk communication in the value chain and consumers is vital in the case of uncertain risks and impacts of nanotechnology and is a key component of voluntary industrial codes like Nanotechnology Industry Association's Responsible Nanocode and BASF's Nanotechnology Code of Conduct. However, there are no quantitative social indicators on the frequency of information sharing in the value chain, quality of information in Material Safety Data sheets, consumer labels for nano-enabled products or effectiveness of consumer complaint redressal. These impacts are best assessed through qualitative or semi-quantitative methods based on expert judgement and guidelines based on risk communication and consumer labels.

The potential role of nanotechnology in supporting the achievement of the SDG has been argued (Cozzens et al., 2013; Salamanca-Buentello et al., 2005). While there are several indicators to monitor the achievement of the SDG, there are no indicators to monitor the effectiveness of technologies towards achieving these goals. For example, while the WHO database has country-level data on the access to clean drinking water, there are no indicators for the effectiveness of different technologies in achieving clean drinking water in countries. Such highly context specific data is difficult to obtain as they require extensive data gathering.

Social impacts of nanotechnology which have a significant ethical and cultural dimension cannot be adequately captured through quantitative indicators, and additional qualitative methods and stakeholder dialogue are required to understand such impacts. However, the proposed methodology is an improvement over the usual s-LCA methodology as stakeholder weights offer a snapshot of the underlying ethical and cultural worldview of the stakeholder. The methodology also offers solution to address a key limitation of s-LCA that it only reflects the values of the company performing the analysis and may neglect the values of stakeholders that are more impacted in the value chain (UNEP, 2009). While the methodology is illustrated for one stakeholder (manufacturer), it is possible to extend this analysis to all stakeholders in the value chain by collecting social indicator weights. In case of diverging preferences, this analysis can also serve as the basis for further investigation using qualitative methods and stakeholder deliberation. Substantial research and multi-stakeholder deliberation have been invested in even defining social impacts and indicators in the literature described (Sect. 4.2), as well as recent effort

by pre-consultants (RPSM, 2014) and ongoing effort by World Business Council for Sustainable Development (in that BASF is involved in).

The indicator scores in the proposed methodology are strongly tied to manufacturing and the national context. When nano-enabled products within different manufacturing or national contexts are compared, relevant demographic characteristics (e.g. number and size of companies in manufacturing sector in the country) and statistical country-level information on social indicators (e.g. mean, median and range values) should be considered in order to compare results.

4.8 Conclusion

This chapter aims to fill the gap in nanotechnology risk governance towards the quantitative assessment of social impact of nano-enabled products by proposing a methodology based on s-LCA and MCDA. This methodology evaluates social impacts through the life cycle at country level and aggregates indicators into benefits to assess net benefit of nano-enabled products. The methodology also calculates the proportion of benefit and costs shared by each stakeholder. MCDA allows inclusion of stakeholder preferences to the analysis, which facilitates decision-making by single stakeholder as well as within multi-stakeholder contexts. While limited indicators can be currently included in a quantitative methodology to assess nano-enabled products, we discuss some steps to be taken to further support nanotechnology risk governance. The methodology described in this chapter will be developed into a software DSS and applied to real case studies in the coming months.

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Chapter 5
International Cooperation on Nanosafety Between Europe and Latin America

Ineke Malsch, Martina Lindorfer, Isabella Wagner, and Maria Lima-Toivanen

Abstract Protecting workers, consumers and the environment against uncertain risks of manufactured nanomaterials is a global issue. While risk assessment research and risk governance are already well established in Europe and North America, other regions are lagging behind. In Latin America, Brazil has recently joined the EU project on nanoregulation NANoREG and is investing in several projects in nanotoxicology. The situation in other Latin American countries is much more fragmented. The present chapter gives an overview of the current state of the art and future plans in nanosafety research and governance in Latin America based on a bibliometric study, interviews, workshops and literature review that were part of the EU funded project NMP-DeLA www.nmp-dela.eu.

5.1 Introduction

Setting the scene, we start by outlining current issues in the global dialogue on nanosafety. We also briefly introduce the international institutions and networks involved in risk governance of nanomaterials in and with emerging economies and developing countries. This presents the context for the focus of analysis in this chapter: examining the state of the art in research, governance and stakeholder engagement regarding nanosafety in Latin America. Ultimately we give recommendations for how international cooperation with European partners may strengthen nanosafety in Latin America.

I. Malsch (✉)
Malsch TechnoValuation, PO Box 455, Utrecht 3500 AL, The Netherlands
e-mail: postbus@malsch.demon.nl

M. Lindorfer • I. Wagner
Centre for Social Innovation (ZSI), Linke Wienzeile 246, Wien 1150, Austria

M. Lima-Toivanen
VTT Technical Research Centre of Finland, P. O. Box 1000, Espoo, Finland

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Back in 2003, the Canadian non-governmental organisation Action Group on Erosion, Technology and Concentration (ETC group)[1] raised the alarm over uncertain risks of nanomaterials and nanotechnologies at a global level (ETC Group, 2003a, 2003b, 2003c, 2003d, 2003e, 2003f, 2004). A key issue was the introduction on the market of sunscreens containing nanosized TiO_2 and ZnO without prior testing. While the chemical composition was the same, the nanoformulations of these materials had different properties from the bulk material and therefore could introduce unknown risks. The ETC group's actions effectively set the agenda for international risk governance of nanotechnology, a continuing quest until today.

Most of the current discussions and research on the topic of nanosafety are concentrated in industrialised countries, in particular in member states of the Organisation for Economic Co-operation and Development (OECD) since the start of the working party on manufactured nanomaterials (WPMN) in 2006. Nevertheless, since nanomaterials and nanotechnologies are increasingly manufactured and used in products all over the world, the issue is also relevant to developing countries and emerging economies. China and South Africa are among the sponsors of the OECD testing programme of 11 manufactured nanomaterials and have actively contributed to the collection of data necessary for the creation of international norms governing the use of these materials in the period 2007–2015.[2] The International Organization for Standardization (ISO) established the Technical Committee (TC) 229 on nanotechnology in 2005. Currently, 33 countries are members, including Mexico and Colombia, and 15 countries are observers, including Argentina and Jamaica. Other Latin American and Caribbean countries are not involved, although Brazil has been engaged until the beginning of 2015.[3]

The Strategic Approach to International Chemicals Management (SAICM)[4] aims at rational governance of chemicals during their whole life cycle and significant reduction of adverse impacts on health and the environment by 2020. In 2012, it included nano as a key topic in its Global Action Plan after it was first nominated as an emerging topic in 2009 (Foladori, Bejarano, & Invernizzi, 2013). This action plan is implemented mainly by the OECD and the United Nations Institute for Training and Research (UNITAR).

UNITAR offers training and capacity building to governments in developing countries, based on its 'Guidance for Developing a National Nanotechnology Policy and Programme' (UNITAR, 2011). UNITAR set up this programme in 2009 in response to resolution II/4, Part E of the Second International Conference on Chemicals Management (ICCM2) and the subsequent invitation in Resolution III/2E of ICCM3 in 2012. Switzerland, the USA, the UK and Sweden are the main sponsors of this programme,

[1] http://www.etcgroup.org/

[2] http://www.oecd.org/chemicalsafety/nanosafety/sponsors-testing-programme-manufactured-nanomaterials.htm

[3] http://www.iso.org/iso/iso_technical_committee?commid=381983

[4] SAICM was adopted by the ministers of environment and health of over 100 countries and is supported by representatives of industry, NGOs and trade unions during the first session of the International Conference on Chemicals Management in 2006. C.f. www.saicm.org

and they have organised two rounds of regional workshops in Africa, the Arab world, Asia-Pacific, Central and Eastern Europe and Latin America and the Caribbean. Since 2011, national pilot projects have been implemented in Nigeria, Thailand, Uruguay, Armenia, Jordan and Vietnam.[5] Capacity development services include training on nanoregulation, occupational health and safety issues, labelling standards for nano-containing products for customs and public awareness raising. These can be considered the main issues in the global dialogue on nanosafety, together with continuing disagreement on definitions and nomenclature. In addition, the Healthy Workplaces Programme of the World Health Organization (WHO) is currently developing guidelines on nanomaterials and worker's health.[6] Dr William Waissmann of the Oswaldo Cruz Foundation (FIOCRUZ) in Brazil is a member of the WHO working group on this topic, which consists of 12 international experts.

The European Union is among the sponsors of the OECD testing programme and is also organising a common European response to the need for risk governance and regulation for nanomaterials by obligatory participation of all relevant EU funded projects in the Nanosafety Cluster.[7] In particular, the NANoREG project (a Common European Approach to the Regulatory Testing of Manufactured Nanomaterials) brings together pan-European government bodies, research and industry in developing common test protocols necessary for evidence-based regulation of the whole value chain of these materials. In addition, NANoREG recently signed cooperation agreements with Brazil and South Korea.[8] The EU and the USA are also engaged in bilateral discussions on a common approach to these issues.[9]

At the level of experts, three international networks coordinate nanotoxicology research of which two focus on water safety. The International Water Association (IWA) has a specialist group on nanotechnology that mainly focuses on environmental risks of nanomaterials in water. IWA does not have a regional representation in Latin America.[10] Likewise, the Society of Environmental Toxicology and Chemistry (SETAC) has a working group on nanotechnology, with 249 researchers as members. A key issue faced by the SETAC is the need to increase its membership outside North America and Europe.[11] The GWRC (Global Water Research Coalition) is also active in this field and has no partners in Latin America (Malsch, Lindorfer, & Lima-Toivanen, 2015).

This short introduction suggests that Latin America is not very involved in the international dialogue and risk governance efforts regarding application of nanotechnologies. Indeed, Latin American researchers and other stakeholders interested in nanosafety lack visibility at global scale. This chapter will therefore address nanosafety initiatives in Latin America and prospects for improving risk research and regulation in cooperation with European counterparts.

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[5] http://www.unitar.org/cwm/portfolio-projects/nanotechnology

[6] http://www.who.int/occupational_health/topics/nanotechnologies/en/

[7] www.nanosafetycluster.eu

[8] www.nanoreg.eu

[9] http://us-eu.org/

[10] http://www.iwa-network.org/

[11] http://www.setac.org/group/AGNano

5.2 State of the Art in Nanosafety Research and Policy-Making in Latin America

In this section, an overview is given of the current research, education, policies and funding for nanotoxicology and risk governance of nanomaterials in Latin America.

5.2.1 Nanosafety Bibliometric Analysis

Within the NMP-DeLA project, bibliometric studies on nanohealth, nanowater and nanoenergy have been realised by the Latin American Nanotechnology and Society Network (ReLANS) and the Centre for Social Innovation (ZSI) (Invernizzi, Foladori, & Lindorfer, 2015). For the topic of nanosafety, ZSI now realised a subsequent bibliometric analysis in order to give an overview on the evolvement of scientific production in this field.

The following figures are the results of keyword-based queries, combining a proven keyword set for nanotechnology-related research (cf. Invernizzi et al., 2015) with a set for safety specific keywords[12] in the nanotechnology context. These sets were applied to the output of authors from preselected regions: the Community of Latin American and Caribbean States (CELAC) countries as well as members of the European Union and the associate partners to Framework Programme FP7. The keywords were searched not only in the fields for author keywords but also in title and abstract, summing up all publications until and including 2014. Results are not directly comparable with the NMP-DeLA bibliometric studies as data sources differ (in this case only Elsevier Scopus without Web of Science).

Results of the bibliometric analysis substantiate the hypothesis of this chapter which says that CELAC is lagging behind in nanosafety research and that few countries within CELAC have visibility in the field. We see in Table 5.1 that before 2015 almost 10,000 authors from the EU were involved in Nanosafety publications and only 790 authors from CELAC. However, the relation of Nanosafety publications to the total of publications in nanotechnology is quite similar in Europe (2.9 %) and Latin America (2.6 %).

The last two columns in the table show co-publications with at least one author from CELAC and one author from the EU in Nano and Nanosafety, respectively. In terms of numbers, we see a remarkable increase of EU-CELAC co-publications in both fields, but even more so in Nanosafety.

The table below lists country affiliations of the most productive authors in Nanosafety. We see, and this goes line in line with our qualitative research, that within CELAC Brazilian authors are by far most productive in the area of Nanosafety. They have been involved in 476 Nanosafety publications until 2015. Mexico and

[12] 'Nanosafety, safety, risk, nanorisk, toxicology, nanotoxicology, toxicity, nanotoxicity, ehs or nanoenvironmental health and security'.

Table 5.1 Nanotechnology + safety research output (no year limit) for CELAC and EU + AC, data from Elsevier Scopus July 2015

Set	CELAC + nano[a]	EU[b] + nano[a]	CELAC + nanosafety[a]	EU + nanosafety	CELAC + EU + nano[a]	CELAC-EU + nanosafety
Total	**30,055**	**342,768**	**790**	**9926**	**7234**	**157**
2014	3398	29,717	181	1465	851	42
2013	3170	30,437	136	1417	753	19
2012	2838	29,130	110	1302	656	23
2011	2425	27,993	72	1115	605	18
2010	2352	25,955	58	880	544	20
2009	2124	24,288	41	763	523	9
2008	2091	23,467	30	590	479	4
2007	1635	19,781	18	448	420	5

[a]See Table A.1

[b]EU in this study means all countries associated to FP7 and candidate states

Argentina lag far behind on second and third place within the group of Latin American countries. The countries marked in bold in the table are countries outside CELAC, but which nevertheless are very active in collaborating with CELAC in Nanosafety publications.[13]

That European countries rank so high in the list of CELAC publications indicates that many of Latin American publications in Nanosafety are done with European (and of course US) counterparts, especially from Spain. It also indicates a generally high level of (transatlantic) collaboration of CELAC countries in this specific field. On the other hand, in the list for Europe, Brazil only appears on rank 31 as the strongest Latin American partner country in Nanosafety publications.

Brazilian authors appear most often in Nanosafety co-publications between CELAC and EU, followed by authors with Spanish affiliations (Table 5.2).

In a further step, we analysed Nanosafety publications according to their affiliations in the Scopus All Science Journal Classification (ASJC) system, which is, with its 27 thematic clusters, the basis for thematic classification and analysis. Each publication (and journal) is attached to at least one ASJC, but multiple allocations are possible.

For Nanosafety publications we see that most are assigned to medicine-related categories, followed by those related to materials and engineering. For the collaborative publications between CELAC and EU, chemistry is the most important subject area. Interestingly, for both geographic areas, around 15 % of the records are classified as Environmental Sciences, and for CELAC-EU co-publications in the field, the share is even a bit higher (16.5 %)—so one thematic focus in the collaboration can be assumed here (Table 5.3).

5.2.2 State of the Art in Nanosafety Research by Latin American Country

As in other fields of research in NMPs, Brazil is the most active Latin American country in research in environmental, health and safety aspects of nanomaterials. The federal government has been funding six nanotoxicology networks, each focusing on a particular aspect of the topic, since 2011. The topics include aquatic nanotoxicology, toxicology of nanocomposites and products, nanoparticles in oil and paint, occupational and ambient nanotoxicology, standardisation and the

[13] This data shows all publications with at least one CELAC author. The result is a set that contains both national and international publications, and therefore other than CELAC countries can have a strong presence in the CELAC selection of publications. If, for example, one Spanish author has co-published a lot with a Brazilian author, Spain might be listed as very productive (although the selection was made for CELAC only).

Table 5.2 Publications according to country of the affiliation institution (full table in Annex)

CELAC + nanosafety		EU + nanosafety		CELAC + EU + nanosafety	
Brazil	476	Germany	1910	Brazil	82
Mexico	147	United Kingdom	1766	Spain	46
USA	**116**	Italy	1353	**USA**	**28**
Argentina	88	France	1323	France	27
Spain	**46**	USA	1193	Portugal	25
Chile	35	Spain	856	Mexico	24
France	**27**	Switzerland	699	Germany	23
Portugal	**25**	Netherlands	610	United Kingdom	21
Germany	**23**	Belgium	376	Argentina	18
Puerto Rico	22	Sweden	359	Italy	14
United Kingdom	**21**	Denmark	336	Chile	13
Canada	20	Portugal	335	Colombia	10
Colombia	17	Poland	299	Switzerland	8
India	16	Austria	253	Ireland	6
Italy	**14**	China	236	Australia	5
Cuba	13	Turkey	212	Belgium	5
…	…	…	…	…	…
		Brazil	**82**		

Table 5.3 Publications according to ASJC classification

CELAC + nanosafety		EU + nanosafety		CELAC + EU + nanosafety	
Medicine	220	Medicine	2581	Chemistry	42
Materials science	202	Pharmacology, toxicology and pharmaceutics	2502	Medicine	41
Biochemistry, genetics and molecular biology	190	Engineering	2470	Materials science	37
Chemistry	185	Materials science	2322	Engineering	36
Engineering	178	Biochemistry, genetics and molecular biology	2253	Biochemistry, genetics and molecular biology	31
Pharmacology, toxicology and pharmaceutics	176	Chemistry	1891	Pharmacology, toxicology and pharmaceutics	30
Chemical engineering	156	Chemical engineering	1560	Chemical engineering	27
Physics and astronomy	118	Environmental science	1531	Environmental science	26
Environmental science	117	Physics and astronomy	1325	Physics and astronomy	23
Agricultural and biological sciences	67	Agricultural and biological sciences	490	Agricultural and biological sciences	11
…	…	…	…	…	…

development of reference materials and applications in agrifood and health. The Oswaldo Cruz Foundation (FIOCRUZ) is a key applied research centre in the field of nanotechnology and health and has been active also in nanosafety research. Their work is done on the link between exposure to carbon nanomaterials and cardiovascular, arrhythmia and respiratory diseases and cancer, worker protection against exposure to nanofibres and carbon nanotubes (CNT) and nanotoxicology for consumer protection. They also study environmental exposure in a laboratory environment and worker exposure in industry in cooperation with the WHO, the United Nations, the National Institute for Occupational Safety and Health (NIOSH) (in the USA) and a partner from Portugal. For example, one project coordinated by William Waissmann (FIOCRUZ) between 2009 and 2014 was on 'The use of nano in food and biofuel—developing risk indicators and regulatory frameworks for workers safety and environmental protection'. The main aim of this project was to analyse the potential consequences of these applications of nanotechnology. The study included stocktaking of nanomaterials present in Brazil; knowledge on potential risks; existing regulatory frameworks in the USA, EU and in the Common Southern Market (MERCOSUR); exposure of workers to nanomaterials; and mapping the awareness and stakeholder positions in the public debate on nanotechnology in Brazil. In a recent publication, Waissmann and colleagues review 17 risk management proposals for Occupational Health and Safety of nanomaterials, concluding that they are similar but not covering exactly the same scope (Andrade, Amaral, & Waissmann, 2013). Engelmann and colleagues reviewed different forms of formal, self- and metaregulations covering nanotechnology for food and biofuels in different parts of the world, proposing a gradual introduction of soft and increasingly harder regulations in Brazil (Engelmann, Aldrovandi, & Berger Filho, 2013). These articles were part of a special issue of the journal *Visa em Debate on Nanotechnology and Sanitary Vigilance* funded by the Nanobiotec Network.[14]

The Laboratory for Nanomedicine and Nanotoxicology was recently established at the Physics Department of the University of the State of São Paulo at São Carlos (UNESP-São Carlos)[15] (Invernizzi et al., 2015). By 2011, some groups were investigating impacts of nanotechnology including the group 'Nanotechnology, Society and Environment' at the Federal University of Parana (UFPR), coordinated by Noela Invernizzi and the group JUSNANO—aiming to build and develop regulatory frameworks for nanotechnology in Brazil. This group was established as a collaboration between the Vale do Rio dos Sinos University (UNISINOS), in Rio Grande do Sul, and FIOCRUZ, in Rio de Janeiro, and coordinated by Wilson Engelmann (Arcuri, 2011).

In Mexico, the Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV) is studying toxicity in in vitro and in vivo studies of nanoparticles for photovoltaic cells (CdS, CIGS) and Bismuth (BISNANO project) in cooperation with a research group in Dublin. The Advanced Materials Research Centre (CIMAV) in Monterrey, Mexico, carries

[14] https://visaemdebate.incqs.fiocruz.br/index.php/visaemdebate/issue/view/6

[15] http://www.nanomedicina.com.br/

out tests focusing on risk, control and monitoring of pollution for companies. Although, the laboratory in Monterrey is not certified by the responsible standardisation body, it tries to follow all the guidelines in order to facilitate its acquisition in the future. By now they have not applied for accreditation due to its high costs and because their clients have not demanded it. In addition to these specialised centres, individual researchers in other universities and research centres are also working on nanotoxicology projects (Malsch et al., 2015). The ethical, legal and societal aspects of nanotechnology are investigated at the Centre for Interdisciplinary Research in the Sciences and Humanities (CEIICH) at the National Autonomous University of Mexico (UNAM). In particular Gian Carlos Delgado discusses the relevance of a social dialogue and management as a democratic way of promoting a responsible development of nanotechnologies (Delgado Ramos, 2013). The University of Zacatecas hosts the other centre of expertise on these issues as co-chair of the ReLANS network.

In Argentina, two groups have been working on nanotoxicology. The Laboratory of Biomembranes (LBM) of the Multidisciplinary Institute of Cellular Biology (IMBICE) at the National University of Quilmes (a CONICET institute) studies micro- and nanovectors, drug delivery, zebrafish animal model and in vitro and in vivo toxicity.[16] The Centre for Environmental Engineering of the Technological Institute of Buenos Aires (ITBA) focuses on environmental impacts, water treatment, purification and toxicity of nanoparticles.[17] (FAN, 2012).

In Colombia, Associate Professor Felipe Muñoz Giraldo, who works at the UniAndes, is an expert on risks of nanoexplosions, and he also contributes to other studies and measures for assessing and managing risks of nanomaterials. End of 2015, he contributed to a nanorisk app for researchers together with PhD Candidate Homero Fernando Pastrana Rendón and Associate Professor Alba Graciela Ávila, Department of Electrical and Electronic Engineering of UniAndes.[18] In June 2015, UniAndes hosted a workshop on nanosafety with participants from 11 Latin American and Caribbean countries: Mexico, Ecuador, Costa Rica, Argentina, Chile, Brazil, Uruguay, Peru, Panama, St. Vincent and the Grenadines and Colombia. This was supported by UNITAR, the OECD, the Colombian Ministry of Environment and Sustainable Development, UniAndes and the Swiss government.[19]

The group on New Nano and Supramolecular Materials coordinated by Alvaro Duarte Ruiz, at the National University of Colombia (UNAL), Bogotá, has also worked on in vitro cytotoxicity by nanophotothermolysis assisted by CNT. At the Autonomous University of the Caribbean (UAC), the Research Group on Mechatronics Engineering (GIIM) is working on a project on cytotoxicity with functionalised CNT against cancer.

[16] www.unq.edu.ar, http://www.imbice.gov.ar/

[17] http://www.itba.edu.ar/es/id/centros/cima-centro-de-ingenier%C3%ADa-en-medio-ambiente

[18] https://nanoseguridad.uniandes.edu.co/nano_en/indexeng.html

[19] https://nanoseguridad.uniandes.edu.co/

In Chile, the University Andres Bello is active in research on the fate of nanomaterials in the environment. All FONDECYT (Fund for Development of Science and Technology) grants make it obligatory to evaluate societal opportunities. This has led most funded researchers to engage in public awareness (TV, newspapers, school), stimulating multidisciplinary research involving natural and social scientists.

In Cuba during the embargo, the national research community has reportedly been working in isolation on nanosafety for medicine and agriculture or food safety. The programme aims at social development of medicine with a dedication to ethics and benefit sharing (Malsch et al., 2015).

Several interviewed European researchers have established contacts with colleagues in Latin America, especially in Brazil, Argentina, Venezuela and Mexico. Current projects targeting nanosafety funded by the European Union include NANOSOLUTIONS, NANOVALID and the earlier mentioned NANoREG with Brazilian partners.[20] The first applies systems biology to nanosafety and includes the Federal University of Brasilia. The second develops reference methods for nanomaterials and includes the National Metrology Institute INMETRO and the Federal University of Minas Gerais. In general, the interviewed European researchers consider Latin American research to be of good quality, but rather fragmented.

5.2.3 Policy-Making

UNITAR has stimulated dialogue on risk governance of nanotechnology in two regional LAC workshops, in Jamaica in 2010 and in Panama in 2011. It also implemented a pilot project in Uruguay. In the first workshop, 29 participants from 21 Latin American and Caribbean countries participated. In the second workshop, speakers represented national and international governmental bodies, natural and social scientists and nongovernmental organisations.[21] The resolution adopted during this second workshop contributed to the subsequent incorporation of nanotechnology in the SAICM Global Action Plan (Foladori et al., 2013).

Emerging economies, including Brazil and Mexico, already have adopted occupational health and safety regulation in general. The main issue for policy-makers is how to verify compliance by the industry with the legislation. Authorities responsible for employment and safety at work from many countries are interested in international cooperation aiming at incorporating nano in occupational health and safety regulations. The above-mentioned World Health Organization (WHO) Healthy Workplace Programme could be the starting point for these organisations to work on compliance of national regulations with international standards. In this programme, 12 global experts advise on occupational health and safety regulations, and they are valid for all UN member states (Malsch et al., 2015).

[20] The NMP-DeLA project that has supported the writing of this article also fosters EU-Latin American cooperation in nanosafety, but its scope is broader: www.nmpdela.eu.

[21] http://www.unitar.org/cwm/nano/workshops/second-round/Latin-America-Caribbean

In Brazil, in 2009, the federal Ministry of Development, Industry and Foreign Trade established the Nanotechnology Competitiveness Forum as an instrument in its Productive Development Policy, which includes nanotechnology as a topic since 2008. Its four working groups include one on the regulatory framework, organising collaborative discussions with the Brazilian Association for Technical Norms (ABNT) Mirror Committee to ISO TC 229 on Nanotechnology.

FUNDACENTRO at the Federal Ministry of Labour and Employment has been the key player in occupational health and safety of nanomaterials since 2006.[22] This centre aims to produce and disseminate knowledge contributing to workers' safety and health. This includes the Chemical Safety Programme, which encompasses a project on nanotechnology. At FUNDACENTRO, Arline Arcuri coordinated the project on the impact of nanotechnology on workers' health and the environment by 2011. This project aims to identify impacts of nanotechnology on workers' health and to suggest control measures. The project also developed educational materials for workers, including comics. The stakeholders are RENANOSOMA (Brazilian Network on Nanotechnology, Society and Environment),[23] IIEP (Information Exchange, Studies and Research),[24] DIESAT (Inter-Trade Union Department of Studies and Researches on Health and Workplaces),[25] DIEESE (Inter-Trade Union Department of Statistics and Socio-Economic Studies),[26] FIOCRUZ (Fundação Oswaldo Cruz—Ministry of Health),[27] IOS (Observatory Social Institute)[28] and SRTE (Regional Labour and Employment Superintendence, Ministry of Labour).[29] FUNDACENTRO also contributes to a WHO project on nanotechnology (Arcuri, 2011; FUNDACENTRO website, 2015).

The National Strategy for Science and Technology is currently part of Brazil Major Plan. This plan includes six strategic sectors: aerospace, agribusiness, defence, energy, environment and health. The Brazil Nanotechnology Initiative (BNI) identified key nanotechnologies for these sectors. Sensors and nanomaterials are the main driving force. These nanotechnologies focus on the short to medium term. An interministerial nanotechnology committee consists of representatives of ten ministries. The Ministries of Foreign Affairs and of Labour who used to be observers recently joined as full members (Souza Mendes, 2015). This committee also discusses regulation. Furthermore, the Brazilian Federal Chamber of Deputies has discussed regulation for nanotechnology on several occasions since 2005. Two proposals tabled in 2005 and 2010 failed. Two proposals submitted in 2013 by Sarney Filho from the Green Party (PV) in 2013 were still under consideration in 2015: proposal nr. 5133/2013 aimed at nanolabelling and proposal nr. 6741/2013

[22] http://www.fundacentro.gov.br/nanotecnologia/inicio

[23] http://www.nanotecnologiadoavesso.org/

[24] http://www.iiep.org.br/index2.html

[25] http://diesat.org.br/

[26] http://www.dieese.org.br/

[27] http://portal.fiocruz.br/pt-br

[28] http://www.observatoriosocial.org.br/

[29] http://portal.mte.gov.br/portal-mte/

aimed at a national nanotechnology policy supporting research, technology development and regulatory control of nanotechnology (Engelmann et al., 2013; Urquijo, 2014).[30] The proposal 6741/2013 has been the object of a manifest by the researcher community, signed by the Brazilian Society for the Progress of Science (SBPC) and Brazilian Academy of Sciences (ABC), which pointed out a lack of conceptual clarification and restrictions to the development of nanosciences and nanotechnologies as their weak points and proposed a public consultation to discuss the matter (Nader & Palis, 2013). Both proposals have further been criticised by the abovementioned scientific societies, which proposed the following (already aware of the Brazilian participation in different projects, e.g. NANoREG):

1. To stop the processing of the regulatory proposals 6.741/13 and 5.133/13, in the committees in which they have been analysed
2. The creation of a congressional working group, to follow up initiatives and policies on nanotechnology regulation by developed countries
3. To define a temporary organisation, involving both the legislative and executive powers (notably the MCTI), to update and consolidate existing information to supply all the powers of the Brazilian Republic with enough evidence for decision-making that allow Brazil to take maximum benefit of economic and strategic opportunities offered by nanotechnology and maximum protection against any potential risks (Rubira et al., 2015)

In Mexico, the Senate has also been discussing regulation for nanotechnology since 2005. In that year, the Commission on Science and Technology approved an appeal for elaboration of an emergency programme in nanotechnology. In 2013, the same commission called for the elaboration of a programme for development and regulation of nanotechnology in order to accelerate development, taking into account potential health and environmental risks. Mexico was also the first Latin American country to elaborate voluntary guidelines for regulation of nanotechnology based on the existing US guidelines. A committee coordinated by the Centre for Metrology of the Secretariat for the Economy elaborated this 12-point plan that was adopted in November 2012 aiming to facilitate trade with the USA and regulate on a case-by-case basis (Foladori & Zayago, 2014; Urquijo, 2014). Participants in the NMP-DeLA project confirm that the Mexican Federal Secretariat for Economy is looking into regulation and exposure reduction for nanomaterials. Reportedly, the Secretariat for Labour is not engaged in discussion on nanotechnology. In the regulatory process, there is more activity on environmental issues, but this has resulted in recommendations more than rules. Laws are not being revised.

In Uruguay, the Ministerial Cabinet for Innovation declared nano- and biotechnology to be priority sectors in the national industrial development strategy in 2008. The tripartite sector council on bio- and nanotechnology was established in 2010, and since 2011, nanotechnology is included in the sector plan for biotechnology

[30] http://www.camara.gov.br/proposicoesWeb/fichadetramitacao?idProposicao=567257 and http://www.camara.gov.br/proposicoesWeb/fichadetramitacao?idProposicao=600333

until 2020.[31] In 2012, UNITAR set up a pilot project on risk governance of nanotechnology in Uruguay. This project was implemented by the Coordination Centre of the Convention of Basel, the Regional Centre for the Convention of Stockholm for Latin America and the Caribbean, the Ministry for Housing, Spatial Planning and Environment (MVOTMA) and the Technological Laboratory of Uruguay (LATU). Two surveys were carried out on the research and industrial state of the art of nanotechnology in the country. These studies revealed several weaknesses in regulation and oversight of nanomaterials and nanoenabled products in the country. The pilot project resulted in a report with concrete recommendations for a national strategy for nanotechnology and nanosafety. This consists of six phases:

1. Identification of key actors handling chemical substances and nanomaterials
2. Capacity building of the relevant stakeholders
3. Acquisition of equipment
4. Managing knowledge of nanosafety and nanoproducts
5. Measures and mechanisms for controlling nanotechnologies and nanoproducts
6. Strengthening and promoting public support (Mendoza Muniz, Correa, & Medina, 2013)

In Argentina, the Committee on Nanotechnologies of the National Institute of Standardisation and Certification (IRAM) coordinates the Argentinean dialogue on standardisation of nanotechnology including environment, health and safety aspects. They represent the International Organization for Standardization (ISO) in the country.[32] The Argentinean Foundation for Nanotechnology (FAN) aims to stimulate sustainable and safe development of nanotechnology through a number of activities including participation in IRAM's committee. The basis for FAN's contribution consists of a collection of literature on these topics.[33] The National Committee on Ethics in Science and Technology (CECTE) adopted propositions for a societally responsible science and technology after a public consultation. It calls among other aspects upon scientists to 'promote and respect norms for safety and environmental care in the research context'. It calls upon institutions to undertake obligations including 'respecting, imposing the respect and disseminating national and international regulations on safety and care for the environment in the research context' (CECTE, 2013). As a follow-up, they are working on propositions for responsible nanoscience and nanotechnology development inspired by the European Commission code of conduct for nanotechnology (EC, 2008).[34]

[31] http://www.miem.gub.uy/consejos-sectoriales/nanotecnologia

[32] http://www.iram.org.ar/index.php

[33] http://www.fan.org.ar/acciones/nanosustentable

[34] www.cecte.gov.ar

5.2.4 Civil Society Engagement and Initiatives

Ever since the ETC group put potential risks of nanotechnology on the international public agenda in 2003, non-governmental organisations (NGOs), trade unions and associations of social scientists have been playing a role in the dialogue on nano-safety, mainly at international levels. Several Latin American organisations have actively been contributing to the discussion on risk governance and regulation of nanotechnologies from the start. Invernizzi and Foladori's (2013) recent review of Unions and NGOs positions on the risks and regulations of nanotechnology gives evidence of Latin American participation since 2006.

A prominent international platform in this respect is the World Social Forum (WSF).[35] Paulo Martins, the coordinator of RENANOSOMA,[36] has been organising workshops on nanotechnology during WSFs since 2004, with on average 40–50 participants per workshop. For example, in 2005, in Porte Alegre, they tabled a discussion between Renzo Tomellini (European Commission) and Pat Mooney (ETC group).[37] During the World Social Forum, 26–30 March 2013 in Tunis, he co-organised two workshops on nanotechnology. The Observatory of Nanotechnology in Americas organised two nanosummits for nanoactivists, exploring opportunities for a global or four-continent observatory. RENANOSOMA and the Institute for Agriculture and Trade Policy, USA, organised two workshops on nanotechnology and public engagement. Two years later, the World Social Forum 2015 featured a workshop entitled 'Civil society in action for the governance of emerging technologies: nanotechnology and synthetic biology', as part of the fourth World Forum on Science and Democracy.[38]

In 2006 the Latin American Regional Secretariat of the International Union of Agricultural and Food Workers (REL-UITA) called for public dialogue on nanotechnology, which was taken over by the 25th congress of this International Union of Agricultural and Food Workers (IUF) in March 2007 (Foladori & Invernizzi, 2007). Six years later, this was followed by a declaration calling upon companies to inform their employees about the nanomaterials in production and upon international organisations to take a precautionary approach to risk governance. The declaration was signed by the participants in a workshop in Curitiba, Brazil, organised by ReLANS.[39] This network includes representatives of trade unions and academics.

NGOs based in industrialised countries also contribute to the discussion about risk governance of nanotechnologies in Latin America and other developing countries and emerging economies. In addition to the ETC group, they include the Center

[35] https://en.wikipedia.org/wiki/World_Social_Forum

[36] http://www.nanotecnologiadoavesso.org/

[37] Paulo Martins, skype interview for the NanoEIS project by Ineke Malsch, 8 March 2013, unpublished

[38] https://fsm2015.org/en

[39] http://www.relans.org/inicio.html

for International Environmental Law (CIEL)[40] from the USA, the International Persistent Organic Pollutants Elimination Network (IPEN)[41] (international), Friends of the Earth Australia and Europe,[42] American Federation of Labor and Congress of Industrial Organizations (AFL-CIO),[43] European Trade Union Institute (ETUI),[44] etc. In 2007, over 70 social organisations and unions from six continents signed the Principles for the Supervision of Nanotechnology and Nanomaterials and established a global alliance of social groups interested in assessing and monitoring nanotechnology (Invernizzi & Foladori, 2013).

In **Brazil**, RENANOSOMA has been stimulating dialogue, organising informal professional training on nanotechnology and nanosafety, that is aimed at awareness raising, not for an official certificate. They also undertook other initiatives to raise public awareness since 2003, as a bottom-up, often unfunded initiative outside the scope of the top-down federal governmental policy and funding strategy. By 2013, RENANOSOMA consisted of 26 researchers from different universities and from different disciplines. According to the coordinator, Paulo Martins, they organised four seminars about nanotechnology with high school teachers in 2009–2011 in cooperation with the union of the public high school teachers. In the seminars they handed out CDs and DVDs on nanotechnology: 'the Future is Now', 'Understanding Nanotechnology', 'Nanotechnology for workers' as well as comics on nanotechnology. RENANOSOMA's seminars and dissemination of materials to teachers and workers fulfil a niche that is excluded from funding by the government, according to him.

> 'RENANOSOMA also regularly cooperates with other partners in organising informal worker training in nanosafety, again raising awareness. The publications are all in Portuguese, allowing outreach to the general public. Another activity is the broadcasting of weekly interviews by internet TV: of different people from different areas and social sectors. By July 2015, over 300 interviews had been broadcasted in the series 'Nanotechnology Inside Out' and over 70 in the series 'Nano Alerta".

RENANOSOMA is also one of the stakeholders contributing to FUNDACENTRO's above-mentioned work on nanosafety, together with representatives of trade unions and research organisations.

[40] http://www.ciel.org/issue/nanotechnology/

[41] http://ipen.org/

[42] http://www.foe.org/

[43] http://www.aflcio.org/

[44] http://www.etui.org/

5.3 Best Practice: Brazil's Participation in NANoREG

In May 2015, the Brazilian federal government signed a cooperation agreement with the European NANoREG project.[45] The cooperation agreement was approved by the Brazilian Interministerial Committee on Nanotechnology. This 'Common European Approach to the Regulatory Testing of Nanomaterials' brings together €50 million of public and private funding, including €10 million from the European Union and the rest from 14 European national governments and industry. It is running from 1 March 2013 until 31 August 2016 and is well integrated with other projects in the European Nanosafety Cluster.[46] Brazil, the Czech Republic and South Korea have joined as partners, while the USA, Canada, Australia and Japan are associated to the project. The key deliverables of NANoREG are a regulatory framework for these materials and a toolbox for testing them (NANoREG, 2015). The NANoREG consortium wanted these countries to join because of their expertise and contributions to the work, but also to strengthen the support for its outcomes (NANoREG, 2014). Brazil foresees that this cooperation will give the country a regulation aligned with international regulations, taking into account the needs of society and industry, according to Anna Tempesta of the Ministry of Science, Technology and Innovation (MCTI) (MCTI press release, 2 June 2015). The objective is to translate results from scientific research in a way that they become useful for regulatory agencies. The role of MCTI is not to impose regulation, but to give scientific support to legislators and regulatory agencies (MCTI press release, 2 June 2015, www.mcti.gov.br). Regulatory bodies including the National Agency for Sanitary Vigilance (ANVISA), as well as the Ministries for Science, Technology and Innovation (MCTI), Health, Environment, Labour and Enterprise oversee progress in the project (MCTI press release 26 August 2014, www.mcti.gov.br).

The following Brazilian laboratories are involved in the research cooperation with NanoREG:

- Instituto Nacional de Metrologia, Qualidade e Tecnologia INMETRO—scientific coordinator in Brazil
- Center for Strategic Technologies for the Northeast (CETENE), Multi-User Nanotechnology Laboratory
- Brazilian Agricultural Research Corporation (EMBRAPA)
- Federal University of Rio Grande do Sul (UFRGS)
- University of São Paulo (USP)
- Federal University of Rio Grande (FURG); Institute of Biological Sciences (ICB)
- Federal University of Minas Gerais (UFMG), Institute of Biological Sciences (ICB)
- State University of Campinas (Unicamp), Inorganic Chemistry Department NanoBioss/Chemistry Institute
- (Tempesta, 2015)

[45] www.nanoreg.eu

[46] www.nanosafetycluster.eu

In addition, a sector dialogue involving the Brazilian MCTI and the EU Directorate General for Research and Innovation on regulation of products based on nanotechnology has been ongoing since 2014.[47] As part of this dialogue, Steve Hankin, of the Institute of Occupational Medicine, UK, and the SAFENANO project, and Nelson Duran, of the Institute of Chemistry at UNICAMP, Brazil, have analysed the state of the art of regulation, risk assessment facilities and risk governance for nanotechnology in Brazil and the European Union (Hankin & Duran Caballero, 2014).

5.4 Future Plans by the Stakeholders

Leading networks and organisations have published strategic visions and plans for improving nanosafety worldwide. In addition, individual stakeholders have also reflected on the desired future developments. These strategies and recommendations are presented here, distinguishing between actions in the areas of research, policy-making, industry and responsible research and innovation.

5.4.1 Research

The Strategic Research Agenda 2015–2025 of the European Nanosafety Cluster sets targets for research in Environment, Health and Safety aspects of engineered nanomaterials. Future research priorities in the European Nanosafety Cluster include discussing the development of measurement methods for real-life exposure to nanomaterials for protecting workers' and consumers' safety. It is necessary to adopt standard protocols and to disseminate information on the correct methodology in the nanorisk assessment community (Savoilanen et al., 2013). Another priority mentioned by a European expert in an interview for the NMP-DeLA roadmap is to develop a 'carcinogen counter' as simple and easy to use as a Geiger counter for radioactivity. This fits in the recent change in EU strategy from funding nanosafety research to integrating nanosafety in larger enterprises and innovation initiatives (Malsch et al., 2015).

Hankin and Duran's above-mentioned analysis resulted in a roadmap of actions related to nanotechnology regulation in Brazil, including the following recommendations: (a) engage sustainably with the European NanoSafety Cluster; (b) continue engaging with relevant OECD and ISO activities; (c) industry and research organisations should engage with relevant accreditation and certification schemes before and after formal regulation is adopted; (d) develop a Brazilian regulatory databank following the example of the EU and other existing databanks. The roadmap also includes detailed recommendations about the role of specific Brazilian institutions

[47] http://sectordialogues.org/pt-br/acoes-apoiadas/498

in the implementation of the individual work packages of the NANoREG project (Hankin & Duran Caballero, 2014).

Other European experts see opportunities in Latin America offered by the Cuban research community that has developed its own nanosafety methods and is interested in establishing cooperation after the end of the embargo, in particular with France.

In several discussions with researchers from Latin American, it became quite clear that the region lags behind in research related to safety issues, risk assessment or environmental impacts of nanotechnologies. This is especially true in comparison with the situation in Europe. The interviewed researchers strongly suggested that the development of new nanomaterials or nanobased technologies should be better accompanied by studies on potential and effective risks and impacts. More risk research would also offer better demonstration opportunities for viable and secure nanobased solutions which could give incentives to policy-makers and consumers to get involved or interested in new nanobased products.

A suggestion is to form a group of stakeholders in nanosafety including regulatory agencies, industry associations and people doing safety relevant research that starts to draft a white paper on how to proceed and how to specifically integrate European and Latin American efforts in that respect. In the longer term, Latin American nanosafety experts should be offered access to infrastructure and equipment and training, e.g. in the European facilities. Priorities in research include the following:

- Establish a partnership between scientific disciplines in this field.
- Be careful with the experimental protocols, and develop protocols for exposure assessment. There is a need for reference materials.
- Study exposure to nanomaterials along the life cycle of consumer products. Study chronic profiles and different exposure routes (e.g. through the nose).
- Study exposure to food with nanoingredients.
- Study links between exposure to nanoparticles and diseases for different groups (workers, consumers, adults, children, etc.).
- Develop new methods for epidemiology (Malsch et al., 2015).

5.4.2 Policy-Making

At global level, the WHO is including nano in its Healthy Workplace Programme in the form of occupational health and safety regulation/guidelines for nanomaterials. Government departments across the globe should apply Occupational Health and Safety rules, manage production, educate workers, fund risk assessment, and discuss social issues. To this end, the OECD WPMN is coordinating international governance and a common research strategy in nanosafety.[48]

[48] http://www.oecd.org/env/ehs/nanosafety/

In discussions during the NMP-DeLA project, we noticed a high demand on the part of Latin American researchers to be able to rely on uniform guidelines for nanosafety with clear references to definitions, standards and assessment criteria of mid- and long-term toxicological effects and social and environmental impacts. Moreover it was recommended to make safety a national research priority in the area of nanotechnology. This would initiate a more comprehensive strategy allowing for initiatives in capacity building and trainings for different stakeholder groups (technicians, employees of regulatory bodies, researchers, etc.), information and awareness campaigns, trans-disciplinary and multi-stakeholder dialogue, etc.

A global approach to nanomaterial safety is needed. This requires the development of a common roadmap of evolving solutions for a variety of nanomaterials in a broad scope of industries. In addition, a better understanding is needed of different preoccupations with risks (e.g. GMOs) between European consumers and American and Asian consumers.

In nanosafety, other Latin American countries than Brazil should also fund longer-term collaboration. This requires the selection of experts, the clarification of objectives, dissemination of results, training of young researchers and professionals and reliable funding for projects.

5.4.3 Industry

In Latin America as well as Europe, there may be local market opportunities for services offering nanosafety evaluations for industry. Potential applications are monitoring safety at the workplace and monitoring consumer's safety, safety by design and failing cheaply, following the example of the pharmaceutical industry: quality by design. Similarly, universities may advise industry about safety by design. The exploiters of a Dutch tool for managing occupational health and safety of chemicals[49] are interested in adapting it to Spanish-speaking markets. There could be an opportunity for local partners to engage in consultancy related to the online tool.

5.4.4 Responsible Research and Innovation

According to participants in the NMP-DeLA project, there is a need for life cycle models for nanomaterials to determine the final fate of nanoparticles during their life cycle, also in the environment. This should be a sustainable and positive endeavour engaging all stakeholders from Latin America, Europe and other parts of the world. The way forward leads via technological networks and social actions to engage the local population and companies in innovation and communication. A

[49] www.stoffenmanager.nl

key question is 'How to remove the pollution including nanomaterials from the environment including water, air and soil?' It is important to foresee what will be the most important polluters in order to develop clean nanomaterials.

Conclusions: A Viable Scenario for Latin American Involvement in Global Risk Governance

In this chapter, we have presented current developments in nanosafety research, policy-making and stakeholder engagement in Latin America and existing cooperation with international organisations and predominantly European partners.

It appears that nanosafety research has more or less taken off in the last 3 years and that Brazil is the clear regional champion in this field. Overall, the Latin American nanosafety research community has shown a good level of commitment and qualifications but is fragmented and lacks international visibility. This is evident from the bibliometric data as well as from comments of some of their European peers.

Risk governance of nanotechnologies has entered the political and policy agendas in several Latin American countries including Brazil, Mexico, Uruguay and Argentina in recent years. This was reportedly in response to initiatives by international organisations including UNITAR and OECD, as well as governmental initiatives from the USA and the European Union.

Civil society organisations from Latin America have actively engaged in global dialogue on risk governance for over 10 years, in close collaboration with their counterparts from other parts of the world. Their influence on UN initiatives for governing nanotechnologies by SAICM and UNITAR has been demonstrated.

The review in this chapter suggests the following starting points for strengthening Latin American involvement in global risk governance of nanotechnologies: researchers from Latin America are welcome to engage more actively in relevant international scientific associations including SETAC, IWA and GWRC and the European Nanosafety Cluster. The UNITAR guidance for developing a national nanotechnology policy and programme as well as its offer of training could be adopted by more Latin American governments following the example of Uruguay. Similarly, the WHO Healthy Workplaces Programme's guidelines on nanomaterials and workers' health, which are apparently still under development, could be disseminated to relevant authorities in these countries and the general public. The European Union might consider inviting other Latin American governments and research institutes, besides Brazil, to engage with NANoREG in a way that does justice to their needs and capacities. The analysis and recommendations made by Hankin and Duran could inspire the organisation of a policy and research community on nanosafety in other Latin American countries. Latin American civil society has demonstrated interest and capacity to engage in dialogue and public awareness raising on risk governance of nanotechnology. Their role as watchdogs and dialogue partners could be strengthened by improving their formal role in decision-making processes and public engagement at national level. The global alliance of these organisations established in 2007 could play a coordinating role if it is still operational.

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Chapter 6
Nanoeducation for Industry and Society

Ineke Malsch, Dorota Rutkowska-Zbik, Albert Duschl, Martin Himly, Thomas Zadrozny, Costas Kiparissides, Olga Kammona, Moshe Talesnik, Yoel Rothschild, David Rosenberg, Bartlomiej Szafran, Paula Queipo Rodriguez, and Iseult Lynch

Abstract A recent study on the needs of employers in industry and other sectors for graduate employees who have received education in nanotechnology shows a mismatch between the existing offers at European universities and the real needs of the labour market. In particular, industry expects to hire employees with skills in

I. Malsch (✉)
Malsch TechnoValuation, Vondellaan 90, 3521 GH Utrecht, The Netherlands
e-mail: malschtechnovaluation@xs4all.nl

D. Rutkowska-Zbik
Jerzy Haber Institute of Catalysis and Surface Chemistry, Polish Academy of Sciences, ul. Niezapominajek 8, 30-239 Krakow, Poland

A. Duschl • M. Himly
Immunology and Allergy Division, Department of Molecular Biology, Paris-Lodron-University Salzburg, Hellbrunner Strasse 34, 5020 Salzburg, Austria

T. Zadrozny
Nanofutures Association, Brussels, Belgium

C. Kiparissides • O. Kammona
Centre for Research and Technology—Hellas (CERTH), Chemical Process and Energy Resources Institute (CPERI) Laboratory of Polymer Reaction Engineering (LPRE), Hessaloniki, Greece

M. Talesnik • Y. Rothschild • D. Rosenberg
Moshinsky R&D Center ORT Israel, 28 Hatayasim Rd., Tel Aviv, Israel

B. Szafran
Faculty of Physics and Applied Computer Science, AGH University of Science and Technology, Al. Mickiewicza 30, 30-059 Krakow, Poland

P.Q. Rodriguez
PRODINTEC, Parque Científico Tecnológico de Gijón, zona INTRA. Avda. Jardín Botánico, 1345, 33203 Gijón, Asturias, Spain

I. Lynch
School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston BI5 2TT, United Kingdom

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nanosafety, regulation and environmental impact assessment within 5 years. However, universities appear to have difficulties incorporating these topics into their curricula. Here, results of our study are introduced. Moreover, the outlines of interdisciplinary model curricula spanning the bachelor, master, and Ph.D. levels of academic education that can support efforts to address the mismatch between study contents and skills needed in the nanotechnologies job market and minimise its possible impact, are discussed.

6.1 Introduction

The risk governance of nanotechnologies that is the topic of this book can only have a chance to succeed if the professionals implementing it are well trained and possess the relevant knowledge and skills. Nowadays, many of these professionals have not come across nanotechnology in their education and struggle to find suitable courses or access to expertise to fill their knowledge gaps.

The community who need to deal with potential risks of nanotechnologies in their daily practice is a more diverse group than one might think. It includes managers and employees of companies and research organisations where nanomaterials and nanotechnologies are handled, and also government officials involved in regulating these materials and their applications, and promoting innovation (Malsch, Subramanian, Semenzin, Hristozov, & Marcomini, 2015), as well as those involved in transporting of nanomaterials and nano-containing products, in remediation of contaminated sites, etc. The dialogue on risk governance and regulation engages an even more heterogeneous community including politicians, civil society organisations, industrial representatives, media and the general public (Malsch, 2013). In reality, all citizens, old and young, are already exposed to products incorporating nanomaterials and nanotechnologies, but most people are unaware of this.

On the other hand, the first generations of students who have come across nanotechnology in their curriculum have graduated and entered the labour market since around 2010. Universities all over the world are now offering nanotechnology courses at bachelor, masters and Ph.D. level, either as fully interdisciplinary nanotechnology curricula or as a specialisation within a traditional discipline such as nanophysics, nanochemistry, nanomaterials or nanobiology. This chapter presents recent findings on the current offering of nanotechnology education at secondary and tertiary levels. Further, this offering is contrasted with the results from the surveys carried out among employers and students regarding their needs for nanotechnology expertise and of job opportunities available for graduates with nanoskills.

6.2 Reaching Out to New Generations: Nano at Secondary Schools

One of the main objectives of introducing nanosciences and technologies to the secondary school system is to invite students to learn and discuss scientific knowledge of social interest relative to nanomaterials (among others), allowing them to evaluate critically what they read in newspapers or see on TV from a more objective perspective. In this manner, it is expected to inspire more students to become interested in nanotechnology and other natural sciences and to pursue science, technology, engineering or mathematics courses at University. Since nanotechnology curricula are flexible, it is easier to let the teacher adjust allocation of hours to workshops, labs or discussions, compared to other classical disciplines. One key approach to nanotechnology is to expose students to the Ethical, Legal and Societal Aspects (ELSA) through discussion and debate. ELSA draws attention to the relevance of nanotechnology to all students and invites them to investigate further 'under the hood'. Taking this perspective of nanotechnology, participation of non-science and technology learning students is also achieved (Talesnik, Rosenberg, Aberg, & Lynch, 2013).

We have explored the state of the art of secondary education in nanotechnology in European Union Member and Associated States through an online survey carried out between April and July 2013. In total 36 science teachers answered it, from eight countries. They were approached through the European Schoolnet (EUN),[1] the Association of Secondary Teachers in Ireland (ASTI) and our own contacts.

In addition, we held in-depth interviews with ten leading persons from ministries of education and academia and several senior teachers. This semi-qualitative study demonstrates that the teaching of nanotechnology at secondary schools is in its infancy. Few students are exposed to nanotechnology in their education, ranging between a few thousands in most countries, to 20 % of all students in Ireland, and to all students (until aged 15/16) in the United Kingdom having at least some exposure to nanomaterials and their properties in KS3 and KS4 science curricula.[2] In all the countries investigated, several nanotechnology programmes implemented since 2008 were identified, yet most included no more than a few schools and the project ended within a year or two. It was expected that teachers would continue the nanotechnology teaching in schools by themselves, even though many projects reviewed here needed significant cooperation with universities and research centres.

[1] European Schoolnet is a network of 31 European Ministries of Education, based in Brussels, Belgium.

[2] Secondary education in the United Kingdom was not covered by our study. However, in the United Kingdom, there are some nanotechnology aspects in both Key stage 3 (11–13, 3 years) and Key stage 4 (14–16, 2 years up to and including GCSE exams) science curricula, with science being a compulsory subject for all students at these stages. Key stage 3 chemistry covers aspects of materials properties, looking at properties of ceramics, polymers and composites. Key stage 4 chemistry covers aspects of structure, bonding and properties of diamond, graphite, fullerenes and graphene.

We found a great variety in the numbers of hours and ways of teaching sciences in general and nanotechnology in particular in the six countries that were the focus of more in depth case studies: Ireland, Spain, Austria, Italy, the Czech Republic and Israel. There appears to be little information about the requirements of universities and few contacts between schools and universities (Talesnik et al., 2013).

A subsequent study of best practices in nanotechnology education at the secondary school level covered 12 projects including EU-funded projects (NanoYou and NanOpinion), initiatives of national (Spain and Austria) and regional governments (Baden Württemberg and Germany), an Israeli school network, academia (Italy and Ireland), industry (Czech Republic), a science museum (Germany) and a local initiative of an individual teacher (Germany). This semi-quantitative study was based on interviews with 11 key persons and an online questionnaire circulated among the teachers involved in the selected programmes, as well as internet sources and reports on the programmes. The selected programmes represent the best practice of teaching nanotechnology in secondary schools. Each programme achieved at least one of the following threshold requirements:

- Programmes that are widely implemented—In terms of the number of participants, the geographical area, etc.
- Comprehensiveness—How rich and innovative the programme was in terms of content, new teaching methods, etc.
- Involvement of the community, industry and academia—Whether there was any collaboration with different stakeholders in the school's immediate surroundings.
- Award winners—Programmes, which were acknowledged through national or local awards.
- Growing programme—Programmes that grow every year, even if the initial phase has been concluded.

We compared the programmes on six parameters in order to outline and compare the various profiles, strengths and weaknesses. They shared similarity in three of these parameters:

- Most programmes were compulsory. This suggests that relying on voluntary attempts does not reach the audience of secondary school students.
- Nine programmes made use of a virtual platform. However, virtual platforms were not found to have been used very much in practice. Virtual teaching methods could improve projects educationally and help to lower the cost of the activity (compared to a real lab).
- The programmes used more theoretical than hands-on pedagogical approaches and practices, suggesting that introducing hands-on activities to the classroom as a general practice has yet to be undertaken.

The projects greatly varied in the other three parameters:

- The degree of independence is the project taught as part of an existing subject or as an independent subject?
- The involvement of industry or academia.

- Community involvement varied but was generally scarce. Virtual teaching methods could broaden the discourse and reinforce the reported benefits of community involvement while also addressing hard to reach audiences.

In the framework of this book on risk governance, the aspect of community involvement is most relevant, because it shows how secondary schools may contribute to awareness raising about nanotechnology among the general public: In the Austrian programme 'Sparkling Science', the students presented their project findings to the local community. The programme offered by the Israeli school network ORT included one 'Nano-day', when parents and guests from the local community were invited to the school. The Swedish programme included an exhibition of students' work that was open to the public. The Czech company Contipro offers lectures by University professors to and for the local community including students. The German Museum hosts an exhibition that is open to visitors including students. The projects undertaken by students of the individual teacher are submitted to national competitions and some of them have won these. No community involvement was undertaken in the following programmes: the EU projects NanoYou and NanOpinion, the Spanish curriculum for the first year of Bachillerato, the programme for high-achieving gymnasium students in Baden-Württemberg, the Italian Nano-lab, or the Irish programme 'Nano in my Life'.

To conclude, the best practices in NST education is compulsory and hands-on activities (experiments). In addition, virtual teaching (that is, teaching through videos, online competitions and so on) increased the attractiveness of science topics and improved the effect of education. The benefit of NST teaching in secondary schools comes in learning about new technologies at an early stage of their development. This provides opportunity to build a highly educated and aware public which is able to discuss and learn about scientific advancements.

6.3 The Current Offer of Nanotechnology Education at European Universities

No comprehensive overview could be identified of all nanotechnology courses offered by European universities. Kiparissides and Kammona (2011) identified 27 bachelor courses in nanosciences and technologies, 106 M.Sc./Ph.D. level courses and five other degree courses in Europe and 17 bachelors, 35 M.Sc./Ph.D. and 25 other degree courses in North America. This gives an idea of the likely size of the present offer of such academic education in Europe also. However, this study is not focused on the quantity, but on the relevance of the current offer to the needs of the labour market outside academia and education.

6.3.1 University Survey

From March until December 2013, we carried out an online survey among representatives of universities to collect information on the current offer of education in nanotechnology at European universities and the strategies to implement this.[3] Forty-three responses, including 35 from European respondents were received. This included six from Germany, four from Denmark, three each from Spain, Belgium, Switzerland and the Czech Republic, two each from Austria, France, Ireland and Israel, and one each from Norway, the United Kingdom, Turkey, Poland and Bulgaria.

The questionnaire included 29 questions on general information to identify the course, the programme details the career of the graduates and the level of cooperation with industry. Ten responses covered B.Sc. programmes, 19 M.Sc. programmes and six Ph.D. programmes. Physics is included in 32 out of 35 curricula, chemistry and materials science in 27, Biology in 15, Biotechnology in 12, Electrical Engineering in 11 and Medicine in 9. Most B.Sc. and M.Sc. programmes produce 10–20 graduates per year.

The skills and knowledge developed in the university programmes are included in Fig. 6.1. The most popular included subject is characterisation and metrology. Over 70 % of the programmes cover nanoelectronics, nanostructures and composites, or nanocoatings and smart surfaces.

The skills and knowledge that are included in the programme which the university respondents considered would be required by industry are summarised in Fig. 6.2.

All the respondents responsible for doctoral programmes indicate that career prospects for their graduates include R&D companies (companies that offer R&D services to industrial clients) and academic routes (Fig. 6.3). Generally, the respondents find that the career prospects are the broadest for the graduates of the doctoral programmes, with one significant exception: only half of the doctoral programmes indicated research staff as the targeted career. On the other hand, 95 % of master programmes chose this option, which included also the Ph.D. studies. The real output figures for the surveyed courses indicate that 54 % of graduates ended up in research, academia and education, 23 % in industry and 14 % in R&D companies.

We also investigated the indicators for a higher likelihood that graduates from a specific programme ended up in careers outside academia. The transfer of graduates of nanoscience and nanotechnology programmes to industry and R&D companies turns out to be most successful when the students participate in cooperation with the industry (e.g. via modules co-taught by industrial experts) or undergo industrial internship training as part of their studies. This factor was established by the present study as the most effective means of providing a productive start towards industrial carriers for graduates. Programmes that include courses taught by industrial experts train graduates are three times more likely to find employment

[3] http://nanoeis.eu/university

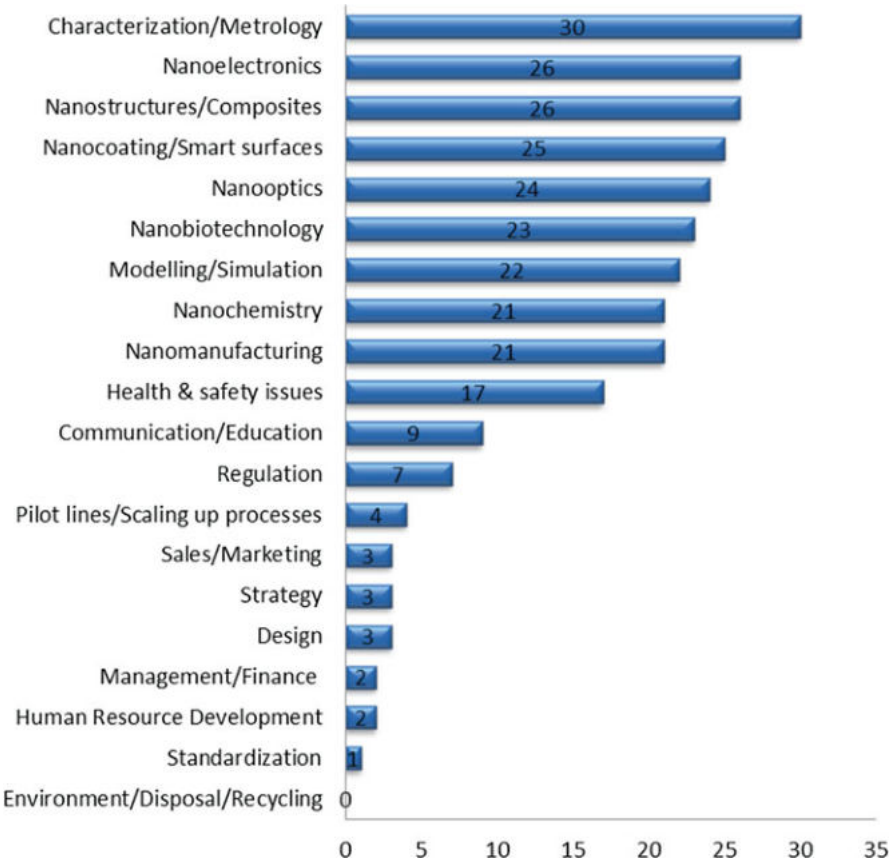

Fig. 6.1 Main nanotechnology-related skills and knowledge offered by the university programmes showing the number of positive responses for the 35 respondents

in R&D companies. Courses introduced to curricula in response to industrial demand increase threefold the flux of graduates to industry but reduce somewhat the number of graduates ending up in the R&D companies. Cooperation with industry in setting up the curriculum has a positive but quite limited effect on the transfer of the graduates to industry and R&D companies (Szafran, Wojcik, Spisak, Griffin, & Rutkowska-Zbik, 2014b).

6.4 Case Studies

In order to gain a better understanding of the factors that influence the relevance of the curricula to non-academic employers, we carried out a number of case studies at each of the three educational levels (B.Sc., M.Sc. and Ph.D.).

Fig. 6.2 Re-ordering of the main nanotechnology related skills and knowledge offered by the universities according to the universities' perceptions of what is required by industry based on the same 35 responses as Fig. 6.1

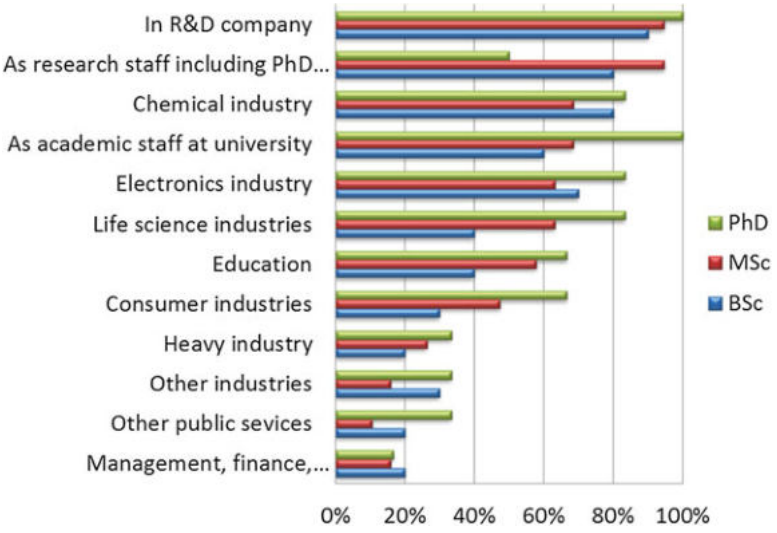

Fig. 6.3 Career prospects per programme level. *Note*: Percentages do not total 100 % because respondents could check all that apply

The B.Sc. courses studied include 4-year courses offered by Trinity College Dublin and Dublin Institute of Technology in Ireland, and 3-year courses offered by the University of Basel in Switzerland, the iNANO centre of the University of Aarhus in Denmark and Saarland University in Germany. The interdisciplinary character of the B.Sc. courses is generally perceived as a strong point of the curricula. The representatives of the programmes, in their opinions given in the questionnaire, interviews as well as on the public web pages, indicated that the interdisciplinary character of the education at the first year of the studies is one of the possible factors to motivate the students to enlist on the B.Sc. in Nanoscience and Nanotechnology. Students with a broad interest in natural sciences have an opportunity to study more than one subject and decide on their specialisation at a later stage. The 3-year B.Sc. is not considered sufficient to enter the industrial labour market, while the Irish 4-year curriculum with strong interaction with industry in the fourth year does qualify graduates for such jobs in a wide range of industries. Nevertheless, most graduates prefer to go for a higher degree. In most, but not all, of the B.Sc. courses, direct interaction and in particular, internships are postponed to higher educational levels (e.g. final year or a 4-year programme). The Dublin Institute of Technology and Saarland University programmes emphasise industrial engagement: the former through a compulsory 7-month industrial internship in the fourth year, and the latter through an 8-week industrial internship before the start of the course. In some Swiss programmes, the students visit companies using nanotechnology as a part of the regular programme. B.Sc. theses in general have mostly a scientific character and are done at the university in one of the research laboratories. An option for the students to prepare the B.Sc. thesis with an industrial or R&D company that is encountered in a part of programmes is certainly a practice that should be recommended. The students willingly use this opportunity if offered. In some cases (B.Sc. by Saarland University for instance), more than half of the students choose to prepare a B.Sc. thesis in cooperation between the university and an industrial company.

At M.Sc. level, we studied national courses offered by iNANO (University of Aarhus) and the Technical University of Denmark, the Swiss Master in Nano and Micro Technology and the Spanish National School on Molecular Materials. We also included European Master programmes (Nanomat European Master programme, a Polish-French Master programme led by Univ. Katowice and Univ. Le Manse as well as a Danish–German programme by the Technical University of Denmark and the Technical University Munich) and Erasmus Mundus projects (Monabiphot by ENS Cachan, Master in Nanoscience).

Most of the respondents representing the studied master programmes agree that successful nanoscience and nanotechnology programmes require an environment composed of both scientific laboratories and industrial companies. We found two alternative ways of formation of such an environment. One is based on a formal structure of a consortium or a centre with an advisory board formed by scientists and industrial companies. The other approach is based on a natural synergy between research, experiment, industry and education. For the latter, the cooperation with industry does not have to be centralised or formalised, but it is left to the researchers and their contacts with industry, the R&D departments in particular, to implement.

Education is adapted to the changing needs of industry by researchers individually. Lecturers suggest new courses or changes in existing ones to their respective study committees. The two approaches (direct and formalised) seem complimentary and not contradictory.

The results of the analysis of the follow-up of the programmes (Szafran et al., 2014b) demonstrate that any form of cooperation with industry has a positive effect on the transfer of graduates to the industrial job market. The more direct in nature the contact of the student with industry is the more positive the result. The necessary ingredient for effective direct contact is a real pre-existing cooperation of the academic scientists with industry that allows the students to participate in preparing their Master theses in collaboration with industry, or work as interns in the companies, or both. The evident recommendation for university level nanotechnology programmes in this context is to ensure a successful career for your graduates in industrial nanotechnology an active cooperation with relevant local companies should start before launching a Master degree. A number of public R&D institutions within Europe play a catalytic role as centres of cooperation between the universities and industrial companies. The personnel of these centres combine scientific excellence with awareness of industrial and commercial applications, and their participation in education brings an extraordinary quality to the programmes.

Modules addressing market and commercial applications are largely missing from the nanotechnology programmes. This shortcoming can have a negative effect on the career of graduates in the context of start-up companies or management in particular. One of programmes that aim to fill this gap is the Master of Philosophy in Micro- and Nanotechnology Enterprise at the University of Cambridge that adopts part of the business management course and covers problems involved in the processes of discovery and exploitation. Training in business related modules is also present in Bachelor courses by Saarland University, TUD and NanoFar Erasmus Mundus.

At Ph.D. level, we investigated two programmes. For the Erasmus Mundus Nanofar programme, the cooperation with industry is based on a number of companies that are partners of the project, with all Ph.D. students undertaking a mandatory 2-month internship in one of the partner companies. Some of the Nanofar courses are led by industrial experts (drug delivery systems for instance). The iNano centre in Aarhus organises as one of the options an industrial Ph.D. in the form of a project undertaken by a student on a topic of common interest to the University and a private company. Funding is acquired from a central organisation external to both the company and the university. This course has a remarkably high output of graduates that are employed by R&D companies (about 50 %) and industry (about 20 %), with only 10 % choosing to stay in academic research. This option is chosen by about 20 % of the Ph.D. graduates of all iNano programmes.

To conclude, best practice for university level teaching and alignment with the European Commission Europe2020 vision to boost growth and jobs include the mission of the ‘New Skills for New Jobs’ initiative which sets out to:

- Promote better anticipation of future skills needs
- Develop better matching between skills and labour market needs
- Bridge the gap between the worlds of education and work

The European Commission supports links between university and business at the European level through a series of initiatives. Closer links between business and higher education can:

- Encourage the transfer and sharing of knowledge
- Create long-term partnerships and opportunities
- Drive innovation, entrepreneurship and creativity

Closer cooperation with business helps universities develop curricula that are relevant and meet the needs of students and society. This helps give graduates the right skills and mind-sets for the jobs market.

There are many examples of successful cooperation between academia and industry in Europe. However, the level of co-operation varies considerably between different countries, universities and academic disciplines (Science-to-Business Marketing Research Centre, 2011).

6.5 Exploring the Demand for Employees with Nanotechnology Skills

In order to analyse the needs for nanotechnology skills and expertise in employees, both at the time of recruitment and afterwards, a specific survey was developed. A total of 67 industry representatives replies were received (Queipo et al., 2013). This online survey was carried out during first semester of 2013.

The answers came from 15 European countries, predominantly Portugal, Spain, Italy and Germany. A total of 61 % of respondents worked in SMEs, 10 % in spin-off companies, 19 % in large industrial companies and 9 % in industry associations. While 19 % of companies were primarily active in manufacturing, 12 % were predominantly active in each of nanotechnology or electronics. The companies whose main activity was in nanotechnology were mainly SMEs and focused on production of nanomaterials or characterisation tools for applications such as textiles, health, environment, etc. Other sectors are included in Fig. 6.4 (Queipo et al., 2013).

Overall, 86.4 % of the participating companies declared to have some knowledge in nanotechnology and 9.1 % were planning to acquire such knowledge. While all spin-offs possessed this knowledge, 92 % of large industry and 83 % of SMEs had it. Around 80 % of respondents were either users or producers of nanotechnology, including all spin-offs, 78 % of SMEs and 70 % of large companies. Companies using nanotechnology were mainly active in construction (16.2 %), nanotechnology[4] (13.5 %), manufacturing, biotechnology and electronics (all 10.8 %). The main reasons for not using nanotechnology (15 companies) included: it is not necessary or not in the company's core business (53.3 %, mainly consultancies), the lack of technology (26.7 %), the lack of knowledge, price and the lack of expertise (6.7 % each).

[4] We did not specify the definition of nanotechnology, so this is according to the companies' own understanding of the term.

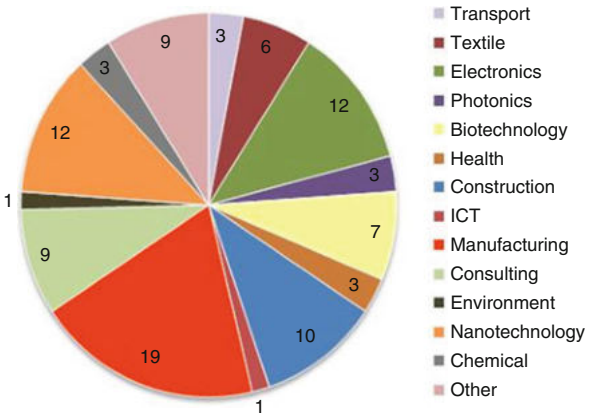

Fig. 6.4 Classification of the companies (in %) responding to the NanoEIS education needs survey according to their main activity area

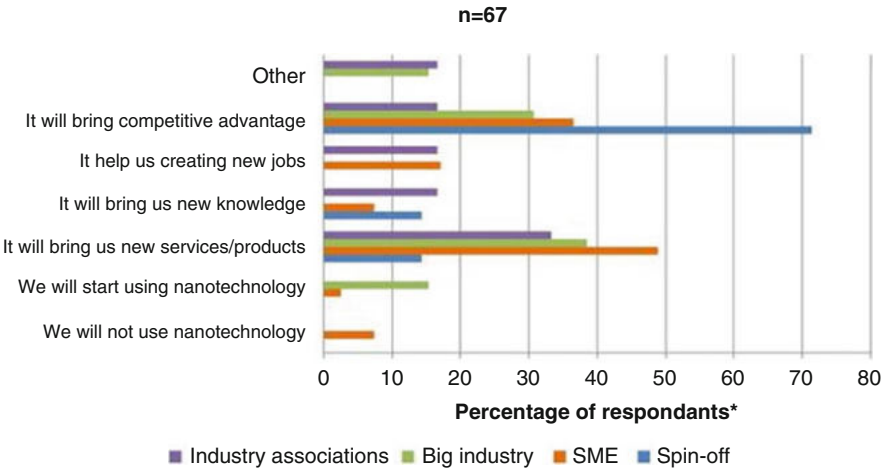

Fig. 6.5 Companies expectations in 5-year time with respect to nanotechnology. **Note*: Percentages do not always total 100 % because respondents could check all that apply

In 5-year time (i.e. by 2018), 71.4 % of spin-offs expect that nanotechnology will bring them a competitive advantage. Half of the spin-offs expect new nanoenabled products or services, as do 37 % of SMEs, 38.5 % of large industry and 33.3 % of industry associations (see Fig. 6.5).

Three quarters of the companies already had employees with nano-related skills. This varied between 86 % of spin-offs and 76 % of SMEs, 70 % for large industries and 83 % of associations. Spin-offs, large industries and associations mainly employed staff at Ph.D. or M.Sc. level, while SMEs also employed staff with a B.Sc. or vocational training background (see Fig. 6.6).

Around half of the respondents do not intend to hire nanotechnology experts, especially spin-offs (71.4 %) and large industries (70 %). SMEs that already employ nanotechnology skilled workers are most likely to hire additional experts within

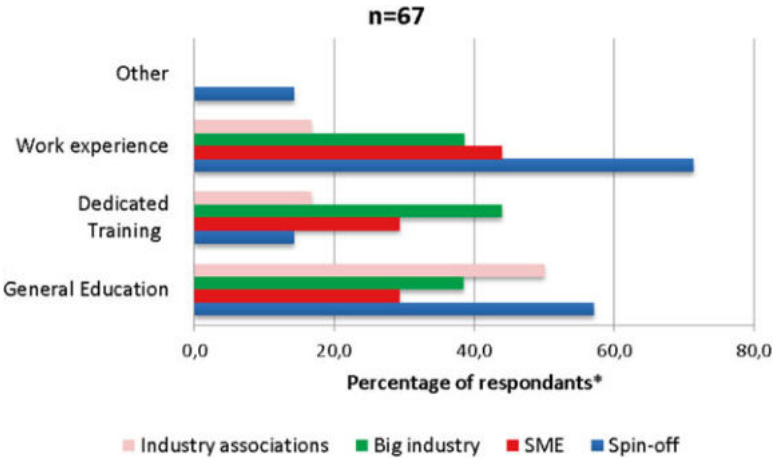

Fig. 6.6 Ways of acquiring nanotechnology skills and knowledge. **Note*: Percentages do not always total 100 % because respondents could check all that apply

1–3 years (56 % of SMEs). Out of the ten SMEs without nano-skilled workers, only two are planning to hire such experts. Those that hired nanotechnology qualified staff in the past, experienced the following problems:

- Scarcity of skilled staff with experience in technology transfer
- Lack of nano-specific knowledge
- Education in universities is too theoretical
- The lack of practical knowledge from schools and universities

The respondents ranked the nanotechnology skills they considered necessary now and in 5 years. This is compared to the current offer at universities in the section below. To acquire these skills, 58.2 % of the respondents declared that they are willing to invest in nanotechnology specialised training. This is particularly relevant to SMEs and industry associations where percentages increase to 68 % and 67 %, respectively. On the other hand, 77 % of large industry will not be investing in training, 41.8 % of the respondents declared that they are involved in education, especially SMEs with almost 58 % and spin-offs with 41 %. However, the way of involvement varies from giving lectures at universities to sponsoring scholarships. Examples are listed in Table 6.1.

6.6 Comparing the Industry Needs with University Offers

The competences most required by the industry are related to health and safety (risk) issues. These are covered by only half of the surveyed programmes. Environment, disposal and recycling has a ranking in the middle of the industry survey, but is not offered by any university participating in the survey. Universities

Table 6.1 Ways of industry involvement in education by type of employer

Type of employer	Ways of involvement
Spin-off	• Provide opportunities to do research for M.Sc. and Ph.D. students
	• Lectures (University Masters level) on nanotechnology (particularly nanofabrication and nanofluidics)
SME	• Sector environment: Partnerships with Universities
	• Industrial training on surface science and nanoparticle-based materials
	• Tours for University students
	• Lectures at educational institutions on life sciences or in masters on Universities (engineering School)
Large industry	• General support of education on chemistry, but not necessarily dealing with nanotechnology
	• Professional trainings for end-users in the construction sector, but not dealing with nano
	• Sponsoring Ph.D. scholarships related to nanotechnology
	• Organisation of workshops
Associations	• Promoting and supporting (by using National projects) Master and Ph.D. tracks specifically oriented to Nanotechnology

rank nanoelectronics, nanostructures and composites, nano-optics, nanobiotechnology and modelling and simulation significantly higher than industry. On the other hand, industry respondents rank standardisation and regulation, pilot lines and scaling up processes and marketing and communication higher than universities. Thus, there is a clear disconnect that needs to be addressed as a matter of priority to ensure that those responsible for introducing new products to market have the necessary skills and knowledge.

Universities and industry respondents agree on the relevance of some other subjects: Characterisation and metrology ranks first in the university and second in the industry ranking. Nanocoatings and smart surfaces rank fourth and third respectively, while nanochemistry ranks eighth and fourth.

To conclude, universities should estimate industry needs on health and safety issues as well as on characterisation and metrology. On the other hand, the university respondents overestimate the needs of industry for skills in nano-optics as well as modelling /simulation.

In 5 years, industry respondents foresee a most pressing need for health and safety aspects, followed by regulation and standardisation and environment, disposal and recycling. There appears to be an urgent need to introduce these competences into educational programmes (Szafran, Wojcik, Spisak, Griffin, & Rutkowska-Zbik, 2014a).

6.7 Views of Students and Graduates

In parallel to the survey among university nanotechnology course providers, we also surveyed opinions of students and graduates on these courses between March and December 2013. We received 317 responses including 139 from Europe.

The European respondents included 44 graduates and 95 students, 43 females and 96 males, 82 discussed M.Sc. courses, 35 B.Sc. and 22 Ph.D. programmes. Relatively many came from Poland and Germany, followed by Belgium, Denmark, Spain and Switzerland. Fewer respondents came from Sweden, Italy, Macedonia, Lithuania, Israel, the Czech Republic, Finland, the Netherlands and Portugal. The sample contains mostly present or former students of programmes that involved physics (64 %). Nearly half of the respondents (45 %) declared that chemistry was present within their programme, with lower values for Electrical engineering (31.65 %), Materials Science (35.25 %) and Biology (21.6 %).

The respondents were asked to indicate the acquired competences that they considered useful for their jobs. Nanostructures and composites are on the top of the students list. This is the third most available topic in the curricula and top of the list of useful skills and knowledge as declared by the academic respondents. On the other hand, these topics are in the middle of the list of the industrial needs. Nanomanufacturing, which is the second on the list indicated by students is available in many of the curricula and is in the first half of the industry needs ranking. Quite similar is the relation of the positions of nanochemistry on the lists. Nanoelectronics and nanobiotechnology are high on both the students and academia lists, although on lower positions in the industry needs ranking.

Health and safety issues, which is on top of the industry needs, was declared by only 6 % of the students answers, although half of the academic programmes declared covering this topic in their curriculum. None of the students declared that the environment/disposal and recycling topics were covered by their studies. This is consistent with the data provided by universities.

Questions on the competences that the students find missing in their curricula were also included. The students and graduates perceive that the most needed but absent topic is the environment/disposal and recycling issues, in perfect agreement with the data declared separately by industry and academia. Management and finance goes second on the missing list. For the rest, the answers are quite evenly distributed. Nanostructures and composites—found useful but already widely present in the curricula are found missing by only 2 % of the answering students and graduates.

Students and graduates were asked which changes should be introduced to the programmes in order to increase the industrial employability. By far the most frequently indicated response was internships at industrial companies and projects. The second change indicated by the students is development of the curriculum in collaboration with industry. This collaboration is frequently declared by the university programmes, but without a very strong effect on the results of education. Quite remarkably, as many as 9 % of the answers by students and graduates indicated that a stronger transfer of general knowledge (e.g. project management, presentation skills, etc.) can enhance their chances for an industrial career. This is the least popular answer, but still the percentage seems surprisingly high (Szafran et al., 2014a).

6.8 Proposed Model Curricula

Our surveys showed a mismatch between the existing educational offers and the expectations of potential employers in regard to nanotechnology graduates. As demand for products that incorporate nanotechnology rises, educational institutes come under increasing pressure to prepare a skilled, nanoliterate workforce. For a long period of time, most nanotechnology education had been occurring informally in lab environments, as well as through elective courses and not within formal degree programmes. It is thus widely accepted that the role of tertiary educational systems should be reinforced. In particular, in order to achieve this goal, the existing training programmes should be improved and revised to take into consideration the industrial point of view and match the available training offers with the current and future job requirements of European industry. Surveys, such as that carried out here, should be performed periodically (e.g. every 5 years) to re-assess current and future needs and allow university curricula to evolve continuously to meet the needs of society and industry.

The modern nanotechnology curricula, which are proposed herein, are mostly based on the industry expectations and the outcomes of the surveys done among universities representatives, nanotechnology graduates and students and reflect the emerging nature of nanotechnology itself. It is generally accepted that nanoscience and nanotechnology are interdisciplinary at their very cores and that is why the education requires basic competences in several traditional disciplines. As such, physics, chemistry, materials science and biology are the most often evoked. On the one hand, conventional educational disciplines and training courses can constrain the introduction of the interdisciplinary approach needed by nanotechnology. It is clearly necessary to overcome such barriers in order to develop the worker skills as demanded by industry. On the other hand, the range of the topics related to nanotechnology is too wide to be covered in detail in a single universal curriculum, calling for specialisation already at the earliest stages of the university education, or the more traditional model of a degree in a core subject followed by nanospecialisation at M.Sc. or Ph.D. level.

The proposed nanotechnology curriculum is designed for a typical Bologna scheme of education, nowadays adopted by most European countries. The students gradually become specialised in nanotechnology-related topics during their first degree of studies (Bachelor or Engineering—during 3 years), second degree (Master—during 2 years),and optionally during their third degree (Doctoral Studies—during 4 years). The emphasis is put on the incorporation of the key skills and knowledge demanded by industry at each level of the education. In such a way, they are not restricted to graduates of higher degrees. Therefore, the courses covering health and safety issues; regulation and standardisation; environment, disposal and recycling; characterisation techniques and ‘ soft’ skills are distributed throughout the whole period of studies. Last but not least, the involvement of nanotechnology industry in teaching through shaping curricula and offering internships is emphasised, as one of the factors facilitating the smooth transition between academia and industry.

In the following, the curricula for each educational level will be presented in more detail with the emphasis on building up the skills and abilities necessary to deal with the risk assessment and risk governance in nanotechnology.

6.9 Model Curriculum for First Degree Studies in Nanotechnology

The presented model curriculum is designed to fit 3-year (sixth semester) programmes ending with Bachelor degree diploma work. The graduates of the first degree in Nanotechnology are intended to continue their studies for the second degree of studies, or otherwise to find employment on the local job market. They will possess the professional skills, necessary to:

- Work in laboratories specialising in nanomaterials synthesis development[5]
- Operate laboratory apparatus and equipment
- Investigate basic properties of this type of material
- Define usefulness of nanomaterials for specific practical purposes
- Develop methods of synthesis of new nanomaterials
- Search for information in the field of nanotechnology and related areas

Further, they will possess general competencies which allow them to:

- Work in teams and task groups
- Solve simple engineering problems in the field of nanotechnology
- Produce reports on issues connected with nanotechnology
- Organise work at his/her workplace (e.g. research laboratory or department)
- Follow occupational safety requirements
- Make use of modern means of communication
- Communicate in a foreign language

The starting semesters of B.Sc. courses should include compulsory intensive courses in the elementary foundations of traditional disciplines: physics and chemistry as well as biology and material science supported by a strong training in mathematics, statistics and computer science. It is proposed that the available modules already existing at universities for the classical subjects (chemistry, physics and biology) are included in the curriculum at the bachelor level, as their value is checked and tested already over a long time. The elements of nanoscience and nanotechnology are intensified in later years, when (often partly) elective courses are introduced. The general education in nanotechnology should be commenced by the introductory lecture on nanotechnology, followed by the more specialised courses, such as bionanotechnology, nanobiology, methods of nanomaterials characterisation, nanoparticles and environment, metallic/polymeric/ceramic/cosmetic nanomaterials.

[5] This includes basic understanding of issues of safe handling, disposal and related legislation.

The choice of electives naturally depends on the overall specialisation of the specific degree programme and is dictated by the profile of the university.

Within the modified curriculum, we propose the following non-standard courses during the first degree of studies:

- Philosophy/ethics of (nano)science (first semester)
- Safety at work (first semester and third semester)
- Cradle-to-cradle product design (second semester)
- Information retrieval (second semester)
- EU regulations regarding nanomaterials (fourth semester)
- Recycling of nanomaterials (fifth semester)
- Regulation, standardisation and management (sixth semester)
- Public speaking—communication to a wide audience (sixth semester)

An integral part of any Nanotechnology programme should be the industrial internship, which will enable mutual contacts between nanotechnology students and their potential employers, planned for the fifth semester of the Bachelor degree. Towards the end of the first degree studies, the student gets an opportunity to specialise in one of the many possible directions, in the B.Sc. thesis in particular. In Europe, students usually continue their studies in the second degree programme, to be fully qualified for the modern job market.

The proposed first degree study programme should yield a graduate, who will be prepared to assess the main risk factors connected with new products containing nanomaterials, or produced with the use of nanotechnology. This is believed to be the first step towards training in risk governance tasks in future employment.

6.10 Model Curriculum for Second Degree Studies in Nanotechnology

This level of education in nanotechnology is designed to fit 2 years (four semesters) and to end with a Master degree diploma work. The graduate of the Master degree in Nanotechnology is intended to be well qualified to work in national/international companies and research institutions, owing to experience gained during the studies and preparation of the M.Sc. thesis, or in a consultancy or regulation establishment as a specialist in nanotechnology and/or nanoscience. The graduates can continue their education via third cycle studies.

The M.Sc. in Nanotechnology graduates will be qualified to work in positions, which require the following professional skills:

- The ability to design nanomaterials with specific properties useful in different areas, e.g. in medicine
- The ability to design, investigate and develop methods of synthesis of nanomaterials
- The ability to develop and plan selection of research methods appropriate for the intended goal

- To supervise technological processes carried out in chemical industry connected with nanotechnology
- The ability to carry out independent investigation of nanomaterials
- The ability to discuss technical and scientific issues connected with nanotechnology

The second degree graduates will possess additional competencies:

- The ability to work in a group and to organise their work
- The ability to use a foreign language
- The ability to define priorities and manage time
- Other abilities acquired during research and development projects in their home countries and abroad

In the course of the second degree studies, the student is introduced to specific topics of nanotechnology. The specialised knowledge is built on the basis of the introductory, background knowledge acquired during the first degree courses. It is advised to further augment the knowledge in specific areas, which are relevant for nanoscience, such as physics, chemistry and biology of low-dimensional systems. Here, by contrast, more time is reserved for nanotechnology-oriented subjects such as design of nanomaterials (computer-based methods and preparation techniques), advanced methods of nanomaterials characterisation and instrumental analysis of nanomaterials. All these should be supplemented by elective courses, reflecting the profile and specialisation of the Master programme. Similar to the first degree, students are delegated for industry internships, to tighten their contacts with industry environment and to confront their skills and knowledge with their future employers' demands.

Within the second degree in Nanotechnology, it seems advisable to further develop skills and gain knowledge, which are identified of high relevance for the job market. As such, the following obligatory trainings are offered:

- Communication through modern media (first semester)
- Safety and clean-room good practices (first semester)
- Regulations: quality management (first semester)
- Nanoparticles and environment (first semester)
- Safety at work project (second semester)
- Communication with media (second semester)
- Life-cycle of nanoproducts (second semester)
- Responsible research in innovation (third semester)
- Entrepreneurship and communication with customers (third semester)
- Communication to a scientific audience (third semester)
- Patent law and intellectual property (fourth semester)
- Strategy planning in science and business (fourth semester)

Following the outcome from our surveys on industry needs, a big effort is devoted to the courses covering safety training, the relation between nanoproducts and the environment, cradle-to-cradle product design and responsible research and innovation. These will result in an increased awareness of the possible risks connected

with the new products incorporating nanomaterials and/or fabricated with the use of nanotechnology. The graduates will be equipped with tools to evaluate the levels of risks and their probabilities. Likewise, the possible solutions to overcome potential problems will be discussed, if possible on the examples from the industrial practice. Moreover, intensive training in communication throughout the curricula is planned. The graduates will have the opportunity to learn how to communicate technical issues to both specialists and non-specialists. The means of communication will include traditional media, such as newspapers, radio and TV, as well as internet with web2.0 tools. It is envisaged that these skills will facilitate better understanding between the producers of nanoproducts, their customers and society in general. Further, he/she will be given background information of social and ethical issues of new nanotechnology applications through a course in philosophy and ethics and patent law and intellectual properties. These altogether will add to the increased awareness of different aspects of such an emerging area as nanotechnology.

6.10.1 Model Curriculum for Third Degree Studies in Nanotechnology

The Ph.D. studies in Nanotechnology are designed to fit 4 years (eight semesters) leading to obtaining the Ph.D. degree. In the course of their third degree studies the student specialises in a specific topic of nanotechnology. Their expertise increases and the holder of the Ph.D. diploma will have a considerable expertise in a particular aspect of nanotechnology. They will be well qualified to work in international companies and research institutions.

The graduate of the third degree studies will be highly qualified to work in positions, which require the following professional skills and knowledge:

- Ability to conduct independent research projects requiring, for example design of nanomaterials with specific properties useful in different areas; design, investigation and development of methods of synthesis of nanomaterials; characterisation of the nanomaterials; testing of the toxicology/ecotoxicology of the produced nanomaterials, etc.
- Ability to develop and plan selection of research methods appropriate for the intended goal

The Ph.D. graduates will possess the following additional competencies:

- The ability to communicate their results to professionals and non-professionals
- The ability to document their work
- The ability to use a foreign language
- The ability to define priorities and manage time (their own and others)
- Knowledge of ethical and legal aspects of their work
- Other abilities acquired during research and development projects in their countries and abroad

The Ph.D. curriculum is least formalised, since Ph.D. curricula take high levels of specialisations into account, so a common model curriculum is not as relevant here as it appears to be in the first and second degrees of studies.

It comprises the introductory lecture on nanotechnology, with the objective to give the students knowledge of the basic concepts and definitions in the field of nanotechnology, the most important properties of nano-objects, selected preparation methods of nanoparticles and selected applications. Such a general course should be supplemented by the elective courses, whose role would be to deepen a certain area of knowledge, and their choice should be left to the Ph.D. student and his/her supervisor. It is advisable that the work done by the Ph.D. student should be enriched either by an industrial internship or by a scientific exchange. An essential part of the Ph.D. programme should be devoted to the training in soft skills. As such, at the Ph.D. level the following is suggested:

- Communication and presentation
- Communication to non-professionals
- Science and the media
- Information retrieval
- Exploitation and commercialisation of research
- Entrepreneurship
- Project management
- Social media in/for science

All these will contribute to the education of the nanotechnology specialist, who will be in a position to identify and evaluate risks connected with emerging nanotechnology issues and will be ready for risk governance tasks. An important part of such a training will be given during the course on project management, as risk evaluation and governance will constitute its essential part. Further, due to the compulsory training in communication to the wide audience, they will be prepared for public engagement through, for example participation in consultancy boards, policy making bodies, etc.

6.11 Conclusions

We have investigated the current mismatch between the offer of secondary and higher education in nanotechnology in Europe and the needs of the labour market. A remarkable finding is that employers in industry foresee a need for training in health and safety aspects of nanomaterials, followed by regulation and standardisation and environment, disposal and recycling aspects. Similar needs were mentioned in interviews with non-industrial employers (reported in Malsch, 2013) and by students themselves on the skills they are most lacking in their current roles. In the current offer by universities, these topics are hardly addressed. While many university professors demonstrate awareness of these gaps, it proves difficult to adapt the already full curricula and incorporate these topics at the expense of

other more traditional subjects. The model curriculum proposed in this chapter may inspire discussion about reorganisation of current or setting up of new curricula. Their modular organisation could also be useful for picking short courses that target training needs of employees in industry and other sectors dealing with nanotechnology.

Placing our chapter in the wider scope of this book on risk governance, risk assurance and risk transfer, we reflect on the strategic importance of interdisciplinary education in nanotechnology to further those goals. Firstly, experiments with nanotechnology in secondary education show that these can help raise awareness of the potential benefits and risks among the new generation as well as their parents and the wider community. The main bottleneck is the limited outreach and ad hoc character of the experiments that have been carried out so far, which limits their potential to be embedded and sustained within schools. Standardisation and dissemination of best practices in secondary education in nanotechnology may be improved by making available practical materials through the European platform Scientix. This should stimulate more democratic decision making on risk governance of nanotechnology as it enhances the capacity of non-experts to form their opinion on these issues, and raises public awareness of the issues more generally.

Secondly, responsible risk governance of nanotechnologies leans heavily on the cooperation of well-trained nanotechnology experts in industry, government and civil society organisations. This calls for integrating courses on health and safety aspects of nanomaterials, followed by regulation, standardisation and aspects of environmental impact assessment and disposal and recycling considerations into the current nanotechnology curriculum within 5 years. In addition, tailor-made short courses and other forms of training on the job should be made available on short notice to professionals overseeing risk governance of nanotechnology.

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Chapter 7
Nanotort Liability at Common Law

Karena Hester

Abstract This chapter explores the possibility of NT-induced injuries leading to toxic tort liability at common law. It outlines the manner in which the Courts have historically dealt with claims for occupational personal injuries in cases involving limited scientific knowledge and scientific uncertainty. Departing from the decision of the House of Lords in *McGhee v National Coal Board*, it follows the adaptation by judicial precedent of the principle of causation under the *conditio sine qua non rule*. This rule is the most basic evidentiary burden of proof which must be overcome by the Plaintiff in a personal injuries action for compensatory general and special damages. However, in two paradigmatic evidential gap case scenarios, which are plaintiff indeterminacy and defendant indeterminacy, causation can become the most difficult evidentiary hurdle for the plaintiff to overcome. This chapter provides salutary insight into the freedom of the Courts to adapt to these scenarios by lowering the evidentiary burden of proof in the interests of social justice and broader social policy. We reflect on the suggestion that a new toxic tort of "no risk", motivated by a general chemophobia and judicial sympathy for deserving plaintiffs, has already been created, which dispenses with the concept of causation as a mechanism for allocating responsibility for harm and effectively collapses firstly, the orthodox conceptual division between factual and legal causation and, secondly, causation into fault. If so, and notwithstanding the existing scientific uncertainty surrounding the consequences for human health and the environment of exposure to nano materials (NM), the existence of some scientific evidence has highlighted the risk of occupational injury. It could be argued in the endorsement of a plaintiffs' claim that this evidence renders the said injury foreseeable. Accordingly, this creates significant risk assessment and risk management challenges for NM stakeholders particularly for NM manufacturers and distributors because it imposes on them a duty to take all risk minimisation measures possible to mitigate their potential exposure to acute and chronic NM-related personal injuries claims as a pre-emptive precautionary measure in the event that claims do arise. Should a mass toxic tort scenario arise, it will ultimately be in the legal arena that the sustainability of the technology will be determined.

K. Hester (✉)
Department of Accounting and Finance, Kemmy Business School, University of Limerick, Limerick, Ireland
e-mail: Karena.Hester@ul.ie

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7.1 Introduction

For the legal system, the main objective is to resolve disputes in a timely manner, striking a balance between the conflicting interests of the parties while taking into account a third interest, the social dimensions, and interest of the activity in question. In terms of concrete realisation of risk, that is to say the finding of nanotechnology (NT) manufacturers and producers liable for adverse incidents if in fact they do occur, it is in the arena of the legal system where the interests of NT stakeholders will play out. There have been instances in the past where the courts have been forced to resolve claims based on limited and/or uncertain scientific knowledge.[1] Parties in litigation require a resolution; they cannot wait for scientific knowledge to develop and catch up with development. The law tolerates uncertainty in the interests of efficient resolution of disputes. If NT litigation ensues, the courts and the law will be the instruments which will ultimately shape and determine the future development and commercialisation of nanotechnology. Moreover, it is in this sphere that the sustainability or otherwise of the sector will be, in large part, decided upon. It is then crucial for the nanotechnology community to gain a better understanding of the legal perspective on the potential for NT liability at common law.

The biggest risk management problems pertaining to new technologies and to NT in particular are the *unknowns*. Despite all of the studies undertaken and ongoing, substantial gaps remain in our knowledge about the risks and impacts of nanotechnology on human health and the environment (D'Silva, 2011). Stakeholders all have different types of objectives and concerns (Glady, Garcia, & Moses, 2012). Consumers want the benefit of this new enabling technology as is evidenced by the demand for products incorporating NT[2], while at the same time they want products which are safe to use and which are not an environmental

[1] There were multiple and mass claims in relation to asbestos, silica, benzene, diethylstilboestrol (DES), lead paint, contaminated blood products and welding fumes. For example in the 1990s silicone breast implant litigation, a huge number of the claims were dealt with by the Courts based on limited scientific evidence and before the scientific evidence conclusively proved that there was no causal connection between silicone breast implants and the alleged injuries. In asbestos claims, there was uncertainty in relation to whether mesothelioma was caused by one single fibre or by multiple fibres or by a single exposure or by continuous exposure and the aetiology of the disease was largely uncertain. There was also the problem of uncertainty in relation to the cause of the disease where there were multiple exposures in different employments and cases of workplace exposure combined with non-tortious exposure e.g. environmental exposure and exposure during self-employment. In DES cases the plaintiffs could not identify the manufacturer of the drug used by their mothers which caused adenocarcinoma which manifested itself after minimum 10–12 years with some claims not filed until 20 years after ingestion of the drug. Generic drugs were often dispensed which lead to problems in the identification of the manufacturer of the particular drug which caused the damage and given the latency period, many of the companies which manufactured the drug were no longer in existence by the time the damage had manifested and legal proceedings initiated.

[2] In 2005 approximately $32billion was spent on products incorporating some form of NT (Lux Research Inc., The Nanotech Report 2006). The National Science Foundation in the US estimates the global marketplace for goods and services using NT will reach $1trillion by 2015 and employ

hazard. Worker have a legal right both at common law and under statute to work in a safe environment where they are not exposed to the risk of personal or fatal injury or disease. Manufacturers and distributors want to get their product onto the market to make a profit while at the same time they want to avoid the spectre of product recalls and the defence of claims for defective products, personal or fatal injuries to consumers and workers in the short or long term. They also want to avoid the cost and negative publicity of claims for environmental damage and remediation and punitive actions by regulators and policymakers arising from non-compliance with or breaches of regulations. Leaving aside the current difficulties of framing an effective EU regulatory policy in relation to NT, regulators want to achieve the optimum regulatory framework in terms of its scope, structure, and effectiveness (Calster, Bowman, & D'Silva, 2011; Marchant & Sylvester, 2006; Mielke, 2013; Wilson, 2006). EU chemical regulatory policy attempts to strike a balance between the competing objectives of ensuring a high level of protection of human and environmental health on the one hand and driving the development of the internal market and the sustainability of NT on the other. It is a delicate balancing act as they aim to enact regulation concurrently avoiding over-regulation, which may deny society of the many well-documented potential benefits of this technology and which would stifle innovation.

Insurers as risk transfer agents are also significant primary stakeholders in the NT environment (Mullins, Murphy, Baublyte, McAlea, & Tofail, 2013). For insurers to be able to offer NT-specific risk products on a financially sound basis, they need to be able to assess and manage the risks associated with the development and use of NT. They are currently handicapped in their risk pricing and underwriting activities by the absence of generally accepted scientific understanding based on meaningful historical data on the potential risks of NT to human health and safety and the environment. This uncertainty is compounded by doubts as to how claims related to NT manufacture and usage will play out in the legal system. Uncertainty about critical issues such as when claims will arise, if indeed they arise at all, if they will appear quickly or after a long latency period, if every nano substance will have a similar impact, the scope, and magnitude of potential claims, and their impact on the insurance industry all add to difficulties experienced by insurers. In that regard, manufacturers and distributors will also be concerned that insurers might be unable or unwilling to offer insurance products for their nanotechnology-specific processes and applications. This would jeopardise the sustainability of this highly potent technology which is seen by many as the next technological revolution.

While the effects and risks of exposure to NM remain uncertain, inhalation studies have found that some NMs are acutely toxic; exposure to nano particles (NP) has been associated with a number of health effects (Savolainen, Alenius, et al., 2010, Savolainen, Pylkkänen, et al. 2010). Carbon nanotubes and nano titanium

two million people Roco, M. C. (2003) 'Broader Societal Issues of Nanotechnology', *Journal of Nanoparticle Research,* 5(3–4), 181–189.

dioxide at low doses[3] are known to induce pulmonary inflammation and fibrosis in animals (Bermudez et al., 2004), exposure to single and multi-walled carbon nanotubes have been shown to induce inflammatory cells and mediators in the bronchoalveolar fluid and increase pulmonary granulomas and fibrosis in rats (Shvedova et al., 2005, 2007), nano titanium dioxide has been shown to cause pulmonary inflammation. Of the animal studies which have been carried out, NMs have been shown to induce cytotoxic and genotoxic effects (Li et al., 2007). Limited availability of exposure and genotoxicity data means that the research is lagging the development and commercialisation of NM products. Animal studies have found that single and multi-walled carbon nanotubes and NM with fibrogenic properties induce oxidative stress, inflammation, granulomas, and fibrosis in lungs leading to fears of their carcinogenic effects and marked ability to induce mesotheliomas (Li et al., 2007; Muller et al., 2008; Shvedova et al., 2005). Nano-titanium dioxide and single and multi-walled carbon nanotubes have induced thrombosis and those studies also provide evidence that NM can reach the systemic circulation. Once in the bloodstream translocation studies have shown that NM can potentially induce effects in any organ in the body including the brain. As data is still very limited, there are extensive knowledge gaps in relation to exposure risk, toxicity, and ecotoxicity and extensive research is ongoing in these areas (Stokes, 2009). In addition, validated analytical methods for characterisation, detection, and measurement of NP are needed, and in this regard, NM-specific instrumentation and metrics are needed. Comprehensive materials characterisation is required before toxicological data can be produced. The availability of exposure data and toxicological study results may well be further hampered by regulatory restrictions on animal testing. The experience of the European Chemicals Agency (ECHA) in the evaluation of registrations under the EU's Registration, Evaluation, Authorisation and Restriction of Chemicals act (REACH) has been that there have been difficulties stemming from the identification of hazards based on a substances bulk form. Of the few NMs which until now have been subject to evaluation under REACH, the difficulty encountered by the ECHA was in the identification of a substance as a NM. Adaptation of standard testing regimes has also presented difficulties in relation to substances in their bulk form.

Inhalation of NMs was one of the first areas to be researched by toxicologists. The Royal Society of Engineers said that the largest hazard is or will be from free nano particles rather than from technologies that embed them. Critically, studies have found that similarities exist between asbestos fibers and carbon nanotubes, and carbon nanotubes are thought to be potentially toxic to humans (Maynard, Warheit, & Philbert, 2010; Muller et al., 2005; Poland et al., 2008). This has created fears of the potential for another asbestos-like scenario leading to mass toxic tort claims particularly in the occupational setting (see next section). In the occupational setting, the primary risk groups for exposure to potentially harmful NMs are employees

[3] For a review of exposure research see: Savolainen, K., Alenius, H., Norppa, H., Pylkkänen, L., Tuomi, T. and Kasper, G. (2010) 'Risk assessment of engineered nanomaterials and nanotechnologies—A review', *Toxicology,* 269(2–3), 92–104.

who work in direct contact with them and, to a lesser extent, those who work close to but do not directly handle NMs. Occupational exposure is "likely to be the most serious and immediate environmental, health and safety concern raised by nanomaterials" (Ludlow, 2007). For instance, one study documented the early development of various pulmonary diseases in the female employees of a Chinese NM manufacturer (Song, Li, & Du, 2009). Due primarily to the nascent state of the scientific evidence in relation to the hazards and effects of NM exposure and to the incremental approach of EU regulatory policy, there is little NT-specific direct command and control type regulation. There is, however, the potential for chronic rather than acute NT-related injuries, which potentially could give rise to toxic tort liability (see next section). These factors have lead major insurers and reinsurers including Lloyds,[4] Allianz[5], and Swiss Re.[6] to publish reports about the potential risks and difficulties insurers may face in relation to underwriting the long tail risks and legal liabilities associated with the NT industry. Therefore, against that background we will consider the law of causation at common law in order to be in a position to take a view in relation to the prospect of liability arising from exposure to NMs, particularly in the occupational setting.

7.2 Legal Liability: Proof of Causation in Toxic Tort

The common law system applies and originated in the United Kingdom where it dates back to the eleventh century. Its medieval origin means that even today centuries-old cases may still be relevant to legal practice. The former British Empire established an extensive legal-cultural imperialism by extending to and establishing the common law system in the United States, Canada, Australia, New Zealand, and India the influence of which has been retained by many of those countries after the end of the former Empire. Common law has also influenced the laws of Cyprus, Ireland, and Malta. Common law is not run by rules but by cases and precedents. When a common law judge is deciding a case, s/he will look for a comparable case rather than an applicable rule. Subsequently, s/he will look for guidance in the decision given in the comparable case. In reaching a decision in a common law case, the emphasis is on comparison of the facts of the case and not on the application of an abstract standard as is the case in most continental systems based on civil law.

In Common law, the basic rule is that the causal relationship between the damaging agent and the resulting injury which is known as causation must be proven on the balance of probabilities by the person who is making the claim—the plaintiff. Causation is the most difficult legal and evidentiary hurdle which the plaintiff must

[4] Lloyd's Emerging Risks Team Report, "Nanotechnology, Recent Developments, Risks and Opportunities" (2007).

[5] Allianz report in co-operation with the OECD International Futures Programme, "Small sizes that matter: Opportunities and risks of nanotechnologies" (2005).

[6] Swiss Reinsurance Company, "Nanotechnology: Small matter, many unknowns" (2004).

overcome in a toxic tort case and causation in common law toxic tort litigation will be the focus of the remainder of this chapter. John Fleming describes the difficulties which causation poses in the law of torts:

> *There is perhaps nothing in the entire field of law which has called forth more disagreement, or upon which the opinions are in such a welter of confusion. Nor despite the manifold attempts which have been made to clarify the subject, is there yet any general agreement as to the proper approach. Much of this confusion is due to the fact that no one problem is involved, but a number of different problems, which are not distinguished clearly and that language appropriate to a discussion of one is carried over to cast a shadow upon the others…[causation] has plagued courts and scholars more than any other … in the law of torts* (Flemming, 1998)

A tort may be defined as "a civil wrong" other than a breach of contract or a breach of trust. The *law of tort* is primarily concerned with private disputes between individuals for which the normal remedy is an action for un-liquidated damages and the provision of compensation. The *tort legal system* is based on the fault principle of liability or strict liability depending on jurisdiction. It acts to deliver distributive, corrective, or commutative justice between the parties or a mixture of some or all three depending on the policy approaches of the jurisdiction in which it operates. Sometimes it acts as a deterrent to future wrongful conduct, thereby acting as a regulatory instrument. As a form of distributive justice, it spreads or distributes burdens, losses, and risks fairly among members of society or a particular part of it.

Toxic torts are torts involving exposures to toxic substances that usually produce latent diseases. Toxic torts sometimes share characteristics with mass torts implicating large numbers of claimants and/or defendants. Toxic torts usually rely on scientific concepts to prove causation.

It is a well-established principle of tort law that the plaintiff must have suffered damage/injury. To succeed, the plaintiff must then show that the defendant *caused* that damage or injury. This means that at the outset it must be satisfactorily established that *on the balance of probabilities*[7] the defendant caused the damage to the plaintiff. The defendant's act must be linked in a factual or scientific way to the plaintiff's injury (McMahon & Binchy, 2013). The negative formulation of the causation rule is helpful. If there is no factual causal link between the defendant's conduct and the plaintiff's injury, then the defendant cannot be liable (except in the case of vicarious liability which is beyond the scope of this chapter). How then do the Courts decide whether the defendant has in fact caused the plaintiff's injury? In order to establish causation, all jurisdictions apply the *conditio sine qua non* test. This test literally means "condition without which the damage would not have occurred". In common law jurisdictions, the *condition sine qua non* test is known as the "but for" rule.

The principle of *conditio sine qua non* stands at the heart of tort law in all jurisdictions whether they operate under the common law or under a civil law code. Under the common law, the test or rule is known as the "but for" rule meaning

[7] The standard of proof in civil claims under common law; *"by a preponderance of the evidence"* is the equivalent standard of proof in most U.S. states.

that an act is a cause of an event if the event would not have occurred without ("but for") the act of the defendant. If the event, for example, an injury or disease would not have occurred without the act in question, then the act can be deemed to be a cause. But the search for *factual* cause is a preliminary one. The purpose of the "but for" test is: "to act as a preliminary filter and to eliminate the irrelevant rather than to allocate legal responsibility" (Rogers, 2010). A problem of the *conditio sine qua non* test is that it accepts equally all events and circumstances as possible causes regardless of whether they are legally relevant or irrelevant causes. When the factually relevant causes have been identified, the legal system seeks to limit the consequences for which the defendant has to answer. In other words, it must then be established whether those factually relevant causes are *legally* relevant to render the defendant liable. This is the second hurdle which the plaintiff must overcome to render the defendant liable. For example, if the defendant crashes his car into the plaintiff because the road was wet, because he was driving too quickly, because there was a sharp bend on the road, and because the brakes in his car were defective. The *factually* relevant causes of the accident are: the wet road, speed, the sharp bend, and the defective brakes. The court would most likely find that the *legally* relevant cause of the accident was the defendant driver's negligence for driving too fast on a wet road with a sharp bend on it with brakes which he knew or ought to have known were defective. There is no precise legal rule. The Courts apply a combination of common sense and mythical formulae to an abnormal or deliberate act and regard that as "the cause". The mythical formulae are the instruments which the courts use in fixing the cut-off point in the line of consequences beyond which the defendant will not be accountable. In the common law system, the reasonable foreseeability test is most commonly used meaning that the defendant will only be responsible for consequences of his act which were reasonably foreseeable by a reasonable meaning objective person. Note that a defendant will always be liable for consequences he *intended* to cause even if these are unforeseeable. In the case of *unintentional* torts, the defendant will not be liable unless he could reasonably foresee damage of *some* sort resulting from his act. Importantly, complete certainty about causation is not required nor is it necessary that the total extent of the damage was foreseeable, which is beneficial for the plaintiff. It is submitted here that even though research in relation to the hazards and effects of NMs are nascent, there is still a sufficient volume of published concerns about the potential risks and adverse effects of NMs that it would be difficult for a defendant to successfully argue that he did not foresee *some* damage particularly in the context of an employer/employee relationship where the employer owes a duty of care to the employee (Van-Dam, 2013).

Some of the most difficult causation issues have arisen in the context of toxic tort in cases involving limited scientific knowledge and scientific uncertainty (Geistfeld, 2011). There are two paradigmatic types of cases, both of which disadvantage the plaintiff to such an extent that application of the traditional *conditio sine qua non* or *but for* rule would lead to injustice. In these cases, the courts have created exceptions by adopting expansive causation principles to compensate deserving plaintiffs

for injuries caused by culpable defendants. In so doing, the reason why causation is such an elastic concept which can be stretched and shrunk according to the circumstances of the particular case becomes apparent.

In the first case, plaintiff indeterminacy, the plaintiff knows what caused her harm but cannot prove on the balance of probabilities that it actually caused the harm because the available scientific evidence indicates that a substance might be hazardous but does not establish that the substance is hazardous and further it is not fully understood how the substance interacts with the human body's biological processes to induce the adverse health outcomes complained of Klein (2008). Many substances are not subjected to epidemiological studies[8] because such studies are expensive and time-consuming and require that a large number of people be exposed to the substance. Consequently, substances are often used in production processes and placed on the market and/or are released into the environment before conclusive evidence of their safety for human health and the environment has been established. In this scenario, the plaintiff cannot prove that the substance caused her or him harm under the traditional "but for" rule. It is possible to envisage an employee who works in an NM production process in a similar difficulty in the future. Case law demonstrates how the Courts have dealt with this problem in the past and provides insight as to how they could deal with NT exposure cases in the future in the event that they arise when the scientific evidence required to prove the causal link between the damage complained of is still limited or uncertain. The case of *McGhee v National Coal Board*[9] was an occupational exposure case in which the plaintiff could not prove that the substance caused him harm under the traditional "but for" rule. However, the House of Lords found in favour of the plaintiff. It modified the established "but for" test because of the insurmountable burden of proof which that test presented for the plaintiff and because of the obvious injustice of refusing a remedy in the circumstances. It was sufficient for the plaintiff to show that the defendants had "*materially increased the risk*" of the plaintiff contracting the disease (dermatitis) complained of rather than having to prove a factual material contribution to its occurrence on the balance of probability. This decision followed and extended a 1956 decision of the House of Lords in *Bonnington Castings Ltd v Wardlaw*[10] where causation was held to be satisfied if the defendant had *materially contributed to the injury*. Any more than a minimal contribution would be material and thereby sufficient. In these cases, a special rule was a pragmatic solution to an intractable problem and could be justified if the plaintiff could satisfactorily show that the defendant acted negligently and that the defendant's tortious conduct more likely than not caused some harm. By showing that the defendant acted negligently, the plaintiff will have established a right in corrective justice to receive some compensation. If that right cannot be adequately protected by ordinary rules, the court is empowered to protect the right by adopting special rules. The court can relieve the

[8] Epidemiology is a scientific discipline concerned with disease distribution and determinants among human populations. The critical measurement is relative risk. Courts rely heavily on epidemiology in the determination of causation.

[9] McGhee v National Coal Board [1973] 1 WLR 1.

[10] Bonnington Castings v Wardlaw [1956] A.C. 613 HL.

plaintiff of the ordinary causation rule in the special context of the paradigmatic case of scientific uncertainty where the aetiology of the disease or injury complained of is not adequately understood. Due to lack of knowledge, causal relationships can be inferred using epidemiological studies. If these are not available, the plaintiff can rely on animal studies, chemical analyses, and laboratory indicators to establish an increase in risk of injury caused by the tortious act of the defendant (Geistfeld, 2011). In the context of NM-induced disease or injury if epidemiological evidence is not available, the plaintiff would be able to rely on other sources of evidence including the results of the studies already referred to and on advances in scientific evidence in the fields of toxic genomics and toxic genetics which will be referred to in a later section.

In the second case, defendant indeterminacy, the cause of the harm is inherently indeterminate because while the plaintiff knows that the harm was caused by one or more within a group of potential defendants, she cannot determine which one/s actually caused the damage. Asbestos exposure is the classic example in situations where the plaintiff was employed and wrongfully exposed to asbestos for various periods of time by a number of different employer defendants and cannot determine which one/s actually caused the damage (Klein, 2008). Case law is particularly useful in this area because it allows us to see the operation of the flexible nature of tort law under common law, which is designed to evolve by adapting to changing conditions and new challenges (Perry, 2012). Salutary insight can be taken from the freedom of the Courts to adapt and relax the evidentiary burden of proof on the plaintiff in the interest of social justice and broad social policy (Farber, 1986). Of particular relevance in the context of NM exposure is uncertainty about the aetiology of mesothelioma,[11] the lengthy incubation period between asbestos exposure and the manifestation of injuries which can run into decades, uncertainty in relation to exactly when and where the exposure occurred, and the fact that there were often multiple exposures in different employment situations. The combination of these factors makes it impossible for the plaintiff to prove causation on the basis of the traditional "but for" test. It is reasonably foreseeable that there could be similar exposure scenarios in the future in the context of NM exposure and it is the latency period and the long tail risk which is of most concern for NM manufacturers and producers and their insurers.

In the landmark UK mesothelioma case *Fairchild v Glenhaven Funeral Services Ltd*[12], the plaintiff had been employed by different employers for different periods and had been wrongly exposed to asbestos dust in each employment as a result of which he contracted mesothelioma. The aetiology of mesothelioma is uncertain. It is unknown whether the disease is contracted due to the inhalation of a certain quantity of asbestos fibres or a single fibre. What is known and what is significant from a legal perspective in the context of establishing causation is that mesothelioma is an indivisible disease meaning that once it has been contracted and materialised, it is not exacerbated by subsequent exposures to asbestos (McIvor, 2013b). The evidence

[11] Mesothelioma is a cancer, predominately of the lining of the body's internal organs, particularly the lung that is strongly associated with exposure to asbestos. Although scientific evidence is lagging it is now accepted that a single asbestos fibre will not cause mesothelioma.

[12] Fairchild v Glenhaven Funeral Services Ltd. [2002] UKHL 22, [2003] 1 AC 32.

before the court at the time of the hearing of the case was that while asbestosis is related to the total amount of dust inhaled, the inhalation of a single fibre may cause mesothelioma,[13] although the risk of contracting it may be affected by constant exposure. Due to the number of different exposure situations arising from employment with a number of different co-defendants, it was scientifically impossible for the plaintiff to prove the origin of the fibre which caused the mesothelioma. On traditional causation grounds, the plaintiffs claim should have been dismissed by virtue of the fact that each co-defendant could claim that the exposure situation which gave rise to the contraction and materialisation of the disease could have been caused by the wrongful conduct of any of the other co-defendants. However, the House of Lords found for the plaintiff, holding that not to do so "would be deeply offensive to instinctive notions of what justice requires or demands". This decision went further than the *McGhee* decision which held that it was legitimate to infer from the established facts that the defendants' breach of duty contributed *a material risk* to the development of the disease. The *Fairchild* decision held that in appropriate circumstances, proof that there was a *material increase in the risk* of contracting the disease is sufficient to prove the causation required to establish liability. This resulted in a logical fallacy where risk was conflated with injury (Amirthalinham, 2010). The conditions necessary for the rule established in *Fairchild* were noted by Lord Bingham and it is worth re-iterating them here because of their potential application in the NM exposure context. The conditions were:

1. C was employed at different times and for differing periods by both A and B
2. A and B were both subject to a duty to take reasonable care or to take all practicable measures to prevent C inhaling asbestos dust because of the known risk that asbestos dust (if inhaled) might cause a mesothelioma
3. Both A and B were in breach of that duty in relation to C during the periods of C's employment by each of them with the result that during both periods C inhaled excessive quantities of asbestos dust
4. C is found to be suffering from mesothelioma
5. Any cause of C's mesothelioma other than the inhalation of asbestos dust at work can be effectively discounted
6. C cannot (because of the current limits of human science) prove, on the balance of probabilities, that his mesothelioma was the result of his inhaling asbestos dust during his employment by A or during his employment B or during his employment by A and B taken together

The *Fairchild* test was a policy decision intended to bridge an evidential gap caused by defendant indeterminacy and was founded on the desire to avoid rendering a deserving plaintiff without a remedy against culpable defendant employers who would otherwise have avoided liability by relying on the law as it stood whereby they could each blame each other for the wrongful act, the outcome of which would have been that no one of them would have been liable. Liability was established in this case on a joint and

[13] Single fibre theory.

several basis under the principle of attribution where each co-defendant is liable for the entire indivisible harm subject to contribution from the other co-defendants.

The *Fairchild* test was applied by the House of Lords in *Barker v Corus (UK) Ltd.*[14] In that case, the plaintiff was wrongly exposed to asbestos at his place of employment (tortious), but he also negligently exposed himself to asbestos when he was self-employed (non-tortious). Lord Hoffman found that where the defendant is caught by the *Fairchild* exception, it is irrelevant that there were other exposures "whether the other exposures be tortious or non-tortious, by natural causes or human agency or by the claimant himself". Liability was held to be several in this case rather than joint and several as in the Fairchild case (the value of the decision as a precedent in relation to the sharing of liability was negated by statute shortly afterwards which stipulated liability to be joint and several—as in the Fairchild case.). The case does not, however, dispense with the plaintiffs obligation to prove a causal connection between the defendant's negligence and the plaintiff's injury. This was referred to by Lord Hoffmann in *Gregg (FC) v Scott*[15] when he stated in that case that "in effect, the appellant submits that the exceptional rule in *Fairchild* should be generalised and damages awarded in *all* cases in which the defendant *may* have caused an injury and has increased the likelihood of the injury being suffered…. Adopting such a rule would involve abandoning a good deal of authority." The appellant in that case could not establish a causal link between the injury and the negligence of the defendant.

Another test for causation was devised around the time that *Fairchild* was decided. *XYZ v Schering Health Care Ltd.*[16] was a non-mesothelioma, class action against three drug companies alleging defective oral contraceptives. The Court held that a claimant could prove causation by proving that the exposure more than doubled the risk of the injury occurring which resulted in the "*doubles the risk*" test. The theory behind this test was that if the defendant had more than doubled the risk of the plaintiff sustaining damage or injury, it could be inferred on the balance of probabilities that the defendant had caused the injury. The test was subsequently applied in a mesothelioma case, *Jones v Metal Box Ltd.*[17], and approved by the Court of Appeal in a bladder cancer case *Novartis Grimsby Ltd. v Cookson*.[18]

Therefore, given the freedom and readiness of the courts to relax the plaintiff's evidentiary burden of proof in the interest of "what justice requires or demands",[19] the pertinent questions for NT stakeholders to ask are: (1) given the state of the art of the scientific evidence in relation to the hazards and effects of NM, could there potentially be nano-related personal injury claims? (2) If there were claims, could they be successful?

The simple answer to the first question is that there will be claims if there is damage. Lord Wilberforce formulated the following general principle in the *McGee* case, "*It is*

[14] Barker v Corus (UK) Ltd. [2006] UKHL 20.

[15] Gregg (FC) v Scott [2005] 2 AC 176.

[16] XYZ v Schering Health Care Ltd. [2002] EWHC 1420; (2003) 70 B.M.L.R. 88.

[17] Jones v Metal Box Ltd. (Unreported January 11 2007).

[18] Novartis Grimsby Ltd. v Cookson [2007] EWCA Civ. 1261.

[19] Lord Bingham in Fairchild v Glenhaven Funeral Services Ltd. (op. cit.).

a sound principle that where a person has, by breach of duty of care, created a risk, and injury occurs within the area of that risk, the loss should be borne by him unless he shows that it had some other cause". However, there are all manner of possible claim scenarios, all of which are purely speculative based on the precedents established in other toxic tort litigation scenarios such as asbestos, silica, benzene, diethylstilbestrol, lead paint, blood products, and welding fumes. The answer is most certainly affirmative if in the most straightforward scenario a disease or condition were to manifest itself and epidemiological studies support the factual causal link between the condition or disease and the NM exposure, the source of which can be identified and proven on the balance of probabilities. Only if the defendant were to successfully raise the full defense of voluntary assumption of risk[20] could the defendant be relieved of liability. Another possibility would be for the defendant to raise the contributory negligence defense.[21] Alternatively, an employer could try to exclude or limit liability based on the state of scientific knowledge, unforeseeable events, and/or events which were beyond his control and could not have been avoided even having exercised his duty of care. Whether any of these would be successful or not and whether they would operate as a full or partial defense is purely conjecture at this stage. In practice, it would depend on the facts of the case, the nature and extent of the injuries, the scientific knowledge and evidence, the decision maker, and policy considerations.

If a disease or condition were to manifest itself but epidemiological evidence did not support the factual causal link between the condition or disease and the NM exposure as was the case in the US Agent Orange claims (Farber, 1986), in theory the claims should fail. However in the Agent Orange litigation, Judge Weinstein accepted the notion of using expansive causation principles based on collective responsibility. The plaintiffs were able to prove that the defoliant could cause the type of harm from which they suffered, but could not prove that it caused the particular harm suffered. The Judge used statistical evidence to estimate the total amount of harm that the defendants had caused and he ordered this amount to be paid to the plaintiffs to be divided between them. In the more unlikely event of the manifestation of a disease or condition the source of which cannot be definitively identified and proven on the bal-

[20] *Volenti non fit injuria* which means voluntary assumption of risk is a defence which negates the defendant's liability on the basis that the plaintiff knew of the risk of harm and accepted responsibility for it. In employer's liability cases, only an informed and communicated waiver of a right of action could ever constitute a voluntary assumption of risk. If an employee working in or proximate to NM processes is made aware by their employer of the potential known and unknowns risks of NM exposure in accordance with the duty of care owed by that employer to that employee and with knowledge of this information the employee decides to work there, if the employer has otherwise taken all due care to provide the latest state of the art in protective equipment and a safe place and system of work this defence may be successful.

[21] Where it is proven by the defendant that the plaintiff is partly to blame for their injury due to their own negligence the amount of compensation could be reduced in proportion to the degree to which they are found to have contributed to the damage by their own negligence. For example, if claimants failed to wear protective clothing issued to them, or if they did not follow company procedures or industry standards of practice, then they may be guilty of contributory negligence and the damages awarded may be reduced or even withheld. If it could be shown by the defendant that the injury sustained was due to the sole fault of the plaintiff the defendant would be relieved of liability.

ance of probabilities, it is possible that the claims could fail. In cases where the scientific evidence is uncertain—"evidentiary gap" cases—the Courts could do what they have done in the past. They could adopt an expansive approach to the plaintiff's burden of proof of causation. By proving that the defendant was negligent and/or in breach of statutory duty which more likely than not caused some harm or doubled the risk of harm or materially increased the risk of harm to the plaintiff, the plaintiff establishes her right in corrective justice to receive compensation. If that right cannot be adequately protected by traditional rules, the court is empowered to protect the right by adopting special rules.[22] There is no reason to consider why this would not equally apply in NM exposure cases in any of the common law jurisdictions particularly when the protection of personal injury victims is acknowledged throughout all legal systems to be of greater importance than the protection of property loss or pure economic loss. In summary, to quote Lord Hope in *Chester v Afshar*

> *the function of the law is to enable rights to be vindicated and to provide remedies when duties have been breached. Unless this is done the duty is a hollow one, stripped of all practical force and devoid of all content. It will have lost its ability to protect [the plaintiff] and thus to fulfill the only purpose which brought it into existence*[23]

7.3 Scientific Advances to Ease Burden of Proof of Causation and Create New Injuries

In the same way that nanotechnology is expected to revolutionize so many aspects of society, scientific advances might hold the key to determine causation in future "nanotoxic tort" cases by producing new forms of evidence to which courts will adapt legal treatment of proof of causation, thereby reducing or eliminating the need for reliance on epidemiological studies. For example, chemical bio-marking enables scientists to observe biomarkers even at the molecular level allowing the detection of previously undetectable, intermediate molecular changes between exposure and the manifestation of disease which will allow scientists to draw definitive conclusions about the consequences of toxic exposure and will narrow the gulf between scientific evidence and legal causation (Grodsky, 2007).

Toxicogenomics[24] and toxicogenetics[25] may also provide dramatic advances in the identification and characterisation of toxins and may be used as biomarkers of

[22] Geistfield (op. cit.) p 1024.

[23] Chester v Afshar [2005] 1 AC 134.

[24] Toxicogenomics is the study of the relationship between the structure and activity of the genome and the adverse effects of chemical substances. It combines the emerging technology of genomics and bioinformatics to identify and characterize the mechanisms of action of known and suspected toxins, cited in Klein, A. R. (2008) 'Causation and Uncertainty: Making Connections in Time of Change', *Jurimetrics,* 49(1), 5–50.

[25] Toxicogenetics is a high-speed, high-volume technology which can scan a human genome for chemically induced changes. See Grodsky, J. A. (2007) 'Genomics and Toxic Torts: Dismantling the Risk-Injury Divide', *Stanford Law Review,* 59(6), 1671–1734.

exposure to demonstrate an individual's exposure to a substance and as biomarkers of effect to diagnose early progression of a disease process. This would make a plaintiff's proof of the *conditio sine qua non* causation link between toxic substance exposure and the consequences of that exposure much more straightforward.

At the same time, these scientific advances could also pave the way for new types of injuries in cases where clinical harm is less clear, for example, changes in subclinical, cellular, and/or subcellular changes. Proof of bioaccumulation of NM in human organs might be sufficient to establish harm or injury.

It is the opinion of Ronald Wernette (Wernette, 2009), a US-based lawyer who specialises in toxic tort, product liability, and personal injuries, that risk perception influences litigation especially in the areas of mass torts and toxic exposure litigation. He opines that even phantom risk—where no scientifically demonstrable cause-and-effect relationship can yet be established—can drive liability conditions. Notwithstanding that it is as yet largely unknown or at least uncertain whether exposure to NM will have harmful consequences, experience has shown that where there are concerns about health and safety hazards, litigation is not far behind. Wernette is of the view that new technology breeds litigation and that nanotort litigation is a virtual certainty because of what he describes as a large well-financed mass tort infrastructure which is already in place. The infrastructure precedented by tobacco settlements was initially used to target substances such as asbestos, lead, benzene, silica, welding fumes, medical devices, and pharmaceuticals and will be used to target NM. At the same time, it is acknowledged that the current high level of scientific uncertainty in relation to the toxicology and epidemiology of NM together with the as-yet absence of a signature illness or condition will present hurdles for potential plaintiffs to overcome in order to meet the burden of proof of causation. That said, as we have already seen, the courts have relaxed the burden of proof of causation in previous toxic tort claims to afford a remedy to plaintiffs and in accordance with general social justice where medical or scientific expertise cannot arrive at a definitive conclusion.

7.4 A New Toxic Tort

As the law stands, the causation tests in existence now are the traditional "*but for*" test, the *Bonnington Castings Ltd. v Wardlaw "material contribution to injury*" test, the *McGhee v National Coal Board "material increase in risk"* test, the *Fairchild mesothelioma exception,* the *Jones v Metal Box Ltd./Novartis Grimsby Ltd. v Cookson "doubles the risk"* test. It is arguable that not only has a new test for causation been established, but that a new tort of "increasing the material risk of injury to the plaintiff" has in fact been created. Per Laleng argues that the asbestos litigation has arguably created a new toxic tort, motivated by a general chemo-phobia and judicial sympathy for plaintiffs, which dispenses with the concept of causation altogether as a mechanism for allocating responsibility for harm and effectively collapses firstly the orthodox conceptual division between factual and legal causation and secondly causation into fault (Lageng, 2010). The question is whether this

lower standard of proof of causation, which as previously stated is the biggest legal hurdle a claimant must overcome in toxic tort cases, could apply in any toxic substance exposure case, for example, in a NM exposure case even when the scientific and medical evidence is unable to prove the connection between wrongdoing and resulting harm? If so, all that the plaintiff would have to prove is negligence or breach of duty by the defendant and an increased risk of harm rather than the harm itself. Therefore for the purposes of the issues central to this chapter, the emerging questions are whether the new standard will be applicable to all toxic torts, including "nanotort" should they arise; whether the House of Lords has effectively created a new tort which requires "no risk" and whether any limitations or conditions have been attached to the application of the new standard with the end-result that we could now have non-causal liability in relation to all forms of risk-creating activity, the risk-creation amounting to the wrong in itself? Laleng contends that the traditional standard or proof in private civil law is already set relatively low but concurs with the generally accepted view that in asbestos exposure cases the conventional test for causation would have produced unacceptable results by leaving mesothelioma victims uncompensated, which would be contrary to basic notions of justice. However, he argues that any further dilution of the standard requires justification and limitations and that it is possible that the "new" tort could become the norm for causal responsibility in the law of negligence generally, but particularly in cases where scientific or pathological knowledge is unclear. This is a legitimate concern because "generally, once an alternative causal approach is first developed in the common law, its use as a future precedent is reduced to a nearly automatic application when the court deems its use necessary" (Knutsen, 2003). Two recent UK Supreme Court decisions both confirmed this view of judicial precedent[26] and did not clarify the scope of the *Fairchild* exception. In the conjoined cases of *Sienkiewicz v Greif (UK) Ltd.*[27] and *Willmore v Knowsley Metropolitan Borough Council*[28] (Sienkiewicz-Willmore), the Supreme Court decided that the exceptional *Fairchild* approach to the proof of causation in negligence applied where a mesothelioma victim had been negligently exposed to asbestos by one defendant at a level well below unavoidable environmental asbestos exposure. In both cases, their Lordships found that the negligent exposure materially increased the risk of mesothelioma and thereby satisfied the *Fairchild* test. It found that the *Fairchild* test applied regardless of whether the relevant exposures were single or multiple and regardless of whether they also involved a non-tortious exposure. While their Lordships appeared to indicate that the *Fairchild* test should be confined to mesothelioma cases, their dicta suggest that extension to all so-called "evidential gap" cases is not precluded. Laleng[29] is of the opinion that confinement of the *Fairchild* test to mesothelioma

[26] Sienkiewicz v Greif (UK) Ltd. [2011] UKSC10. Acknowledging the harshness of the decision, Lord Mance said that it was impossible to go back on Fairchild or to limit it.

[27] Sienkiewicz v Greif (UK) Ltd. [2011] UKSC10.

[28] Willmore v Knowsley Metropolitan Borough Council [2011] WLR 53.

[29] *Sienkiewicz v Greif (UK) Ltd.* and *Willmore v Knowsley Metropolitan Borough Council*: A Material Contribution to Uncertainty?, The Modern Law Review (2011) 74(5).

cases is not rationally possible because the boundaries, if any, of the exception are no clearer after the *Sienkiewicz-Willmore* decision and that effectively there is a new tort of *increased risk of harm above de minimis*, the threshold of which has not been defined but which loosely means any contribution to the risk of harm which is more than minimal, trivial, or inconsequential will count as "material". The judgments in the *Sienkiewicz-Willmore* case have been criticised as appearing to be based on a flawed understanding of and ambivalence towards the role of scientific evidence, in particular epidemiological evidence in toxic tort cases which is a worrying development for manufacturers, producers, and insurers of NM in the event that there are plaintiffs who bring claims in the future alleging harm (Lageng, 2010; McIvor, 2013a, 2013b). While the Court unequivocally held that the *Fairchild* test of causation applied, it went on to discuss the "doubles the risk" test. It has been argued that in the *Sienkiewicz-Willmore Sienkiewicz-Willmore* cases, the "doubles the risk" test has been equated to the epidemiologic concept of "relative risk" (RR) whereby RR > 2 is equivalent to the doubles the risk test, taken to mean causation.

The asbestos litigation became a litigation explosion in which hundreds of thousands of claims were filed by claimants some of whom had little or no injuries (Henderson, 2002). In 1997, the US Supreme Court called it an "asbestos-litigation crisis". Between 1991 and 2004, U.S. insurers paid over $24 billion in asbestos claims; companies having anything to do with asbestos have paid approximately $70 billion in claims and costs. The ultimate number of claims could reach one to three million with up to half of them filed by people with little or no physical impairment.[30]

7.5 Conclusion

We may not know whether NT will lead to mass tort or toxic torts claims for at least another decade because both exposure levels and scientific evidence establishing a factual and legal connection between exposure and resulting injury/disease are minimal at this stage. Moreover, there is also likely to be a latency period. Among the factors which could lead to mass nanotort/toxic nanotort litigation are (1) ubiquitous exposure; (2) sympathetic judiciary; (3) sensational media coverage; (4) reactive politicians; (5) NM identification capability; (6) scientific and medical evidence proving causation; (7) a signature condition; injury or disease; (8) deep pockets of recovery—insurance policies and/or large companies; (9) corporate irresponsibility—a failure by nanomaterial manufacturers, producers, distributors, and users to progressively, proactively adopt and comply with industry guidelines and codes of practice, EU and International standards, regulations and legislation, implementing supplementary policy measures and information disclosure measures; (10) the establishment of a statutory compensation programme (Delany, 2012). Against this, the extent of liability could be potentially reduced by demonstrative evidence of

[30] National Underwriter April 13th 2009.

corporate responsibility, the defenses of voluntary assumption of risk, contributory negligence and the state of scientific knowledge, unforeseeable events, and/or events which were beyond the employers' control and could not have been avoided even having exercised his duty of care. For now, for NM stakeholders it is a case of developing in so far as is possible sound risk assessment and management strategies with the flexibility to adapt as the state of the art develops. Evidence of compliance with regulatory obligations, industry codes and standards of practice and guidelines, and the establishment of sound risk management systems are all crucial both to securing NM risk cover and to defending liability claims if they do arise.

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Part II
Risk Assessment and Management

Chapter 8
INSCX Exchange: The Hub Approach to Self-regulation in Support of Risk Governance, Assurance, and Transfer

Charles Mcgovern

Abstract The drive to regulate nanoscience and nanotechnology (N&N) continues to evolve in tandem with the efforts to structure sustainable commercial exploitation of the field. Regulation agencies and risk stakeholders require tools to balance commercial and societal interest effectively with clarity and rapid embedment. This chapter suggests one such tool of benefit both in a commercial and stewardship context, is that of a formal commodity exchange system specifically established to structure trade in compliant, validated, and inspected nanomaterials, the raw materials base of N&N. The author suggests that a greater use of a formal commodity exchange system can be considered to impose an ethos of self-regulation on physical supply and use of engineered nanomaterials, thus aiding the ongoing efforts of regulation agencies and risk stakeholders to regulate with increasing cohesion and industry acceptance this emerging field of advanced materials science.

8.1 Introduction

Commodity exchanges have long been used to organize materials sectors, from metals to grains, oils, and others used across industry to the benefit of both commerce and societal interest. By and large, these exchanges operate as self-regulating organizations (SROs) where, by definition, self-regulation in itself serves to strengthen the ability of official regulation agencies to develop formal regulatory structures. Aspects of commodity exchange trade procedures enable real-time trade reporting/track/trace, mandatory inspection to prove material quality, efficient price discovery, spot and forward trade, and uniform trade settlement structured to eliminate fraud as standard.

C. Mcgovern (✉)
INSCX Exchange, Chapel House, Chapel Street, Cheshire CW12 4AB, UK
e-mail: cmg@inscx.com

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With the launch of a dedicated commodity exchange system for engineered nanomaterials (ENMs), INSCX exchange,[1] the benefits of an exchange can now be employed to aid the commercial development of trade in nanomaterials, while providing regulation agencies and risk stakeholders such as the insurance industry with tools to better aid the compliant development of this diverse materials sector. The formal launch of INSCX exchange was described in Ramsden (2010) as:

> *a milestone that provides an indispensable framework for enabling effective commercialization, including issues such as standardization and insurance.*

In the context of insurance, another useful quote from the above source is the following:

> *This report fulfils a most valuable role in sensitizing the insurance community to some aspects of nanotechnology that have hitherto been largely confined to the realm of the technical expert. If nanotechnology is to be advantageously exploited for the benefit of humanity, a comprehensive approach involving all stakeholders is very necessary, and the first step in developing such an approach is effective dialogue between the different groups involved. This report is an excellent example of how such dialogue can be initiated.*

INSCX™ exchange is based in the United Kingdom and the deliverable provided is an electronic secure web-access trade platform to registered producers and end users of listed materials. The exchange is a formal, rule bound, closed user commodity exchange specific to physical trade in ENMs and commodities complimentary to driving near-term demand in nanomaterials, such as Base oils, Polymers, and Titanium Dioxide. In regard to nanomaterials, the exchange offers the ability to sell/purchase nanomaterials and ancillary services through collaborating partners engaged with services such as materials dispersion/formulation, inspection, and toxicology. Although not a financial or speculative exchange, as a system, INSCX operates similar to other exchanges, such as the US-based CME (Grains, Oils) or the London-based LME (Metals) for example. These institutions have in common a feature insofar as they allow materials proven to specification to be bought and sold where the "market" is governed by the exchange according to defined rules and procedures. These "rules" serve to guarantee market neutrality towards best price and the trade performance of counterparties (buyers and sellers) to one another. Another feature of commodity exchange systems including INSCX is the ability offered to participants to trade on a Spot or Forward basis, aiding participants to plan ahead their supply allocations and requirements for listed commodities much more efficiently than is the case off-exchange. Forward trade was first introduced on metals and grain exchanges as a means to both finance production and hedge against adverse price shocks. An exchange therefore constitutes the most perfect practical form of a market with the same qualities of transparency and openness that make the exchange an attractive medium for doing business.

[1] http://inscx.com.

8.2 INSCX Offers a Number of Supports for Risk Governance, Risk Assurance, and Risk Transfer

8.2.1 Standardization

Standardization is the ability to engage with several producers each of whom supply to set specifications for ENMs using the optimum process of fabrication in a structured royalty-based licensing mechanism to generate supply redundancy necessary for high volume application of ENMs across industry; composites for example.

Commodity exchanges have proven central to materials standardisation where "Standardised" meant the materials listed for trade by the Exchange (e.g., particular grades of copper or wheat) fulfilled published specifications. "Standardised", while a term synonymous with "commodity", is highly relevant to nanomaterials despite the case where many of these materials are often unique to a single producer. The case for standardisation of nanomaterials stems from the fact that high volume industry rarely, if at all, can afford to rely on a single supply source for an essential material. By definition therefore, in a commercial context, the ability for CNT's, graphene, and many nanomaterials to drive high volume application in areas such as composites, metals, electronics, or agriculture as examples going forward will require multiple as opposed to singular supply sources, each agreeing to supply to a set series of specifications required by industrial users.

An exchange medium where inventors of the optimum process to fabricate nanomaterials can use the exchange to license for other producers' royalties, while competing for the order, is available via INSCX. The ability to use the exchange to drive multiple supply sources of a given material anonymously until trade is confirmed offers a solution to the supply redundancy issue while enforcing a neutral marketplace.

8.2.2 Trade Reporting

Trade reporting is the ability to establish real-time a physical trade in an ENM, thus creating a trade reporting/track–trace system. Access to this information will serve the interests of both risk mitigators, such as insurers and official regulation agencies with definitive points of departure and means to trace the flow of nanomaterials across the supply chain.

INSCX operates a trade reporting system termed Downstream Audit Sequencing (DAS), which uniquely records each transaction in a listed nanomaterial real-time. DAS in effect goes further than many of the national registers for supply of nanomaterials (France for example) insofar as reporting is continuous and a reported trade is proven compliant with the published specification as a condition of trade.

8.2.3 Quality Control

Quality control is the ability to establish conformity to published specification through a mandatory independent inspection of a traded material as a condition of trade settlement, sale/purchase.

An exchange will generally have the means for testing to ensure that items offered for sale on the exchange fulfill the specifications of the commodity listed for trade on the Exchange. In order to ensure smooth running, both sellers and buyers have to register (i.e., become members of the exchange). By doing so, they agree to abide by the rules of the exchange. These rules (such as the prohibition of front-running, declaration of open-interest, and conduct of agents through whom commercial users instruct trade) are strict, in order to ensure that both seller and buyer are offered a neutral marketplace to get the best possible deal.

In terms of materials testing as standard, a condition of buyer payment for a supplied nanomaterial sourced via INSCX is independent conformity to specification established on supply. Where a nanomaterial supplied in bulk quantity is proven not to conform to specification (beyond an internal producer analysis), exchange rules result in non-payment as of right by the buyer, coupled with the instigation of a process of arbitration to assist the producer resupply to specification. Characterization (inspection) failures are common in industry and the INSCX model follows on from that followed by other exchange systems.

8.2.4 Compliant

Compliance is the ability to register and approve multiple nanoproducers and gear same to be compliant with chemical registration legislation to list multiple variants of nanomaterials and derivatives thereof for trade on the exchange as single and/or multiple producer grades.

To comply with EU and US regulatory legislation (which in the case of ENMs continues to evolve), many nanoproducers face alone the requirement to comply with directives such as SIEF (Substance Information Exchange Forum), REACH registration, limited access to insurance as the industry beds down to gain commercial traction. INSCX offers producers a collaborative approach to overcoming the isolationist stance and the cost burdens that are imposed to ensure compliance. In addition, INSCX acting in concert and collaboration with partners in risk modeling and toxicology follows on the spirit of mutual cooperation in a common interest.

As standard also, INSCX is bound to ensure compliance with anti-bribery and corruption legislation, ITAR, the laws of contract, and anti-money laundering practices, thus aiding commercial compliance of its members.

8.3 Importance

The rationale for INSCX exchange is a commercial focal point for trade in nanomaterials, while the benefit to regulation and risk stakeholders is the creation of a compliant environment. The opening of INSCX is a significant event, as it means that for the first time nanomaterials may be traded in the same way as the basic commodities that have for many years been the foundation of industry and food production. The historic trade in commodities allowed purchasers across the world to buy goods sight unseen, knowing that since they were commodities the goods they were buying had to have met minimum standards of quality: this greatly facilitated the trade in these raw materials, and ceteris paribus had a downward effect on price. Larger quantities were available for lower prices, allowing the cheaper production of finished goods and foodstuffs. The opening of INSCX means the same benefits will now pass to nanomaterials: large volumes will be available to producers, and the nanomaterials purchased will be of assured quality and will be more competitively priced. This step is essential if the manifold benefits promised by nanotechnology are to be realised: the producers of the first generation of nanotechnology-based products that are widely available to consumers and industrial clients will have to have access to large amounts of quality-assured raw materials to facilitate research, development, and mass production.

One of the most important commercial innovations ushered in by exchanges was the concept of forward selling, a concept dating from the mid 1800s, in which the supplier is contractually bound to deliver a certain quantity of the commodity at a certain time in the future and the buyer is contractually bound to pay for it. The more sophisticated the technology, the more important this is, because the preparation of the commodity demands more and more time and investment. Forward selling overcomes the often ruinous risk of production in advance of demand. A fisherman, for example, spends all night at sea, but he does not know how many fish he will catch, nor does he know, when he returns to land, how many he will sell, although in both cases experience and learning strategies help to reduce uncertainty. The exchange provides as nearly perfect a mechanism for adjusting supply to demand as is practically possible. If a good X (e.g., a certain grade of copper) is in short supply relative to the demand, this will be noticed by the suppliers and they will increase the price. The higher prices will attract more suppliers (e.g., those with more expensive means of production who would have been unable to sell at the previously lower price). It will also encourage forward selling, which provides the financial guarantee enabling investment to expand production facilities. (Nowadays, metal is nearly always sold when it is still in the ground as ore; as soon as the sale is agreed, the miners rushed to dig it out and put it through the extraction and refining processes.) Conversely, if there is a glut, the price will fall and suppliers will withdraw until a balance is again achieved (Allen & Strathern, 2008)**.** These commercial benefits via INSCX now accrue in favour of nanomaterials.

8.4 Alternative

So what could be deemed the alternative to greater use of the INSCX exchange model? In terms of standard trade cohesion, in a commercial context, the alternative could very well prove the mode of business such as is practiced by the chemical industry, in which there is no exchange, even for the chemicals made in the largest volumes, and is typically characterized by enormous price differences among suppliers, enormous price fluctuations, and extreme fluctuations of supply. Business has arranged itself to accommodate this endemic uncertainty, but a huge amount of effort is essentially wasted in the process, compared with organizing an exchange, exacerbated by the inertia due to the large capital investment needed for many chemical production facilities. Presumably, exchanges have never been organized in the chemical industry because suppliers believe they can command premium prices through the lack of transparency. The semiconductor industry has also traditionally eschewed exchanges for "chips" (very large-scale integrated circuits), perhaps because they were considered to be too sophisticated and special to be labeled "mere" commodities. This viewpoint is, however, based on a fundamental misunderstanding. Just because a good fulfils published specifications and can be traded on an exchange does not preclude it from being sophisticated. (Indeed, food products are, in terms of their internal structure, incredibly sophisticated—so much so that it is still impossible for humans to mimic them artificially.) In fact, "chips" are produced to strict specifications and, in effect, we have seen to commoditization of a range of microprocessors (e.g., the 386), without which their ubiquitous introduction into the domestic appliances, for example, would scarcely have been possible.

8.5 Challenges

The present era of ultrahigh technology provides the most interesting challenge to an exchange. It is easy enough to test a batch of gold, or copper, whether it fulfills its specifications. Similarly, it is with wheat (the testing of which does not, of course, involve detailed structural investigation at the molecular level). But the more sophisticated the product, the more difficult it is to specify it and test it for fulfillment. Rising to this challenge is INSCX™ exchange (McGovern, 2010), an exchange dedicated to nanotechnology: nanomaterials, nanodevices and, eventually, nanosystems which were founded at the end of 2010, INSCX™ exchange.

Nanomaterials themselves being the raw materials of nanotechnology face immense difficulty transcending to become commercially viable. The main commercial difficulty of nanotechnology at present is there is a multitude of very small companies (many of them are university spin-outs), each making a different product, in very small quantities. This makes it very difficult for a potential user with a large-scale application to do business. Take, as an example, carbon nanotubes as an additive to create conductive polymers. A polymer manufacturer would need large

quantities of a uniform specification with regular deliveries guaranteed. At present, no manufacturer is able to give this. If, however, all the small suppliers joined the exchange and produced their nanotubes according to the exchange's specification, the polymer manufacturer might be able to meet his demands. Furthermore, through forward buying some of the small suppliers would again the financial guarantees enabling them to invest in order to expand their production facilities. As well as the direct benefits to both suppliers and buyers, this process would also lead to a general increase in the vitality of the industry, resulting in further growth, etc.

In the absence of the exchange, we will either see nanotechnology remaining as an essentially academic activity with little commercial significance (excluding materials such as carbon black, which were traded in large volumes long before the emergence of nanotechnology) or it will follow the route adopted by the chemical industry (indeed, many large chemical firms are now actively pursuing nanomaterials, developing them both through their own research and through buying up small, innovative companies). In the latter case, the industry will be characterized by the same problems of price and supply fluctuations experienced by the chemical industry. But in the case of nanotechnology, because its products are more sophisticated than chemicals, and as nanomaterials become smarter, becoming in effect devices (e.g., "sensorial materials" (Lawo, Lehmhus, & Langer, 2009)), the difference between nanotechnology and the chemical industry will become more marked, and the commercial difficulties of coping with the fluctuations might simply become so great that the industry is not viable.

8.6 Key Considerations

The model adopted by INSCX™ exchange is aimed at providing the tools required by producers to strive toward greater commercial dependence on nanomaterials, while enabling a market-driven system to embed self-regulation in a commercial and societal context. As regards regulation, the Exchange formally operates a definitive track/trace system (designed to ensure visibility as a nanomaterial moves through the supply chain) and supports individual NM producers to acquire conformity to good industry practice as defined by the AssuredNano www.assured-nano.eu standard.

Equally, supply of materials through the Exchange system is subject to mandatory independent characterization to establish conformity to the promoted specification. Thus in summary, trade through the Exchange offers the following assurance:

- The nanomaterials exchanged are inspected (characterized) so as to establish conformity to specification.
- Nanomaterials producers are operating compliant with best industry practices as defined by the AssuredNano www.assurednano.eu programme.
- The nanomaterials exchanged can be track/traced for both commercial reasons such as insurance, and societal reasons.

- Finally, beyond such considerations, the exchange clearly reflects a democratic ideal for the equitable organization of human society, in which transparency and openness is a vital element to ensure universal participation in society. As technology becomes more and more sophisticated and widely diffused, ensuring that all members of society participate and feel that they have a stake in its continuing development appears to be essential to avoid anarchy.

8.7 Commercial Considerations Summary

A brief summary of the commercial considerations relevant to nanomaterials producers is as follows;

- Producers are offered the means to finance upscale through listing materials with the Exchange for forward sale. (The financing of production is a fundamental role long associated with the commodity exchange system.)
- Producers can combine to work with the Exchange to set specifications that require collective supply to meet current and future industry requirements. (At present, many NM producers lack the ability in isolation to supply in volume at economies of scale, thus reducing many applications using nanomaterials to the novel as opposed to industrial.)
- The Exchange track/trace system enables insurers to identify risk as a nanomaterial moves through the supply chain from source to finished product, object, or device.
- The Exchange trade reporting system is complaint with the basic requirement for commercial confidentiality, while can function transparent to official regulation agencies.

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Chapter 9
In Support of the Inclusion of Data on Nanomaterials Transformations and Environmental Interactions into Existing Regulatory Frameworks

Iseult Lynch and Robert Gregory Lee

Abstract Research traditionally outstrips regulation leading to a lag between scientific advances and regulatory frameworks. This is nowhere more apparent than in the arena of nanomaterials (NMs) safety testing. Here, regulatory focus has been on assessing the suitability of existing regulatory regimes and standardised assays for use with NMs. Meanwhile scientific focus has moved towards an acceptance of the fact that as-made or so-called pristine NMs do not exist in real products or the environments as a result of physical, chemical, biological and binding-related transformations which drive the NMs towards lower surface energy states. Thus, in parallel with the move towards alternative test methods, there is a need to support regulatory authorities in understanding the relevant species to test in the case of NMs risk assessment and how to best incorporate such new knowledge into regulation. This chapter appraises some of the steps that could support such a transition, including looking for precedent in contiguous regulatory models for assessing transformed variants (e.g. pesticide metabolites), considering grouping and read-across strategies for likely NMs transformations, and validating standard tests for NMs ageing. Finally, it will consider the legal issues surrounding manufacturer's responsibility for providing safety data for materials that are no longer the as-produced materials. As there is an essentially infinite array of uses/formulations for NMs, all of which can transform the NM from its original form and composition; where does and should a manufacturer's responsibilities end?

I. Lynch (✉)
School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston B15 2TT, UK
e-mail: i.lynch@bham.ac.uk

R.G. Lee
Birmingham Law School, University of Birmingham, Edgbaston B15 2TT, UK

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9.1 Introduction

Nanotechnology is a rapidly evolving enabling technology with the potential to revolutionise modern life. The global market for nanomaterials (NMs) is estimated at a market value of €20 billion, with the current direct employment in the NM sector estimated at up to 400,000 in Europe alone.[1] An estimated 20,000 different NMs are under development around the world, expected to total 11 million tonnes annual production (see Footnote 1). However, an increasing body of scientific evidence would suggest that some materials in their nanoform may induce harmful biological or environmental effects through a variety of potential mechanisms linked specifically to their nanoproperties, not all of which are fully understood or quantified as yet. A key confounding factor is that NMs, unlike conventional chemicals, are highly affected by their surroundings, transforming chemically, agglomerating and/or acquiring an evolving coating of environmental or biological macromolecules, which provides them with an 'environmental' or 'biological' identity that is distinct from their initial 'synthetic' identity (Fadeelet al., 2013; Lynch et al.,, 2014; Walczyk et al., 2010). Indeed, NMs are at the boundary between molecules and solid state behaviour, meaning that they can often display new and unusual properties, linked to both their small size (e.g. quantum confinement effects and access to biological receptors facilitating active internalisation by cells) and enormous surface area-to-volume ratios leading to highly reactive surfaces and enormous capacity for adsorbing molecules from their surroundings. Indeed it is the presence of such qualities and capacities that has driven research in nanotechnology and the development of products containing NMs. Factoring this context- and time-dependent evolution into assessment of the fate, behaviour and impacts of NMs is essential to move forward in terms of ensuring the safe implementation of nanotechnologies, and science-based regulation of new materials and the products that these enable (Valsami-Jones & Lynch, 2015).

There is, for instance, a clear need to increase the 'environmental realism' in the design and understanding of nano-(eco)safety assessments to account for the non-static nature of NMs in the environment, with the environment here including also human exposure (i.e. changes to NMs as a result of contact with skin, airways etc.). Increasing the realism of nanosafety studies includes, for example: use of relevant NM forms; consideration of the appropriate exposure medium (e.g. in light of the ongoing debate as to the ethics (Brunner et al., 2010) and relevance of the 10% serum conditions used for in vitro studies to the in vivo situation (ESAC, 2008) and the potential for differential protein binding under the different conditions (Monopoli et al., 2011)) which can manifest as different uptakes and toxicities under the different conditions (Kim et al., 2014); testing of environmentally relevant (e.g. appropriately transformed, see below) chemistries and longer term and lower-dose exposures, again based on the physicochemical aspects of the properties of the NM driving their environmental fate. Given this complexity, the rapid pace of development of

[1] http://ec.europa.eu/enterprise/sectors/chemicals/reach/nanomaterials/

science, the cross-disciplinarity and cross-sectoral span of knowledge required, and the lack of skilled professionals in this area, there is a clear and pressing need to train a cohort of professionals to bridge academic and policy/regulatory/industry approaches to risk assessment of NMs.

A recent review of the (environmental) transformations of NMs categorised the types of transformation reactions undergone by NMs as chemical (e.g. photooxidation and photoreduction), physical (e.g. agglomeration or dissolution), biological (e.g. oxidation and carboxylation) and interactions with biomolecules, including proteins, polysaccharides, lipids and natural organic matter, all of which ultimately influence the NMs' persistence, bioavailability/biouptake, reactivity and toxicity. Natural organic matter (NOM; originating from the decay of plant and animal matter) is a complex polydisperse polymeric mixture, whose properties echo their structural diversity as well as their state of aggregation, conformation and surface charge distribution (Lynch et al., 2014). The observed interactions of NMs and NOM are analogous to the interactions with proteins and the formation of 'protein coronas' in biological systems; the behaviour and impacts of NMs depends on the types and amounts of these biological and environmental molecules attached to their surfaces. Collectively these interactions provide a contextual or 'environmental identity' to the NMs that has to be taken into account when, for example effects are assessed in the environment (Cerrillo et al., 2015; Lynch et al., 2014; Nasser & Lynch, 2015).

There has been considerable debate worldwide as to whether existing regulatory approaches are sufficient to assess the human and environmental implications of NMs (Frater et al. 2006). Indeed, it is the dual role of REACH,[2] protecting both health and safety and industrial competitiveness, that is at the heart of much of the debate surrounding the applicability of REACH regulation for NMs, as industry are among the strongest voices saying that current regulations are sufficient to capture any potential risks of NMs, while the scientific community continue to call for additional research to answer this question (Malkiewicz et al., 2011; Lee and Vaughan 2010). The identification and mitigation of potential human and environmental risks is vital for consumer confidence and the continued growth of the nanotechnology sector.

A 2012 study by the Center for International Environmental Law in Switzerland, 'Just Out of REACH' identified four key gaps for NMs in the registration phase of REACH, an essential step that requires chemical manufacturers and importers to provide key health and safety information (Azoulay, 2012), namely:

- REACH does not define NMs, and contains no nano-specific provisions
- Most NMs evade registration until 2018; yet, they can still enter the EU market
- REACH's schedule for registration hinges on the number of tonnes of a chemical, essentially missing all NMs, which are generally produced in far smaller quantities
- REACH test guidelines fail to consider the special properties of NMs.

[2] http://www.hsa.ie/eng/Your_Industry/Chemicals/REACH/

The authors explored possible remedies to close these loopholes, but rejected the possibility of renegotiating REACH to add specific provisions on nanotechnology, as this would be practically challenging and could invite further weakening of the current regulation, in favour of developing a stand-alone regulation, carefully aligned with the chemical rules, but specifically tailored to NMs, with sufficient flexibility to allow for future adjustments as NMs are better understood, without requiring additional changes to REACH (Azoulay, 2012). This was preferred to amendments to the technical guidance, as it was suggested these would fall short of bridging the existing legal gaps (Azoulay, 2012).

A report funded by the SKEP ERA-NET (Scientific Knowledge for Environmental Protection) assessing the applicability of REACH to NMs also identified several challenges, including those listed above, as well as questioning the basis for the classification of some NMs as phase-in.[3] Thus, nanoforms of existing substances (i.e. those with an EINECS number) would, by default, be treated as phase-in substances. Thus, some NMs are considered as phase-in substances (e.g. gold and TiO_2), while others are non-phase-in substances (e.g. fullerenes). The report indicates that there is no scientific evidence to suggest that those two groups of NMs (phase-in or non-phase-in) represent a different likelihood of causing a concern, and thus that there is no reason to treat them differently. Among the 22 recommendations in the report was that nanoforms of substances should be treated as different substances from their bulk counterparts and that none of the phase-in provisions should apply (Malkiewicz et al., 2011).

However, despite these and other reports calling for change, the approach chosen by the European Commission and the European Chemicals Agency has been to amend the Technical Guidance annexes to REACH rather than amend REACH itself:

> *Some needs for adjustments have been identified [by the REACH review report,[4] February 2013], but balanced against the interest of ensuring legislative stability and predictability, the Commission concludes that changes to the enacting terms of REACH will not be proposed.*

The introduction of a major re-focussing of REACH by guidance raises questions of legitimacy given the lack of democratic engagement with such technical revision (Vaughan, 2015). The scope of the revision is focused on the technical aspects related to NMs set out in the REACH annexes. The final version of the amendments to REACH Annexes for NMs is still pending at the time of writing (November 2015), following an extensive consultation as to the costs and benefits

[3] NMs will be considered as "phase-in" if they or their base substance are listed on the European Inventory of Existing Commercial Chemical Substances (EINECS) are considered as No-Longer Polymers or have been manufactured in the EU but not placed on the market between 1st of June 1992 and 1st of June 2007.

[4] Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the regions in accordance with Article 117(4) of REACH and Article 46(2) of CLP, and a review of certain elements of REACH in line with Articles 75(2), 138(2), 138(3) and 138(6) of REACH {COM(2013)0049}. Available: http://www.ipex.eu/IPEXL-WEB/dossier/document/COM20130049.do.

Table 9.1 Options proposed in the questionnaire on potential amendments to REACH annexes to account for NMs as part of the public consultation (2014)

Options considered in the solicitation of opinion on potential amendments to REACH (2013)	
a.	Explicitly require registrants to describe the scope of the registration dossier
b.	Explicitly require registrants to provide more detailed characterisation of nanomaterials/nanoforms
c.	*Require that nanoforms are explicitly addressed in the endpoint sections
d.	*Require detailed description of the test material/sample and sample preparation
e.	*Require scientific justifications for grouping/read across/QSAR and other non-testing approaches for different forms
f.	**Require considerations of most appropriate/relevant metric with preferable presentation in several metrics
g.	Require that bioaccumulation is addressed specifically for the nanoform
h.	Specify that absorption/desorption behaviour of nanomaterials should not be assessed based on Kd values derived from Koc and Kow
i.	Require identification of uses and exposure assessment of the nanoform
j.	When considered together what do you believe the impact of the measures outlined above would be?

These questions were to be considered in light of the potential impact on cost of registration, safety of NMs and regulatory process efficiency

A measure marked with * is supposed to be introduced in the REACH Annexes for substance identification, physicochemical properties, human health hazards, environmental fate and environmental hazards. A measure marked with ** refers to human health hazards, environmental fate and environmental hazards only

of a proposed range of modifications, from business as usual through to introduction of a range of additional data and testing requirements (see Table 9.1), with the questionnaire asking participants to consider the implications of each measure for cost of regulation, safety of NMs and efficiency of the regulatory process. Given the focus on amending the technical annexes, the questionnaire was also of a technical nature and was designed primarily for the informed expert user.

The focus of regulatory research to date has been on assessing the suitability of existing regulatory regimes and standardised assays for control of NMs dispersion and presentation to the test system/organisms. For example, the OECD expert meeting on Physical-Chemical Properties of Manufactured Nanomaterials and Test Guidelines (2013 in Querétaro, Mexico) assessed the applicability of existing OECD Test Guidelines (TG) on Physical-chemical Properties of Manufactured Nanomaterials and identified the need to update current or develop new OECD Test Guidelines and/or OECD Guidance Documents (GD) which are relevant for safety and regulatory decision making (OECD, 2014). The categories of endpoints selected were (a) State of Dispersion, Aggregation and Agglomeration of NMs; (b) Size (and Size Distribution) of NMs; (c) Surface Area and Porosity and (d) Surface Reactivity (OECD, 2014). An ecotoxicology and environmental fate (of NMs) focused expert meeting suggested that tiered approaches or decision trees be established in order to provide guidance on three main steps (a) stock/stem suspension preparation, (b) preparation of exposure suspension and (c) conducting the tests (Kühnel & Nickel,

Table 9.2 Sub-set of the recommendations from the OECD expert meeting on ecotoxicity and environmental fate (Kühnel & Nickel, 2014)

Recommendations regarding environmental fate from the OECD expert meeting	
Fate and behaviour	Improved understanding on transformation, dissolution and dispersibility in environmental media
	More knowledge on effects of aged or transformed NM as the environmentally more relevant fraction
	Development of 'nano-relevant' endpoints replacing K_{ow}, BMF or BCF
	Identification of soil parameters affecting fate and behaviour of NM
	More knowledge on exposure pathways (e.g. via sewage sludge) and modelling studies
	Long-term studies

2014). Among the key recommendations (see Table 9.2 for the sub-set related to environmental fate) were that 'more knowledge on effects of aged or transformed NM as the environmentally more relevant fraction' is needed. This was also linked to the widely agreed need for physical chemical characterisation of NM, which is considered essential for all subsequent steps of testing (and thus includes any interactions and transformations) (Kühnel & Nickel, 2014). These expert recommendations are supported by a recent evaluation of the REACH guidance with regard to NM which indicated that REACH guidance was found not to fully cover the specific environmental fate of NM (alterations, dissolution and partitioning) and hence needs adjustments (Meesters et al., 2013). In this context, degradation was defined as changes in the NM surfaces, for example by oxidation processes or changes of coatings while transformation was defined as basic changes in NM composition or form, for example dissolution processes or heteroaggregation (Levard et al., 2012).

Thus, consideration of the dynamic nature of NMs, and their evolution and transformation by their surroundings, is slowly trickling into regulatory consciousness, although is still a long way behind scientific knowledge regarding environmental transformations of NMs. For example, scientific focus has moved towards an acceptance of the fact that as-made or so-called pristine NMs do not exist in real products or the environments as a result of physical, chemical, biological and binding-related transformations which drive the NMs towards lower surface energy states. This is evidenced by the fact that scientific journals are demanding characterisation in the relevant test media as a condition of publication, for example. Additionally, multiple studies are emerging in the literature showing quite different physicochemical properties of pristine versus aged NMs which are often linked to significantly different (eco)toxicological responses; for example, a comparison of the aqueous behaviour between newly purchased commercially manufactured copper nanoparticles (NPs) to NPs that were allowed to sit in the laboratory environment for several years under ambient conditions revealed that the (aged) NPs exhibited unique chemistry including oxide phases that form during storage and surface adsorption properties (Mudunkotuwa et al., 2012). Additionally, the aged NPs exhibited differences in solubility, aggregation and reactivity that can affect the mobility and

toxicity of these materials (Mudunkotuwa et al., 2012). The authors of the copper NPs study suggested that having a clear understanding of how these NMs will change upon aging, and consequent alterations in their physicochemical properties will enable establishing reliable structure–activity correlations, a critical step in moving beyond the current case-by-case analysis risk assessment of NMs (Mudunkotuwa et al., 2012). Taking this a step further, Izak-Neu and co-authors assessed the effect of storage time and storage conditions on the observed toxicity of AgNPs and demonstrated that AgNPs' 'aging' during storage (even under optimal conditions) resulted in changes in their cytotoxicity and suggested that a clear and time-resolved understanding of the changes in physicochemical characteristics of any metal NPs occurring under different conditions seems to be crucial for the interpretation of their biological effects (Izak-Nau et al., 2015). The most influential factors of AgNPs' 'aging' were found to be higher temperature and exposure to daylight, with the nature of the capping agent and the stabilisation mechanism also contributing. On the basis of the evidence presented here, one important recommendation for nanosafety assessment studies is to periodically monitor the crucial NMs' physicochemical parameters such as size/agglomeration, surface charge and dissolution throughout the duration of the study to ensure that any changes can be accounted for in the data interpretation and analysis. It might also be good practice to note the total time period between NM synthesis, characterisation and toxicity testing, with periodic (e.g. monthly) re-testing of parameters such as size distribution to ensure relevance of the characterisation data to the toxicity data (Izak-Nau et al., 2015). Similar impacts of ageing (in Milli Q water) of Zinc oxide NMs on the mutagenicity of the NMs to human–hamster hybrid (AL) cells were found, whereby the ZnO NMs underwent sophisticated physicochemical transformations with aging such as microstructural changes, the formation of hydrozincite ($Zn_5(CO_3)_2(OH)_6$) and the release of free zinc ions (Wang et al., 2015). Interestingly, the aged ZnO NMs resulted in much lower cytotoxicity but a relatively higher degree of mutation than fresh ZnO NMs (Wang et al., 2015).

9.2 Understanding/Predicting the Relevant Species to Test

Based on current knowledge, predicting the distribution and bioavailability of any NM in the environment is highly speculative, but may depend on a number of the following variables (Malkiewicz et al., 2011):

- Initial physicochemical characteristics of the NM. Core chemistry, size, particle charge and surface functionality (Jarvie & King, 2010) are of particular relevance.
- The form in which it is released (free/embedded in a matrix).
- The environmental compartment into which it is released (air, soil/sediment matrices, freshwater and marine) (Navarro et al., 2008).
- The interactions that occur with both abiotic and biotic components of the natural environment, and how these may transform the NM (Lowry et al., 2012).

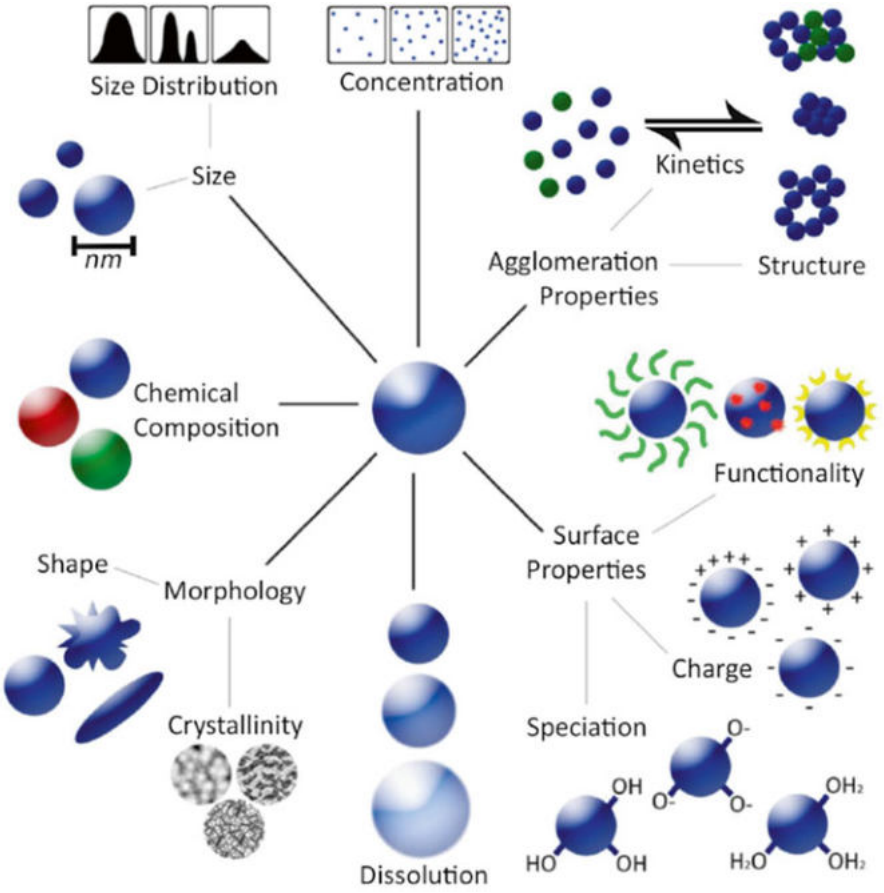

Fig. 9.1 Schematic illustration of the important physicochemical properties of manufactured/engineered NMs in aqueous media. From Malkiewicz et al. (2011), adapted from Hassellöv and Kaegi (2009)

Figure 9.1 shows possible mechanisms of interactions between an idealised NM and abiotic and biotic elements that are predicted to be the most influential in determining NM fate. Research is underway to determine the kinetics of these different transformations, both in the environment generally (Ma et al., 2013), and in cells or organisms specifically (Chen et al., 2013), and which occur under such circumstances (Dale et al., 2015) such that in the future quantitative structure–transformation relationships will be a possibility, linked with the chemistry (Liu et al., 2013) or biochemistry (Prins, 2015) of the surroundings. For example, using water chemistry data from across Europe coupled with data regarding NM agglomeration rates in vitro, it was possible to predict NM stability in the water column (Liu et al., 2013), which provides insights regarding NM transport and bioavailability, for example.

Prins (2015) suggested that the multivalent nature of gold NMs in contact with biological systems permits functional roles in biomolecular affinity and signal transduction, as multiple non-covalent interactions with small molecules that enhances affinity, but is also the basis of simple signal transduction pathways and adaptive behaviour (Prins, 2015). These relationships can then be further linked to quantitative structure–activity relationships (QSARs) for toxicity (Gajewicz et al., 2015) utilising either the pristine or transformed forms, depending on which proves to be more predictive of uptake and toxicological effect of NMs (Toropova et al., 2015).

Additionally, due to the enormous surface area to volume ratio, and the high proportion of molecules at the surface, NMs have a high surface energy that they seek to lower by binding to available biomolecules from their surroundings such as components of product formulations, proteins or lipids in living systems, natural organic matter (NOM) components of water or soil or exuded and secreted biomolecules in complex ecosystems (Lynch et al., 2014; Nasser & Lynch, 2015). Formation of a biomolecule corona around NMs is a ubiquitous phenomenon that occurs instantaneously upon contact with available macromolecules. Research to date has focussed on the interactions of NMs with blood proteins (human or animal sera) or lung surfactant proteins to correlate corona composition with NM uptake and impacts on living systems (Albanese et al., 2014; Di Silvio et al., 2015; Duan et al., 2015; Halamoda-Kenzaoui et al., 2015). Environmental interactions to date have focussed on NM–NOM interaction studies, primarily assessing the impact of the humic substances on particle stability/bioavailability (Lynch et al., 2014). Much less work has investigated the potential for NMs to bind the exuded biomolecules central to much of the plant and microorganism world (Nasser & Lynch, 2015), where secretion of biomolecules can be a defensive response to repel insect attack, or an offensive habit to repel other incompatible or competitive plants (Nordlund & Lewis, 1976). Early work in this direction has assessed the binding of proteins secreted by Daphnia magna and their influence on NM uptake and toxicity to Daphnia, illustrating a clear enhancement of NM uptake and a lower EC_{50} in the presence of the secreted corona (Nasser & Lynch, 2015).

Approaches to predict the reactivity of metals, and thus the transformations that they will undergo in the environment and subsequent uptake by biological organisms include the Hard–soft acid base theory (HSAB theory; also termed Pearson's acid base theory) (Pearson, 1963). According to the HSAB concept, hard acids prefer binding to the hard bases to give ionic complexes, whereas the soft acids prefer binding to soft bases to give covalent complexes. The HSAB classification, which has been determined empirically, provides an ordering of transition metals according to their preferences for specific organic ligands (Fig. 9.2). For example, soft acids (such as Hg(II), Cu(I), Ag(I) and cadmium(II) (Cd(II))) and borderline acids (such as Co(II), Ni(II), Cu(II) and Zn(II)) tend to associate tightly with soft bases, such as the sulfhydryl (R–SH) groups that are found in proteins. Consequently, the antibacterial toxicity of these metals is approximately proportional to their affinity for soft bases (Workentine et al., 2008), again potentially allowing for development of predictive transformation–activity relationships. Since many of the commonest NMs are composed of elements in the soft acid category (see Fig. 9.2), HSAB is a

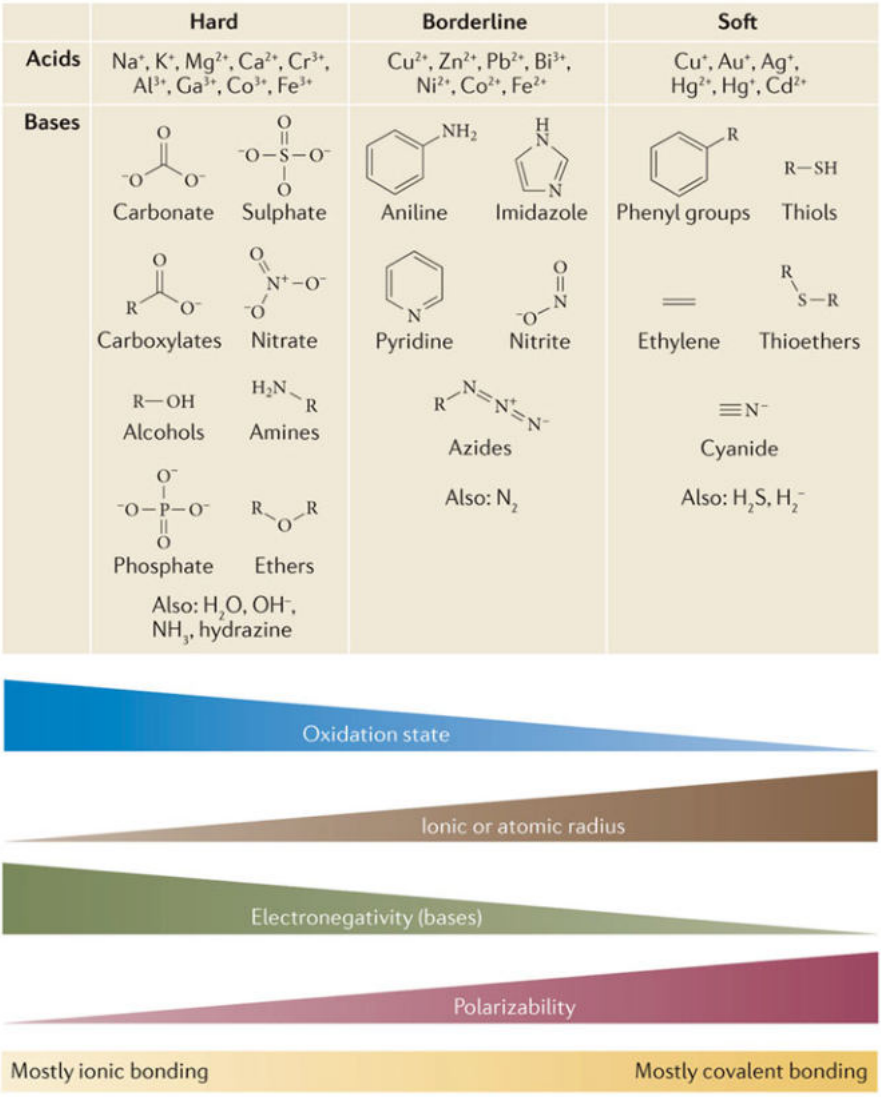

Fig. 9.2 Pearson's Hard–soft acid base (HSAB) theory (Pearson, 1963) can predict the selectivity of metal ions for biological donor ligands. Hard acids and bases tend to have a smaller ionic radius, a high oxidation state and weak polarisability. By contrast, soft species tend to have a large ionic radius, a low oxidation state and strong polarisability. Hard acids react preferentially with hard bases, and soft acids with soft bases. The affinity of a hard acid for a hard base is mostly ionic in nature, whereas the interaction between a soft acid and soft base is mostly covalent. Acids and bases that have an intermediate character are classified as borderline. This classification scheme is qualitative and can be used to predict the binding preferences of metals even in complex mixtures of donor ligands (Haas & Franz, 2009; Waldron et al., 2009). Electronegativity describes the tendency of an atom to attract electrons towards it. By contrast, polarisability refers to the tendency of the electrons around an atom to be distorted from their regular distribution, typically towards the nucleus of another, more electronegative atom. With permission from (Lemire et al., 2013)

useful tool to predict environmental transformations in the environment, such as the tendency for AgNMs to be sulphidised in environments containing high sulphur contents, such as fresh or sea water or waste water treatment plants (Kent et al., 2014). While the concept is well established in assessing metal toxicity, including for predicting metal toxicity to microbes (Lemire et al., 2013); for example, it has yet to be applied for assessing or predicting the binding of specific protein sequences (epitopes) to metal or metal oxide NMs or as a means to predict toxicity for NMs. HSAB has been used to predict propensity for covalent binding of electrophiles to biological substrates (Carlson, 1990), and since protein binding is linked with NM uptake (Albanese et al., 2014; Walkey et al., 2014), there is certainly scope for predicting NMs biological and ecological coronas on this basis.

Grouping of substances and read-across is one of the most commonly used alternative approaches for filling data gaps in registrations submitted under REACH.[5] This approach uses relevant information from analogous ('source') substances to predict the properties of 'target' substances. If the grouping and read-across approach is applied correctly, experimental testing can be reduced as there is no need to test every target substance[e]. A recent proposal from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 'Nano Task Force', for a Decision-making framework for the grouping and testing of NMs (DF4nanoGrouping) identifies four main NMs groups encompassing (1) soluble NMs, (2) biopersistent high aspect ratio NMs, (3) passive NMs and (4) active NMs. Since the exact correlation of intrinsic material properties and apical toxic effect is not yet established, the DF4nanoGrouping uses the 'functionality' of NMs for grouping rather than relying on intrinsic material properties alone. However, in light of the transformations that NMs undergo, including in cells and organisms, grouping on the basis of transformed or aged forms may prove more predictive. To illustrate this, Fig. 9.3, adapted from the grouping proposal of Stuber et al. (as the outcome from a Swiss workshop on REACH applicability to NMs), illustrates that grouping NMs according to e.g. their initial (Time 0) or transformed (during exposure) physicochemical properties and linked to their toxicological characteristics would reduce testing efforts.

9.3 Understanding Appropriate Timescales and Formats for Testing NMs

Given the dynamic nature of NMs and their transformations in the environment, current (although limited) approaches to long-term exposure and hazard testing may also need to consider the appropriate form of the NM to test. Since many such approaches require replacement of the exposure media periodically, usually with freshly dispersed NMs, the exposure form introduced at the subsequent timepoints will not be representative of the real (continuous) exposure, as a result of re-introduction of the

[5] http://echa.europa.eu/support/grouping-of-substances-and-read-across

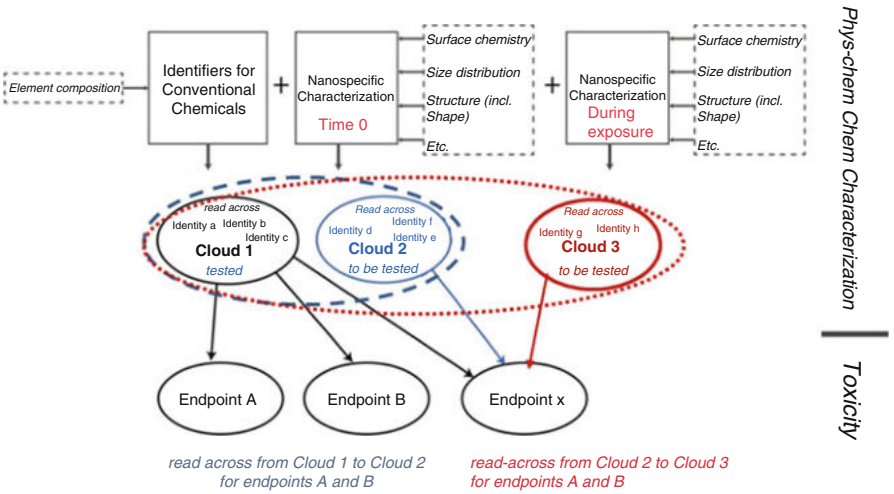

Fig. 9.3 Adaption of read-across strategy proposed by Studer et al. (2015) for NMs. NMs require additional characterisation in comparison to conventional chemicals. After their characterisation, they can be associated with predefined clouds of similar NMs that require the same testing strategy. Some clouds behave similarly for a particular endpoint, which allows read-across clouds for this specific endpoint (*dashed blue oval*, in this example endpoint A and B for Cloud 1 and 2). Therefore, testing efforts can be significantly decreased the more information is known. In the example above, Cloud 2 needs only to be tested on Endpoint(s) x, because information from Cloud 1 can be used for endpoint A and B (but not for endpoint x). A prerequisite for an efficient testing strategy is a validated grouping scheme. As an extension to this approach, we also consider that the characterisation during the exposure time might actually be the more relevant one, and thus that read-across should be from Cloud 1 to Cloud 3 (*red dotted line*) assuming that the transformed NMs characteristics are similar. Adapted from Studer et al. (2015)

pristine NMs. One possible approach would be to determine the total media amount needed and add the NMs to the media from the outset such that the replacement media contains NMs the same 'age' as the organism-exposed media.

At present, only limited information about the potential impact of aging on NM toxicity to organisms is available, although what is published indicates the need to re-assess how we do toxicity studies and what form of the NM is appropriate to test. A study investigated acute (96 h) and chronic (21 days) implications of systematically aged titanium dioxide NMs ($nTiO_2$; ~90 nm) on the standard test species *Daphnia magna* following the respective test guidelines. The $nTiO_2$ were aged for 0, 1, 3 and 6 days in media with varying ionic strengths (Milli-Q water: approx. 0.00 mmol/L and ASTM: 9.25 mmol/L) in the presence or absence of natural organic matter (NOM). Irrespective of the other parameters, aging in Milli-Q did not change the acute toxicity relative to an unaged control. In contrast, 6 days aged $nTiO_2$ in ASTM without NOM caused a fourfold decreased acute toxicity. Relative to the 0 day aged particles, $nTiO_2$ aged for 1 and 3 days in ASTM with NOM, which is the most environmentally relevant setup used here, significantly increased acute toxicity (by approximately 30 %), while a toxicity reduction (60 %) was observed for 6

days aged $nTiO_2$. Comparable patterns were observed during the chronic experiments. A likely explanation for this phenomenon is that the aging of $nTiO_2$ increases the particle size at the start of the experiment or the time of the water exchange from <100 nm to approximately 500 nm, which is the optimal size range to be taken up by filter feeding *D. Magna* (Seitz et al., 2015). If subjected to further agglomeration, larger $nTiO_2$ agglomerates, however, cannot be retained by the daphnids' filter apparatus ultimately reducing their ecotoxicological potential. This non-linear pattern of increasing and decreasing $nTiO_2$-related toxicity over the aging duration highlights the knowledge gap regarding the underlying mechanisms and processes (Seitz et al., 2015).

Another study addressed the relative importance of particle coating, sewage sludge amendment and aging on aggregation and dissolution of manufactured Ag NPs in soil pore water. Ag NPs with citrate (CIT) or polyvinylpyrrolidone (PVP) coatings were incubated with soil or municipal sewage sludge which was then amended to soil (1 % or 3 % sludge (w/w)). Pore waters were extracted after 1 week and 2 and 6 months and analysed for chemical speciation, aggregation state and dissolution. Ag NP coating had profound effects on aggregation state and partitioning to pore water in the absence of sewage sludge, but pre-incubation with sewage sludge negated these effects. This suggests that Ag NP coating does not need to be taken into account to understand fate of Ag NPs applied to soil through biosolids amendment. Aging of soil also had profound effects that depended on Ag NP coating and sludge amendment (Whitley et al., 2013).

9.4 Manufacturer's Responsibility Regarding 'Transformed' NMs?

Underpinning the REACH regime is the notion that industry is best placed to monitor the chemicals which they place on the market. Manufacturers, importers and downstream users are required to ensure that the chemicals they manufacture, import or use do not adversely affect human health or the environment (Lee & Stokes, 2009). Currently, the onus is on the NM (chemical) manufacturer or importer to ensure safety for proposed applications of their downstream users. In light of NMs and nanotechnologies status as an enabling technology and the vast range of products that incorporate NMs, is it possible for the manufacturer of an NM to foresee the eventualities of use, especially in fast-growing areas such as green energy? Can the person at the beginning of the NMs life-cycle (the manufacturer/importer) foresee all eventualities, including the transformations of the NMs under different exposure scenarios and test for them?

The enormous reactive surface area of NMs confers many NMs the ability to sorb and transform pollutants, a feature that has been exploited for bioremediation applications of, for example heavy metals, pharmaceuticals or pesticides using nanoscale zero valent Iron particles (El-Temsah et al., 2015; Kanel et al., 2006; Machado et al., 2013). Whether the presence of an NM in a polluted environment ameliorates (e.g. influence of carbon nanotubes (CNTs) on pyrene bioaccumulation

in earthworms (Petersen et al., 2009)), or intensifies (e.g. increase in uptake of Cu by *D. magna* in the presence of single-walled CNTs (Kim et al., 2010)), the toxicity of the secondary compound will be dependent on the specific form these interactions take, which in turn depends on the physicochemical properties of the NMs, its chemical composition and the properties of the surrounding medium (ionic strength, pH, etc.) (Lynch et al., 2014; Malkiewicz et al., 2011; Yang et al., 2013). A scenario can also be envisaged whereby an interaction with an NM widens the environmental distribution of a secondary pollutant, for example the aggregation and sedimentation of an NM with a secondary pollutant sorbed from the water column. This dual ability of NM to both elute (e.g. catalyst or other contaminants (Kim et al., 2010)) and sequester and transport potentially toxic materials (known as the Trojan-horse effect (Auffan et al., 2012)) is shown schematically in Fig. 9.4. Such effects, and specifically who is responsible in the legal and regulatory sense for the transformed NMs, needs to be addressed within regulation.

The question then becomes whether a manufacturer could foresee that his harmless NMs would end up in an environmental compartment where it collected substances from conventional industrial discharge and concentrated them to a degree where the exposure became significant to organisms that encountered/ingested the NMs? Is the manufacturer responsible for providing safety data for materials that are no longer the as-produced NMs? As there is an essentially infinite

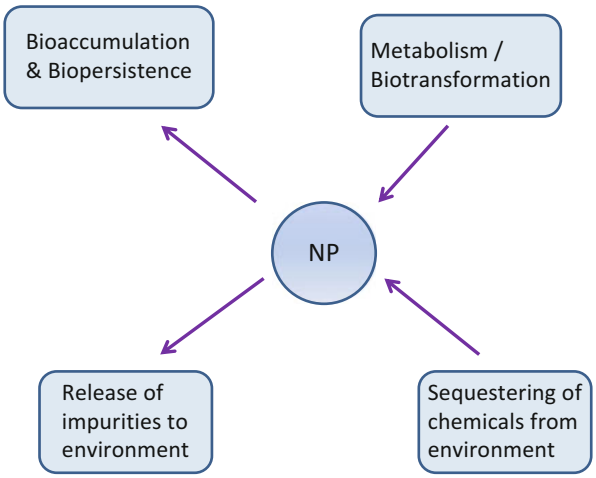

Fig. 9.4 Illustration of some of the new challenges related to regulation of NMs, whereby they can release chemicals to the environment, and also sequester chemicals to them, presenting the adsorbed chemicals in new ways at the NMs surface. Both of these phenomena can lead to increased bioavailability of the chemicals, and to new toxicities not previously regulated for. Additionally, fate and behaviour of the NMs in the environment must be addressed critically, including assessment of their bioaccumulation and biopersistence rate and their metabolism or biotransformation potential in various environmental and biological compartments and species

array of uses/formulations for NMs, all of which can transform the NM from its original form and composition, where does and should a manufacturer's responsibilities end?

The 27th Report of the Royal Commission on Environmental Pollution (RCEP), which focussed in large part on NMs (Royal Commission on Environmental Protection (RCEP), 2008), also picked up on some issues surrounding manufacturer responsibility within REACH. RCEP warns that substantial amendments will be needed, and considers several options including the extension of product 'take-back' requirements, such as those contained in the Waste Electrical and Electronic Equipment (WEEE) Directive, to products containing NMs, with the goal of minimising environmental exposure to potentially hazardous substances at the end of their life by enabling consumers to return a product to the original retailer or manufacturer (Lee & Stokes, 2009).

9.5 Mechanisms to Support Regulatory Authorities Regarding NMs Risk Assessment

While clarifying uncertainties with regard to existing regulatory frameworks is essential, there is also a need to organise and use the information that is available in a more productive and integrated manner. One approach to doing this is building integrative technology roadmaps for nanotechnology-risk governance, and continuous refinement of the methodology through application via case studies (Malkiewicz et al., 2011).

Pastoor et al. (2014) suggest a comprehensive framework for bringing together knowledge to enable effective decision making (Pastoor et al. 2014). The so-called RISK21 framework is presented as a problem formulation-based, exposure-driven, tiered data acquisition approach that incorporates exposure and toxicity estimates and their respective uncertainties to guide informed human health safety decisions as soon as sufficient evidence is acquired to address the specific problem formulation (Arts et al., 2015; Pastoor et al. 2014). The value of the roadmap, as described by the authors, is its capacity to chronicle the stepwise acquisition of scientific information and display it in a clear concise fashion: detailed exposure and toxicity data can be coalesced into an understandable rendering that can be flexibly revisited as new information is generated. The approach is non-judgemental with regard to the methodological origin of the data, as long as they can be expressed in a common metric (Pastoor et al. 2014).

Meesters et al. propose that incorporation of the specific environmental fate processes of engineered NMs into the environmental-risk assessment framework of REACH requires a pragmatic approach; they identified three major assumptions made in REACH guidance that are not applicable to NMs and suggest prioritisation of efforts accordingly: (1) in REACH, environmental alteration processes are all thought of as removal processes, whereas alterations of NMs in the environment may greatly affect their properties, environmental effects and behaviour; (2) in REACH, chemicals are supposed to dissolve instantaneously and completely on

release into the environment, whereas NMs should be treated as non-dissolved nano-sized solids and (3) in REACH, partitioning of dissolved chemicals to solid particles in air, water and soil is estimated with thermodynamic equilibrium coefficients, but in the case of NMs, thermodynamic equilibrium between 'dispersed' and 'attached' states is generally not expected (Meesters et al., 2013). By focusing on the specific aspects of where NMs differ from classical chemicals, it is possible to rapidly assess where additional or alternative testing approaches are required, such as alterations to the Technical Guidance and/or annexes of REACH. A similar pragmatic approach has been suggested for consideration of a framework for regulation of nano-formulated pesticides, where it was proposed that the nanocomponent only needed to be considered from a regulatory perspective as long as it was associated with the active ingredient and thus could potentially affect its toxicokinetics (rate of uptake) or toxicodynamics (function) (Kookana et al., 2014). Thus, it was recommended to consider the durability of the NM-active ingredient (a.i.) complex and its persistence and mobility in order to identify cases where only the a.i. needed to be tested (in the usual manner as for non-nano a.i.s) versus those cases where only the NM-a.i. complex needed testing due to the fact that the a.i. is never separated from the nanocarrier, or the intermediate scenario where all three species needed to be assessed (Kookana et al., 2014).

A similar strategy, of focusing on the specific aspects or emergent properties that made new hierarchical NMs (called nanohybrids) different from their conventional NM counterparts, has recently been suggested (Saleh et al., 2015). Within the existing regulatory framework, the guiding principle remains to determine the influencing property or properties that will dictate nanohybrid materials' release, fate and transport, exposure and toxicity. However, when such properties are the result of conjugation or hybridisation, the possible combinations of multiple materials are extremely large and go beyond the challenges around NM size, shape and coatings type that are currently being addressed systematically by the nano safety community. Strategies are needed to rationally narrow down this ever-expanding space, so that comprehensive nano safety evaluation can be performed with reliability and in a timely manner. Central to evaluation of nanohybrids (NH) is an assessment of the stability (integrity) of the ensemble material during environmental transport, transformation and exposure (Saleh et al., 2015). NHs that maintain their unique properties in environmental and biological media could have unique, yet to be studied, environmental health and safety implications; so the stability of these NHs under environmentally relevant conditions needs to be evaluated (Saleh et al., 2015).

9.6 Regulatory Precedent for Assessing Transformed Variants (E.g. Drug and Pesticide Metabolites)

The European Commission Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC (2003) provides a framework to assess the relevance of metabolites

found in groundwater, the major environmental compartment of concern in the EU. Groundwater was identified as a natural resource which should be protected using a 'limit value' for active substances and their relevant metabolites (provided in Annex VI of Directive 91/414/EC (and Directive 98/83/EC)). The guidance document describes a scheme to determine whether a metabolite is relevant or not relevant using criteria of biological activity, genotoxicity and toxicological hazard (Terry et al., 2015). Relevant metabolites are subject to the 0.1 μg/L limit value in groundwater. Non-relevant metabolites are non-genotoxic metabolites without specific hazard properties (toxic, carcinogenic and toxic to reproduction) and with no, or significantly reduced, biological efficacy against pests and are subject to a refined human health-risk assessment when their concentration in groundwater is estimated to be above 0.75 μg/L.

Originally proposed for substances intended for use in food-packaging materials (Frawley, 1967), the threshold of toxicological concern (TTC) describes a level of exposure that is considered to represent negligible risk to humans. TTC was extended (Munro et al., 1996) to develop human exposure thresholds for non-genotoxic chemicals for three structural classes of chemicals based on the Cramer decision tree (Cramer et al., 1978):

- Class I: structurally simple chemicals that are efficiently metabolised, with low potential for toxicity.
- Class II: chemicals of intermediate concern that are less innocuous than class I substances but that lack the positive indicators of toxicity that are characteristic of class III chemicals.
- Class III: chemicals which have structures suggestive of significant toxicity or those which cannot be presumed safe.

TTCs are analogous to chemical-specific reference doses, such as an Acceptable Daily Intakes, but as generic reference values, a TTC can be used to assess the risk from estimated exposures for chemicals with limited toxicity data (EFSA, 2012; Terry et al., 2015).

A recent development of the TTC concept was to introduce the approach of comparative toxicity, which was used to determine the environmental metabolites of a new chemical, sulfoxaflor (X11422208) (Terry et al., 2015). The ultimate aim was to address the human safety of the metabolites with the minimum number of in vivo studies, while at the same time, ensuring that human safety would be considered addressed on a global regulatory scale (Terry et al., 2015). The comparative toxicity component was designed to determine whether the metabolites had the same or similar toxicity profiles to their parent molecule, and also to one another, with the ultimate goal of establishing whether the metabolites had the potential to cause key effects—such as cancer and developmental toxicity, based on mode-of-action (MoA) studies—and to develop a relative potency factor (RPF) compared to the parent molecule (Terry et al., 2015).

Another domain where metabolites are a well-established concern is pharmacology and medicine design. Here, species differences in drug metabolism present challenges that may confound the non-clinical safety assessment of candidate drugs:

The first challenge is encountered when metabolites are formed uniquely or disproportionately in humans (Powley et al., 2009). Another challenge is understanding the human relevance of toxicities associated with metabolites formed uniquely or disproportionately in a non-clinical species (Powley et al., 2009). Approaches suggested to overcome this include development of genetically modified organisms (e.g. human P450 expressing models) whose metabolism profiles more closely resemble humans. When compared to the current strategy for handling metabolite challenges (i.e. direct administration of metabolite), identifying an appropriate human P450 expressing model could provide a number of benefits, including improved scientific relevance of the evaluation, decreased resource needs and a possible reduction in the number of animals used. These benefits may ultimately improve the quality and speed by which promising new drug candidates are developed and delivered to patients, and could potentially be adapted for assessment of NMs transformation products.

9.7 Lessons from Other Areas: What Could Be Adapted for Transformed NMs?

While NMs do present multiple new challenges for regulators, specifically around transformation and ageing from the pristine or as-produced material, they are certainly not alone in this. A well-known example from regulation is the issue of metabolites and degradates of pesticides and their residues in food, and indeed, there has recently been a suggestion that these should be regulated alongside the starting active ingredient in terms of the residue definition for dietary-risk assessment (EFSA Panel on Plant Protection Products and their Residues (PPR), 2012). Thus, while a comprehensive toxicological dossier is developed for parent compounds, prior to approval of substances for use within the EU (Regulation EC (No) 1107/2009), there is often only limited information available about the toxicological properties of metabolites (EFSA Panel on Plant Protection Products and their Residues (PPR), 2012). In light of this, in 2012 the European Food Safety Authority (EFSA) asked its Plant Protection Products and their Residues Panel to develop an opinion on approaches to evaluate the toxicological relevance of metabolites and degradates of pesticide active substances in dietary-risk assessment. A key issue was to determine whether a metabolite would be tested along with the parent compound in laboratory species as part of routine assessment, or whether, due to its formation in vivo in specific plants or livestock following exposure, a specific metabolite was not available for testing. On the basis of this analysis, the panel made a series of recommendations regarding an alternative approach to assessment of pesticide metabolites. The report developed 12 recommendations for pesticide metabolites, summarised in Table 9.3, many of which could also be applicable to aged or transformed NMs.

Table 9.3 The EFSA Panel's conclusions on these approaches, and our suggestions as to their applicability for environmentally transformed NMs

	EFSA Panel conclusions	Applicable to NMs?
1	The potential impact of structural metabolic changes to parent compounds on the toxicological properties of derived metabolites cannot be predicted, and metabolic pathways are in most cases specific for each chemical group and toxification/detoxification potential cannot be reliably attributed to specific metabolic steps	Yes
2	Three critical steps were identified in the application of the TTC scheme in risk assessment of pesticide metabolites (1) the estimate of the level of the metabolite, (2) the evaluation of genotoxicity alerts and the (3) detection of neurotoxic metabolites arising from a parent compound with a structural alert not covered by the scheme	Yes
3	The application of solely (Q)SAR approaches to predict the potential genotoxicity of unknown pesticide metabolites is not satisfactory and cannot support decision making	Yes—QSARs are not yet sufficiently developed/validated for NMs
4	The predictivity for neurotoxicity of the (Q)SAR models, tested alone or in combination, is currently inadequate to be applied for pesticide metabolites. A stepwise approach involving (Q)SAR analysis and read-across, resulted in an improvement in the identification of potential developmental toxicants and complemented the TTC approach in the assessment scheme for pesticide metabolite exposure	Would need to be validated but should be applicable
5	Estimates of exposure to pesticide metabolites are based mainly on residue metabolism studies. These data have also been adapted using a metabolite to parent ratio applied to the available residue endpoints from supervised trials data to give estimates of exposure for both chronic and acute exposure. The approaches tested allowed a dietary exposure tree for pesticide metabolites to be proposed. However, different methodological approaches produce different outcomes and risk managers would need to advise on the level of protection that is desired	Could be applied for environmental exposure. Method development needed for detailed evaluation of pristine versus transformed and degree of transformation of NMs
6	The scientific principles that underpin pesticide metabolite exposure calculations (above) are also directly relevant to the derivation of conversion factors which are established during the regulatory evaluation of parent compounds in the framework of Regulation (EC) No 1107/2009 when the residue definitions for monitoring and dietary-risk assessment differ. The PPR Panel recognises that currently, there is no unambiguous approach to deriving conversion factors and recommends the developing further guidance in this area	Such calculations are the goal for NMs and their transformed counterparts but significant work needed to establish the scientific principles still

(continued)

Table 9.3 (continued)

	EFSA Panel conclusions	Applicable to NMs?
7	Chronic and acute assessment schemes are proposed for the risk assessment of pesticide metabolites considering different strategies for mammalian and plant-specific metabolites. A chronic exposure estimate is necessary in all cases, while an acute exposure assessment is needed only when an Acute Reference Dose (ARfD) has been allocated for the parent compound or structural alerts for acute neurotoxicity and developmental toxicity are detected	Adaptable for NMs and their transformed forms
8	The chronic assessment scheme involves comparison of chronic exposure with the corresponding threshold values given in the decision tree. If exposure estimate exceeds the identified TTC values, different approaches are proposed for mammalian rodent and plant or livestock metabolites. A weight of evidence approach is recommended to determine if the toxicological profile of rodent metabolites is covered by the data on parent compound. Plant or livestock-specific metabolites need to be assessed using an appropriate testing strategy	The TTC approach would be suitable for NMs, but the exposure limits for the pristine NMs have to be defined first
9	An acute exposure assessment scheme was developed by the PPR Panel. Ad hoc acute TTC values of 0.3 μg/kg bw/d for substances with a neurotoxicity alert and 5 μg/kg bw/d for substances allocated in Cramer class II and III were derived. A combination of (Q)SAR and read-across approaches is proposed for the prediction of developmental toxicity	Similar approaches for NMs would be relevant. However, exposure limits are not yet established and would be needed
10	Where exposure to a metabolite exceeds the respective TTC value, acute and chronic toxicity testing strategies were proposed, considering the need to derive health-based limits for human exposure	Similar approaches for NMs would be relevant, especially in relation to food (Priester et al., 2012)
11	Risk assessment of pesticide metabolites that are stereoisomers should be addressed due to isomer ratio changes reflected in the composition of metabolites. Further development of (Q)SAR tools would be beneficial, both to predict genotoxicity and to address stereochemistry aspects. Metabolism guidelines should require compositional information on stereochemistry to consider the full impact on the dietary-risk assessment	NM chirality has not been investigated to any significant extent as yet (Sokolov, 2009), but could be a relevant factor

9.8 Conclusions

Given the undisputed fact that NMs age, transform and evolve from their pristine state as-produced, through their formulation and use phase, and upon contact with living systems, be that intentional (e.g. nanomedicines, nano-enhanced foods, textiles or cosmetics) or unintentional (e.g. following excretion of nanomedicines into wastewater, washing of textiles, etc.) regulation for NMs needs to evolve to capture these transformed states and assess their toxicity relative to the parent NM. There is emerging regulatory precedent for this in food, pesticide and medicine regulation that could be adapted for NMs in consumer and industrial products. For example, analysis of the toxicity of metabolites produced in human and non-human species is encoded in medicine and pesticide regulation, and the TTC concept has been extended to include comparative toxicity, which has been used to determine the environmental metabolites of a chemical, for example. In all cases, a clear focus on where the NM and the transformed NM differ from conventional chemicals/macroscale particles needs to be centre stage in considering additional testing requirements in order to be pragmatic and not stifle innovation or commercial activity. Thus, if the transformation is to the ionic metal, then classical metal toxicity testing applies, while if the transformation is to an increasingly stable sulphidated form, then the testing should consider NM lifetime, stability in various environments and final environmental sinks, in addition to the types of degradation and metabolites that might result over time in these sinks. A point for clarification remains in terms of manufacturer/importer responsibility for ensuring the safety of environmentally transformed variants of the original NM, which will require further debate and discussion as more data on this topic emerges and fate and behaviour data are more deeply embedded into life cycle approaches and regulatory frameworks.

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Chapter 10
Applying Safety by Molecular Design Concepts to Nanomaterials Risk Management

Anna L. Costa

Abstract The health impact assessment and control of nanostructures has been recognized as part of the key areas of nano science. Sustainable development of nanotechnologies in clinical as well as in other relevant industrial application must avoid any adverse effect on the health of humans and environments exposed to nanomaterials, justifying close attention to safety issues. In particular, the concrete possibility to act on material design to mitigate any adverse biological effect (safer by molecular design approach) represents one of the most recent and amazing capabilities to design out risk at the source. The components of a "Nano design" framework for designing a new generation of "safer" engineered nanomaterials is introduced and some examples of its integration within realistic nano manufacturing exposure scenarios is discussed.

10.1 Introduction

Safety issues associated with nanomaterials (NMs) essentially deal with nanoscale reactivity and the peculiar properties that NMs present. Nanophase-heterogeneity creates a huge interface between nano-objects and the surrounding media that amplify surface energy and surface-dependent phenomena such as non-stoichiometric dissolution, crystallinity defects, and the degree of interaction with surrounding molecules. Moreover, the nano confinement scale, being below that of many physical phenomena (wave length of visible light, distance between electro-hole pair), generates new quantum effects and more generally new electrical/redox properties. While this new reactivity is exploited in relevant technological applications, it presents some uncertainties regarding potentially dangerous side effects (nanorisk). The control of nano-bio reactivity from the initial design stage of product development improves the potential for success of nano medicine research and

A.L. Costa (✉)
ISTEC-CNR, Via Granarolo, 64, Faenza (RA) 48018, Italy
e-mail: anna.costa@istec.cnr.it

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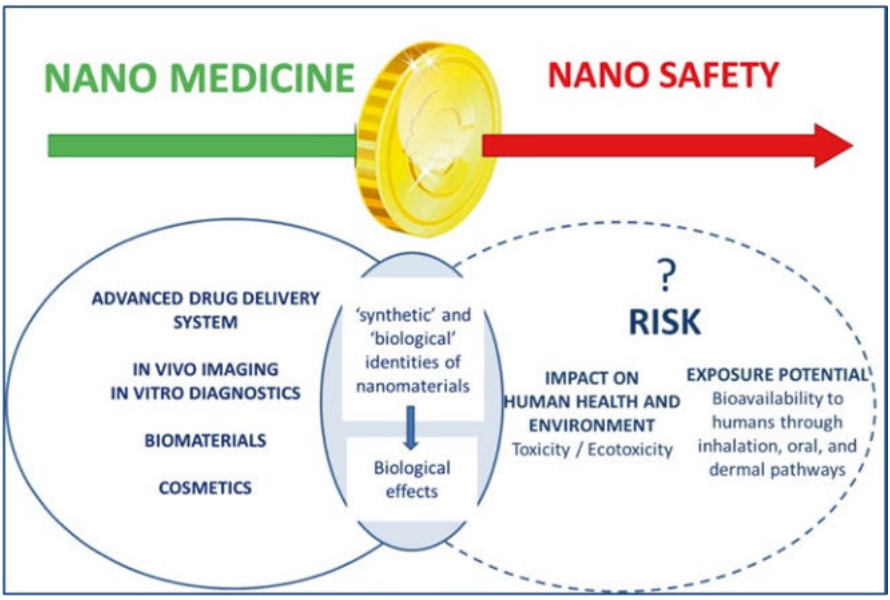


Fig. 10.1 Connection between the two sides of nano-bio research

opens a new promising approach to the risk management of nanomaterials (safety by design approach) as illustrated in Fig. 10.1 and deeply stressed by Fadeel, Feliu, Vogt, Abdelmonem, and Parak (2013). The link between nano-medicine and nano safety research is the need to understand "synthetic" and "biological" identities of nanomaterials and to correlate them to biological effects.

An exhaustive conceptual framework to drive the exploration of bio-physicochemical interactions occurring at the nano-bio interface has been provided by Nel et al. (2009). Three dynamically interacting components drive the nano-bio interactions: (1) nano surface physiochemical properties form the general basis of nanoscale reactivity; (2) biological media, characterized by intercellular components; (3) biological substrates, characterized by cellular membrane and intracellular components. These dynamic domains undergo continuous transformations due to their interactions, affecting the impact on biological receptor structure and function. Traditional interfacial and surface characterization tools exploited in colloidal and catalyst science[1] need to be integrated with nano-bio interface-specific characterizations[2] for the creation of a hazard-specific characterization tool where nanosurface physicochemical properties could provide useful information to predict toxicity mechanisms, informing the general design principles for a potential framework to

[1] For instance, that measure colloidal stability, zeta potential, particle size distribution, wetting, interfacial tension, specific surface area, crystal structure, band-gap energy, SEM/TEM morphology.

[2] For example, TEM cryomicroscopy, fluorescent labeled nanoparticles and corresponding imaging techniques, nanobiosensors for the detection of ROS and surface-enhanced Raman scattering.

mitigate toxicity. A very impressive simplification of the above concepts is reached by Donaldson et al. (2013) where the biologically effective dose (BED) issues are discussed. BED is used to identify and quantify the actual component(s) of the total dose that drives adverse effects such as particle size distribution, specific surface area, aspect ratio, zeta-potential, oxidative potential, and the soluble toxins released from nanomaterials. They can take the form of one or more physicochemical characteristics associated with the particles as soluble or ionic species released from the particle, reactive oxygen species, ROS, produced or can be characteristics integral to the particle surface or the particle shape. The uses and importance of the BED are suggested in terms of different uses: as the most relevant exposure metric, as key component driving structure–reactivity relationships as well as nanoparticles categorization for hazard evaluation purposes. Furthermore, a BED-based classification of nanoparticles can have a primary role in the development of safety by design strategies. Design solutions affecting a BED dose indicating a decrease in adverse effects can actually represent an effective primary prevention strategy for NMs exposure risk management. Before starting a study about remediation for occupational risks, the structural alerts of nanomaterials should be identified. Nevertheless, the integration of toxicity-mitigating design solutions in product development will face the challenge of finding equilibrium between the BENEFITS in term of health and safety and the COSTS in terms of product functionality reduction and the introduction of additional process steps. In most cases, the nano-scale properties affecting performances exploited in technological application such as surface redox reactivity, surface ions, non-stoichiometric dissolution, surface energy, and surface wettability etc are the same that drive adverse biological reactivity. In this chapter, concepts specifically related to a safety by molecular design approach will be discussed and some examples from the FP7 Sanowork and Sun projects will be presented.

10.2 From Passive Nanostructures to Complex Nanosystems by Design

The long-term vision of nanotechnology presented by the USA National Nanotechnology Initiative (NNI) in 2000 estimated that nanotechnology would grow in two foundational phases as reported in Fig. 10.2.

A first phase, essentially science-centric, is focused on the synthesis and collection of nanostructures, the discovery of new nanoscale properties, and the improvement of existing products by incorporating simple nanostructures. The second phase, which is essentially technology-centric, will focus on the development of active nanostructures and integrated nanosystems.

The nano environmental health and safety (EHS) research from 2000 can similarly be described in terms of a characteristically scientific first phase, based on a case by case approach that is now being followed by a more technologically orientated second phase that will exploit new predictive tools such as modelling, high-throughput, and rapid screening platforms, allowing for the design of safer materials and environmentally friendly manufacturing (Fig. 10.3).

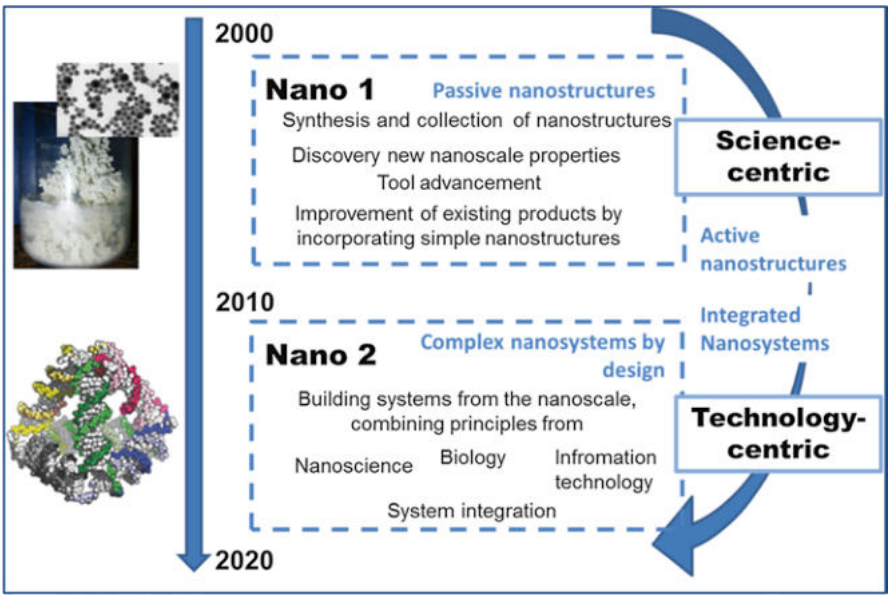


Fig. 10.2 Main phases of nanotechnology research. *Source: (Nanotechnology Research Directions for Societal Needs in 2020, Retrospective and Outlook, Edited by M.C. Roco, C.A. Mirkin, and M.C. Hersam, NSF, WTEC report, September 2010)*

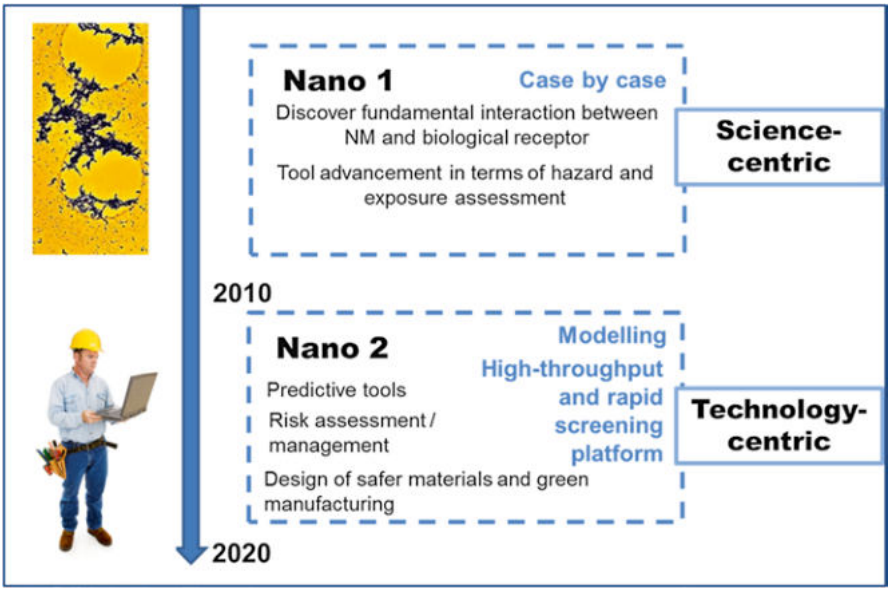


Fig. 10.3 Main phases of nano EHS research. *Source: (Nanotechnology Research Directions for Societal Needs in 2020, Retrospective and Outlook, Edited by M.C. Roco, C.A. Mirkin, and M.C. Hersam, NSF, WTEC report, September 2010)*

In summary, the current research is mainly focused on engineering simple structures with a view towards creating more complex ones that satisfy both performance and safety requirements.

10.3 Safety by Design

The proposed definition of safety by design applied to risk management of nanomaterials involves both process and materials:

> ***Engineering*** *of* ***Nanomanufacturing Process*** *or* ***Products*** *with specific attention to* ***Design Out Risks*** *rather than address them when they occur*

Safety by Process Design makes reference to a more traditional approach that has an affinity with risk management measures used to control hazardous chemicals. The proposed solutions essentially comprise the integration of analytical/automation tools within critical product life cycle stages in order to prevent releases of nanomaterials. Otherwise, safety by design solutions applied to materials (Safety by Molecular Design) are essentially material surface modification strategies proposed to control exposure risk determinant properties. As mentioned in the discussion of biological effective doses, risk determinant properties are key components driving the two main risk factors: exposure and hazard. In Fig. 10.4, some of these properties

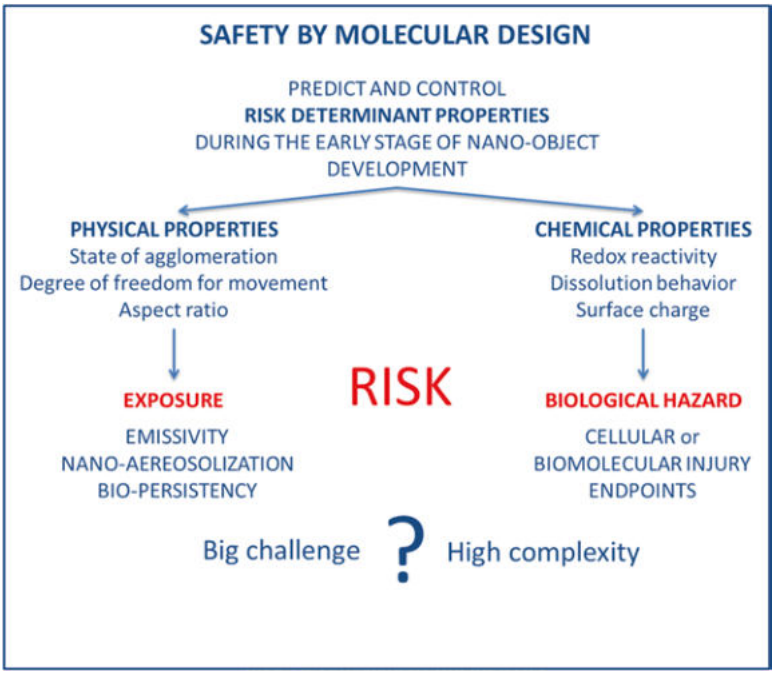


Fig. 10.4 Safety by molecular design framework

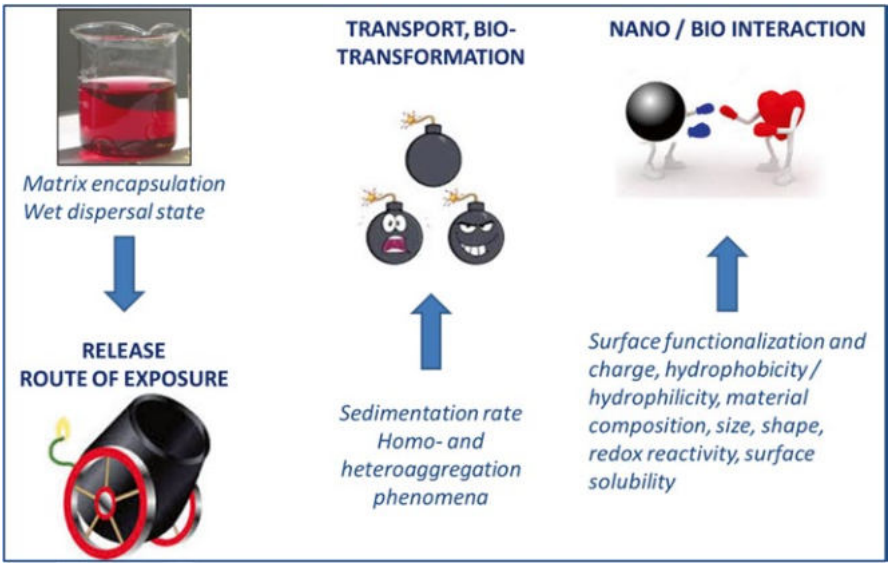


Fig. 10.5 Exposure scenarios and properties affecting exposure

are reported in which a distinction is made between physical properties that mainly affect exposure mechanisms and chemical properties that mainly affect nano-bio reactivity. The aim of molecular design is to predict and control risk determinant properties during the early stage of a nano-sized object's development, in order to mitigate adverse effects arising at the nano-bio interface.

Exposure scenarios considered in the nano-risk assessment are schematized in Fig. 10.5, together with nano material properties mainly involved at each step. The proposed design solutions should take into account how such properties affect exposure scenarios as well as specific nano-bio reactivity and promote mechanisms that decrease nano-risk, meaning both exposure and hazard potential.

The knowledge levels towards the development and promotion of safer by design NMs passes through four main steps (Bergamaschi et al., 2015; Roca, Rallo, Fernandez, & Giralt, 2012):

1. *Data generation/gathering*: understanding the synthetic and biological identities of engineered nanomaterials, focusing on selected cellular or bio-molecular injury endpoints, and identifying risk determinant properties (structural alerts, BEDs).
2. Definition of key components driving structure–reactivity relationships and development of adverse-effects, informing *predictive models*.
3. Understanding how designs of risk determinant properties could be used to optimize the utility of the engineered modified nanomaterials for *safety*, *therapeutic use,* or other *technologically relevant applications*.
4. Explicitly including potential nanomaterial exposure risks in existing liability *insurance contracts* to support insurers' *risk selection decision making process*.

10.4 FP7 Collaborative Projects Sanowork and SUN

Both FP7 collaborative projects Sanowork (NMP4-SL-2012-280716) and SUN (FP7-NMP-2013-LARGE-7) addressed safety by molecular design issues as part of the development of risk management measures for new nanomaterials. A strategy developed by the Sanowork project was slightly revised in the SUN project in which the results collected by the Sanowork project were exploited with the aim of improving existing methods for controlling exposure and hazard determinants. In Fig. 10.6, the two approaches are schematized in order that they might be better understood.

The Sanowork approach began with the identification of paradigms highlighting exposure and hazard mechanisms associated with nanomaterials. It applied material surface modifications (DESIGN) in order to control key risk properties (STRUCTURAL ALERTS) and, as a consequence, the exposure and hazard potentials, as well as the final performance of the material or product in question. A cost-benefit analysis of the proposed solutions was evaluated by collecting nanomaterial performance feedback from companies involved in the project in conjunction with the risk outputs. The final aim was to improve knowledge for the generation of molecular design guidelines, while indirectly contributing to better understanding of the current exposure and toxicity paradigms.

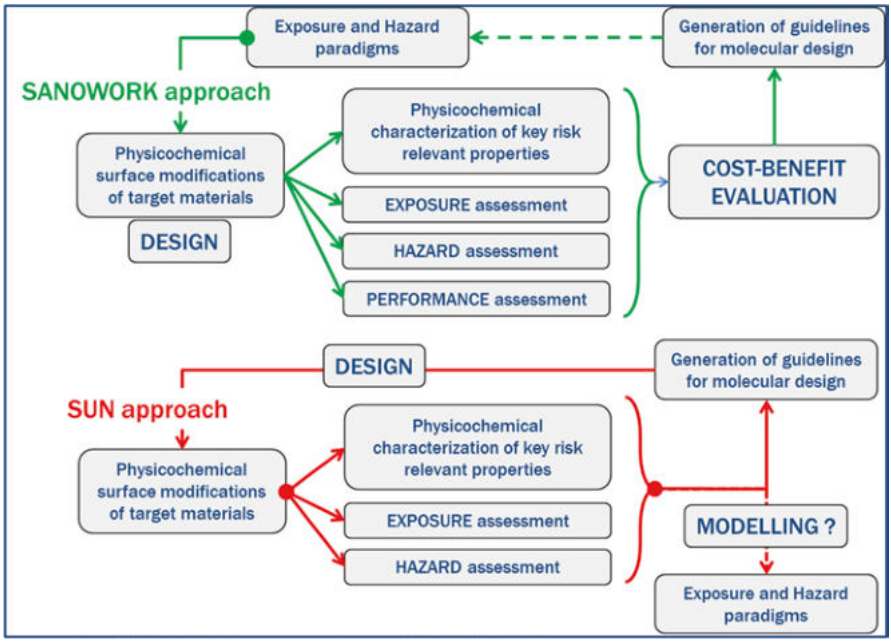


Fig. 10.6 FP7 Sanowork and SUN projects addressing safety by molecular design approaches

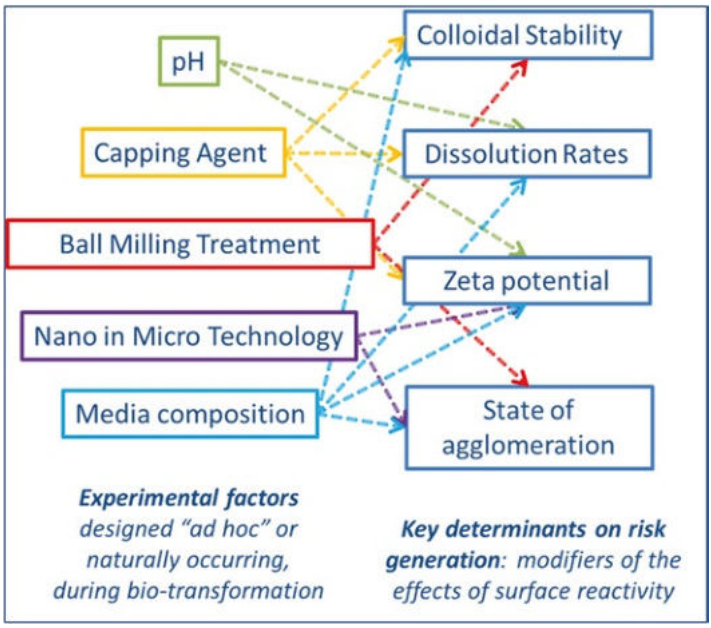


Fig. 10.7 Trends investigated between experimental factors and key determinants of risk generation

In order to evaluate the impact that proposed design solutions had on potential risk generated by production, use, and disposal of nanomaterial-enabled products, the SUN approach was to perform a systematic characterization of key risk relevant properties in order to identify links with physicochemical surface modifications, designed ad hoc or occurring in the real environment. In particular, the trends investigated are reported in Fig. 10.7. The effects of surface modifications on the left were correlated to properties driving nanoparticle hazard or emission potential (key determinants on risk generation) on the right. The results opened the way for a sound correlation with (eco) toxicological outputs that contributed to an improved understanding of exposure and toxicity paradigms that will help generate useful guidelines for the safe design of nanomaterials.

The safety by molecular design strategies that both projects developed were essentially surface modification solutions, easily transferrable from colloidal science and exploitable at industrial scale level. There are two main approaches to surface functionalization: in a chemical approach the new phase is made to react with a surface, starting from soluble species that form covalent, irreversible bonds at the nano-surface, while in a colloidal approach self-assembly of pre-existing phases is employed, essentially driven by chemisorption (self-assembling monolayer, SAM) or inter-surfaces attractive and repulsive forces (electro steric self-assembling) as shown in Fig. 10.8.

The main strategies developed in both the SANOWORK and SUN projects are described in Fig. 10.9, with a specific reference to structural alerts and proposed solutions.

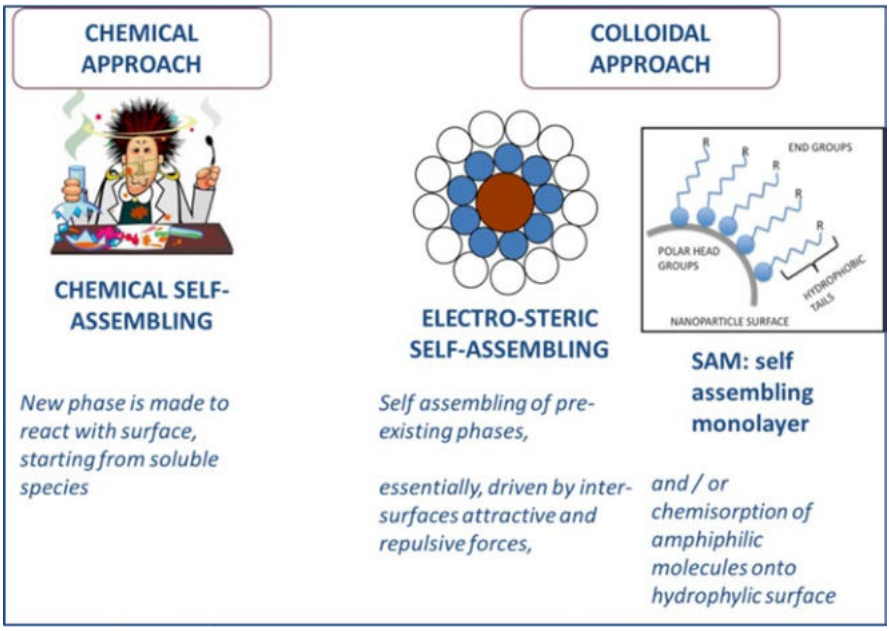


Fig. 10.8 Different chemical and colloidal approaches to surface functionalization

The surface coating strategy together with a purification treatment are chemical remediation strategies that aim to control and mitigate the reactivity of two main toxicant agents, namely ROS and free cations that are exposed to dynamic equilibrium of desorption and adsorption at the inorganic surface level. Organic salts or moieties used in colloidal science as stabilizers have the potential to control inorganic nanophase dispersability and can influence directly the nano-bio mechanism of interaction. Additionally, antioxidant molecules, such as citrate and ascorbate, can mitigate the production of ROS. Inorganic coating phases such as silica that mask active structures by encapsulating their surface sites have the potentially to mitigate their reactivity.

As far as toxicity driven by ions leached or transported by the surface is concerned, purification treatments and surface coatings were proposed in order to influence the equilibrium between free and adsorbed ions and find the best compromise between toxicity and antibacterial reactivity. They latter are exploited by antibacterial technological applications. “Nano in Micro or Macro” refer to the immobilization of the nanophase by micro or macro scale structures that preserve the primary nano scale structure and reactivity, similar to what occurs in heterogeneous catalysis. The nanophase represents the active phase that is fixed within stable structures through forcing agglomeration, embedding within inorganic or organic gel that is easily removable after critical nano-manufacturing steps, or homogeneously granulating with an instantaneous drying technique such as spray-drying.

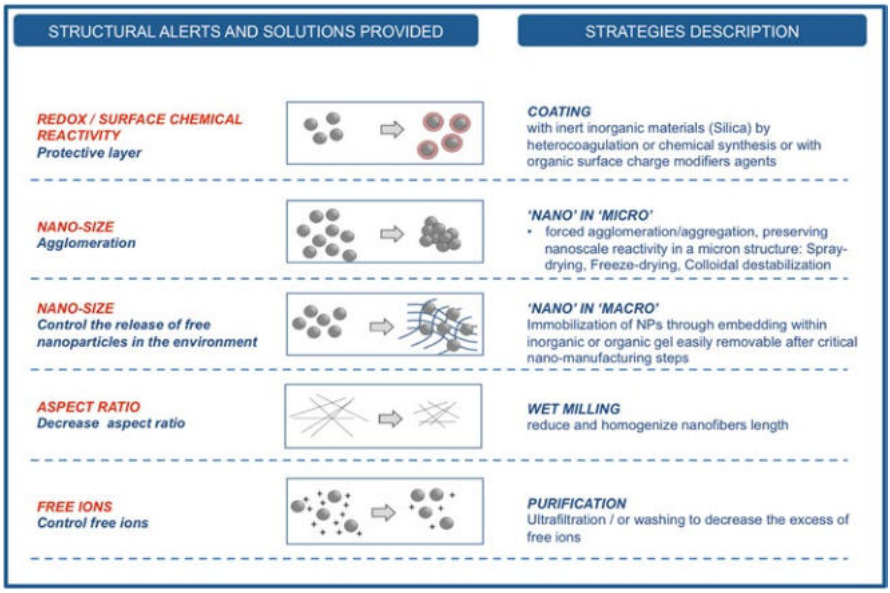


Fig. 10.9 Strategies addressed by Sanowork and SUN projects

The final proposal was the optimization of a wet milling treatment to decrease the aspect ratio of high aspect ratio nanofibers (HARP) below the dangerous limits established by the "fiber pathogenicity paradigm" (Donaldson, Murphy, Schinwald, Duffin, & Poland, 2010).

10.4.1 Case Studies

10.4.1.1 TiO_2 NF (Sanowork)

The standard description of a fiber in workplace air (World Health Organization, 1997) is that of an object having a diameter less than 3 μm, length greater than 5 μm, and an aspect ratio (AR) greater than 3:1. The fibrous shape of a NM has been considered as a "structural alert" as it is the cause of failed phagocytosis and of the translocation in various biological compartments. Moreover, long fibers cannot be phagocytized and cleared, resulting in a higher toxic potential (Donaldson, 2009; Donaldson et al., 2010).

The Sanowork project investigated TiO_2 nanofibers (NF) produced by the Elmarco company (CZ) as an active material for photo catalytic applications. Steps considered critical for potential exposure to free NFs were the recovery and manipulation operations, performed at the end of the production and calcination steps. To decrease NF exposure health risk, a wet milling step was introduced and developed

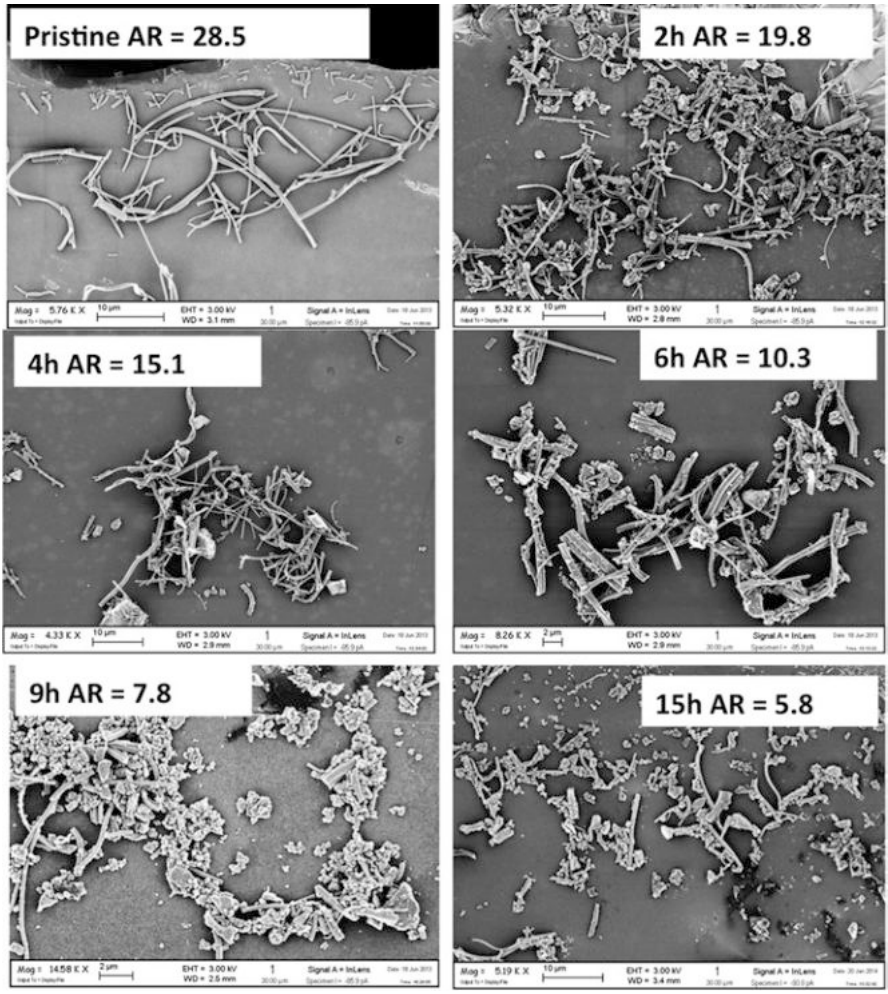


Fig. 10.10 FE-SEM micrographs of pristine and ball milled samples

in order to reduce and homogenize the length of nanofibers, thereby decreasing their aspect-ratios. Modified samples were obtained by dispersing the pristine sample in acidic (pH = 2.7) DI water (US, 10 min, nominal [TiO_2] 3 % w/w) and then ball milling the samples for different times (respectively 2, 4, 6, 9, 15 h) using ZrO_2 beads of 3 mm diameter as grinding media. The effect of ball milling treatment on samples morphology can be observed in Fig. 10.10, where FE-SEM images of dried samples are reported. The pristine material showed a broad AR distribution, ranging from about 5 to 90. By increasing the milling time, the mean NF length was reduced from 9.9 to 2.1 μm despite the fibers' mean diameters remaining around 300–400 nm, corresponding to lower AR materials. In order to evaluate the effect that the dra-

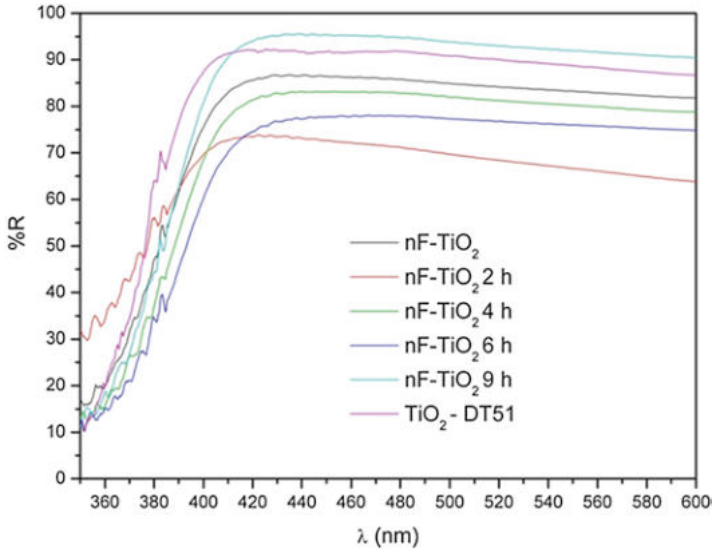


Fig. 10.11 Diffuse reflectance spectroscopy of pristine and ball milled samples

matic reduction of AR had on toxicity, several end points were analyzed using reference materials, Aeroxide P25 TiO_2 nanoparticles and UICC Asbestos crocidolite. It was found that pristine PristineTiO_2 nanofibres caused depletion of intracellular antioxidants, cell death, and frustrated phagocytosis, which were all effectively remediated by ball milled NF. The functional properties of pristine and modified samples were assessed by evaluating the band gap energy (E_g), through diffuse reflectance spectroscopy exploiting the graphical method based on the Tauc graphs (from Tauc's equation), as shown in Fig. 10.11. It was found that with increasing the time of ball milling, the value of E_g slightly increased, with an expected increase of final performances. On the basis of data obtained, the process of ball milling seems to be an efficient method to homogenize and control nanofibers' aspect ratios without affecting their functional properties.

10.4.1.2 TiO_2 Silica (Sanowork)

Nano TiO_2 is known as an exogenous source of ROS that can interact with redox metabolism and induce inflammogenic responses. For this reason, a nanomaterial's potential to induce ROS production is one of the structural alerts taken into account when assessing hazard potential. The material studied in Sanowork project was nano TiO_2 sol provided by the Colorobbia Company (Italy). Commercial silica Ludox was used as coating agent. The solution proposed, optimized, and evaluated was silica coating by matrix encapsulation. Modified samples were prepared by mixing through ball milling TiO_2 and SiO_2 nanosols at different weight ratios for

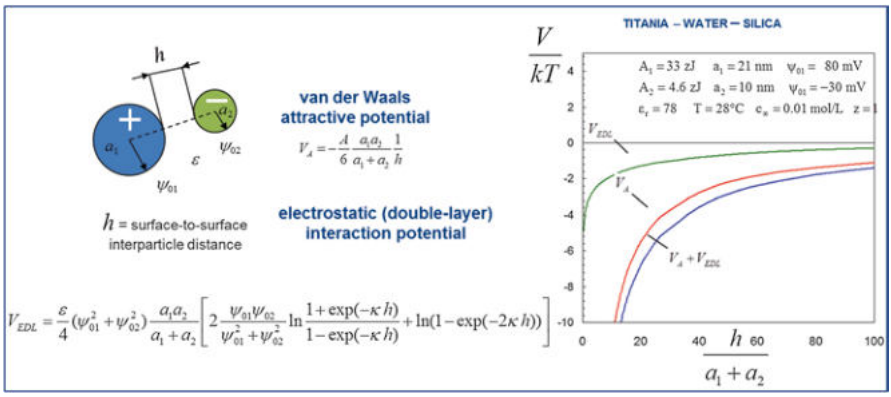


Fig. 10.12 Hetero-coagulation applied to sanowork TiO_2/SiO_2 nanosols

24 h at pH levels where surface powders showed opposite charges but without being so high as to prevent the expected hetero-coagulation (colloidal approach, easily scalable as shown in Fig. 10.12). The production of ROS under UV light irradiation was assessed to predict surface redox reactivity and correlate it with biological response. In order to evaluate the functional properties of pristine and modified TiO_2 nanoparticles, photocatalytic tests at sol state and NO_x/NO abatement tests on coated ceramic tiles were performed. The colloidal properties of titania/silica samples were characterized. As can be observed in Fig. 10.13, the hydrodynamic diameter of TiO_2–SiO_2 sample increased as a function of the TiO_2:SiO_2 ratio due to the electrostatic destabilization that occurred with the progressive neutralization of positive TiO_2 surface charge from the increase of the concentration of negative SiO_2 particles. The production of ROS was monitoring by EPR spectroscopy, using tempone-H hydrochloride as spin-trap agent, while photocatalytic performances were evaluated by assessing the abatement of NO_x. Both tests were carried out under UV light irradiation. As reported in Fig. 10.14, the reactivity of TiO_2 and TiO_2/SiO_2 samples was evaluated by comparing the samples at the same total amount of solid (not normalized for the content of TiO_2) and at the same concentration of TiO_2 (normalized samples). It was found that the presence of silica progressively reduces the production of ROS only if comparing samples that have not been normalized with respect to their TiO_2 content, thereby accounting for the expected ROS production reactivity that is TiO_2 surface dose-dependent. This result apparently, banally predictable, was not confirmed by the photo-catalytic performance properties that were better also when comparing non-normalized samples. The interesting conclusion was that the presence of silica improved photo catalytic properties of TiO_2 in all cases. These results strongly impacted positively the cost-effectiveness of the proposed strategy with a cost estimation that decreases because the more expensive TiO_2 phase can be diluted by SiO_2, also providing a benefit in terms of a health risk reduction due to the reduction of ROS production for samples not normalized with respect to their TiO_2 content.

Sample	pH	d_{DLS} (nm)	ζ-pot (mV)	$pH_{i.e.p.}$
TiO_2	2.8	53 ± 0.9	+38 ± 1.8	7.1
Ti:Si 1:0.3	3.0	78 ± 1.1	+33 ± 1.5	-
Ti:Si 1:3	3.1	110 ± 0.9	+31 ± 1.0	6.0
Ti:Si 1:5	3.4	577 ± 39	+25 ± 0.1	5.4
SiO_2	9.6	20 ± 0.3	-42 ± 2.2	<3

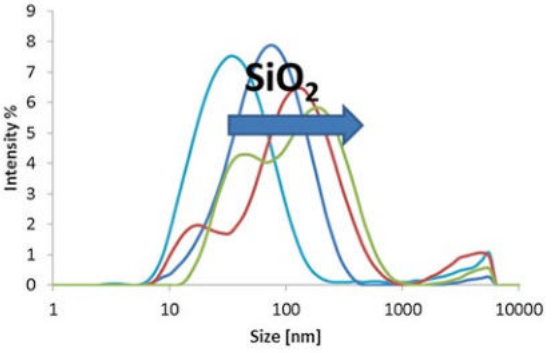
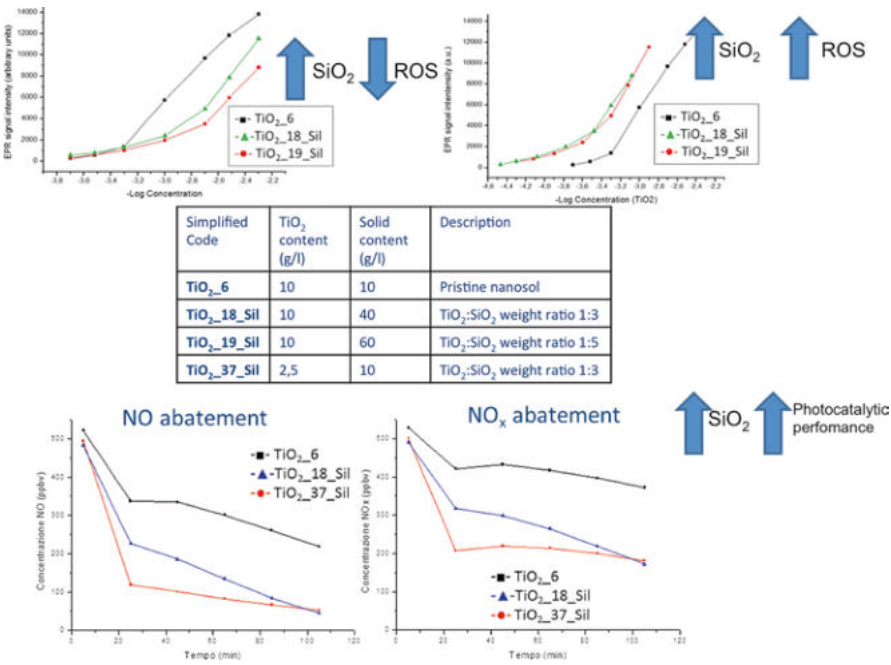


Fig. 10.13 DLS hydrodynamic diameter and ELS zeta potential of pristine and modified samples



Simplified Code	TiO_2 content (g/l)	Solid content (g/l)	Description
TiO_2_6	10	10	Pristine nanosol
TiO_2_18_Sil	10	40	TiO_2:SiO_2 weight ratio 1:3
TiO_2_19_Sil	10	60	TiO_2:SiO_2 weight ratio 1:5
TiO_2_37_Sil	2,5	10	TiO_2:SiO_2 weight ratio 1:3

Fig. 10.14 ROS production and photo-catalytic performances versus NO_x abatement

10.4.1.3 Ag (Sanowork)

Silver-based materials have been commercialized for health and medical reasons since the early twentieth century, and at present, they are marketed as a dietary supplement and alternative medicine cure-all. The improved capabilities in nanoscience and nanoparticle synthesis and engineering justify the revived attention to Ag NPs for antimicrobial applications, with an estimated amount of about 320 tons per year produced and used worldwide (Lara, Garza-Trevino, Ixtepan-Turrent, & Singh, 2011; Nowack, Krug, & Height, 2011; Seltenrich, 2013).The mechanisms by which Ag NPs exert toxicity and, consequently, antimicrobial effects are not fully understood, but it is commonly accepted that the release of silver ions (Ag^+) represents the primary mechanism of antibacterial action, with a negligible particle-specific activity (Ivask et al., 2014; Ma et al., 2012; Xiu, Zhang, Puppala, Colvin, & Alvarez, 2012). Additionally, a complex mechanism that drives toxicity is activated by the partial oxidation that occurs at surface level once nanoparticles come in touch with O_2, under UV light irradiation. Ag^+ ions leached from the surface interact directly with cell membrane, binding SH groups and so damaging cellular protein, furthermore a redox-mediated toxicity occurs at surface level, involving distribution between Ag^0 nanoparticles and Ag^+, Fig. 10.15.

As part of the Sanowork project, the potential for worker exposure during Colorobbia's spray-coating deposition process of Ag nano suspensions (nanosols) to produce antibacterial ceramic tiles was considered (Fig. 10.16). Different nanosilver sols were investigated: a sample was obtained by diluting a commercial sol (Ag1), a sample arising from the latter after a purification treatment (Ag31), a sample synthesized at lab scale under controlled conditions (AgL) and samples obtained by silica matrix encapsulation with or without ultrafiltration treatment (Ag15, Ag34). See Fig. 10.17. The physicochemical identity of the samples, in particular the Ag^+/Ag ratio, was related to biological properties; a decrease in cell viability (IC50) and antibacterial performances within industrially relevant applications (antibacterial coatings on ceramic tile surfaces).

In terms of colloidal properties, the DLS-hydrodynamic diameter and ELS-Zeta potential of pristine Ag_1 and modified samples Ag_L, Ag_31, Ag_15 and Ag_34 did not present significant differences, while the formation of a hierarchical structure

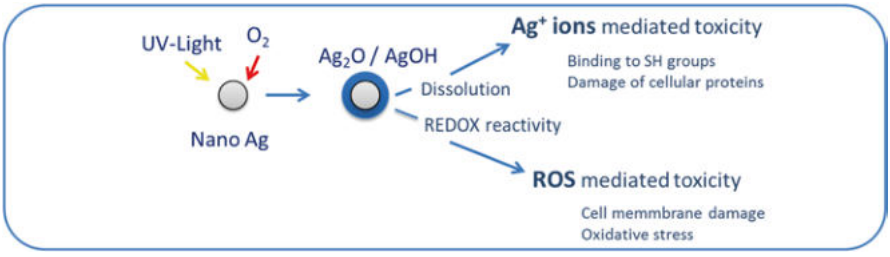


Fig. 10.15 Nano Ag toxicity mechanism

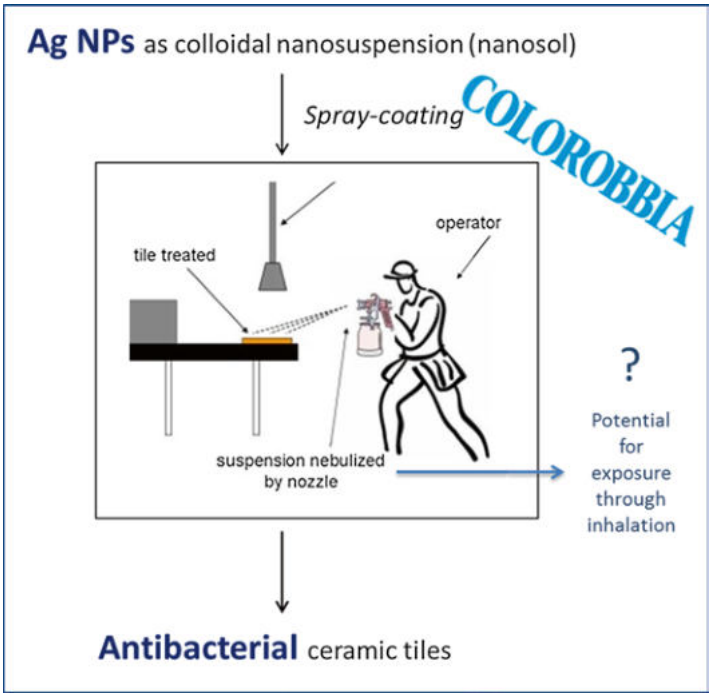


Fig. 10.16 Exposure scenario involved in Sanowork Ag nanosol case study

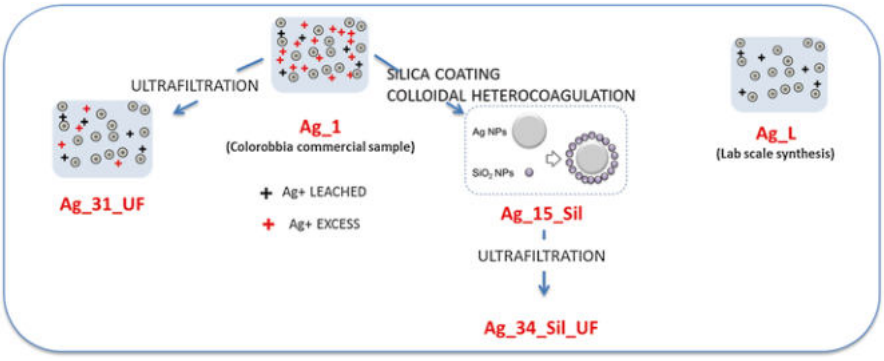


Fig. 10.17 Sanowork nano Ag pristine and modified samples

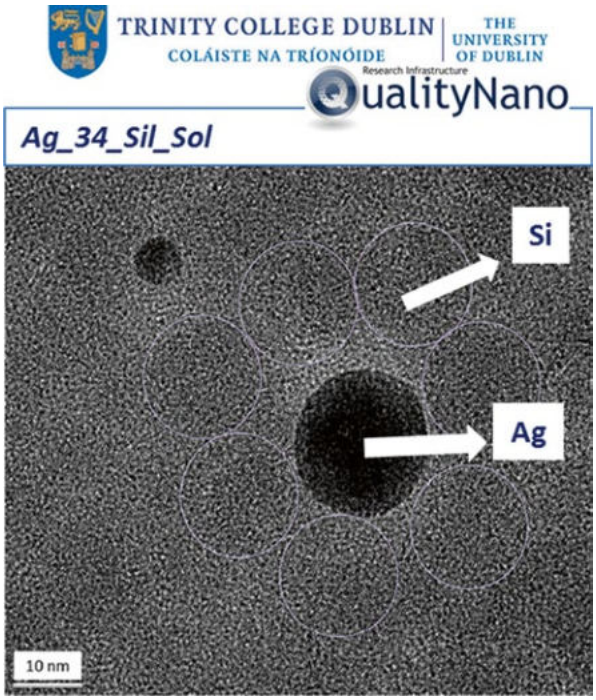


Fig. 10.18 TEM micrograph of silica matrix encapsulated nano Ag sample

consisting of Ag NPs surrounded by silica matrix was detected by TEM when observing Ag/silica samples (Fig. 10.18).

By performing consecutive ultra-filtration steps on a commercial sample of Ag, it was possible to assess the content of Ag^+ ions released at equilibrium. The fraction of Ag^+ ions decreased after each ultrafiltration step until it reached an asymptotic value of 0.08 %, a value close to data reported in the literature (Ivask et al., 2014). Table 10.1 shows that the Ag^+/Ag ratio for AgL sol is what is expected at equilibrium, while the other sols contain an excess of ions that reflects the capacity of each sample to store different amount of ions distributed between the solution and solid surface. In particular, the high excess of Ag^+ ions presents in the commercial sample can be due to an incomplete synthesis occurring at the industrial scale level, suggesting the possibility of improving the reaction yield after the optimization of synthesis parameters.

In order to assess toxicity and antibacterial properties and evaluate the effect of the proposed strategy, cell viability was assessed in cultures of Raw264.7 murine macrophages using the resazurin method (University of Parma), while the *E. coli* strain ATCC8739 was chosen as a model microorganism for inactivation experiments (Colorobbia labs). The results of biological characterization are summarized in Table 10.2. The doses were reported in terms of ppm of Ag^+ present in the sample

Table 10.1 pH and mass fractions of silver ions $\copyright^{(0)}_{Ag^+}$ for the target sols

	pH	$\copyright^{(0)}_{Ag^+}$ (%)
Ag1	2.4	55.00
Ag31_UF	3.5	2.69
AgL	4.5	0.10
Ag15_Sil	2.5	72.70
Ag34_Sil_UF	4.3	5.50

$\copyright^{(0)}_{Ag^+}$ = percentage of silver ions with respect to the total amount of silver in the starting sol

Table 10.2 Summary of biological tests results

	$\omega^{Tox}_{Ag^+}$ (IC_{50} ppm)	$\omega^{AntiB}_{Ag^+}$ (MIC_{99} ppm)
Ag1	2.48	0.022
Ag31_UF	2.04	0.015
AgL	0.05	0.004
Ag15_Sil	9.7	0.015
Ag34_ Sil_UF	5	0.015
$AgNO_3$	2.6	0.004

analyzed and $AgNO_3$ was used as a reference material in order to detect whether or not the silver NPs contributed to biological reactivity. It was found that the half maximal inhibitory concentration (IC50) values for Ag_1, Ag_31, and $AgNO_3$ were roughly comparable (with Ag31 slightly lower than the other two), while the IC50 of AgL was markedly lower. The last result suggested an Ag NP-dependent contribution to cytotoxicity, most probably due to an increased bioavailability of Ag^+ ions. Otherwise, silica-modified samples Ag_15 and Ag_34 showed a reduced toxicity, suggesting these NPs entrapped a portion of the Ag^+ ions, making them less available. All the samples showed a high antibacterial activity with minimum inhibitory concentration (MIC99) in the order of a few ppb, if expressed as an Ag^+ dose; Ag_L showed the same reactivity of $AgNO_3$, exhibiting an antibacterial activity dependent only on Ag^+ concentrations. Conversely, the Ag_1 and modified samples seemed to be less reactive, as if in these cases some of the Ag^+ ions present were not bioavailable for the antibacterial action. Based of these results, an effort was made to identify the dilution range, such that it was below the toxicity limit but above the antibacterial one, in order to safely apply the sample. See Fig. 10.19.

Nevertheless, in order to better identify the safe zone, two different exposure scenarios were considered. The first occurs when a worker handles the starting nanosol for preparation, while the second occurs during the antibacterial spray coating and subsequent washing of the tile surface. In both cases, a dilution step is foreseen: the dilution in the first case is deliberate in order to satisfy the first condition that the Ag^+ concentration of the starting sol should be below the toxicity limit, while in the second case a further decrease of the initial concentration occurs owing

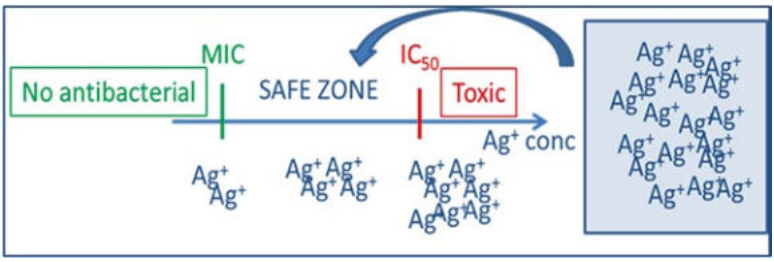


Fig. 10.19 Scheme representing the safe dilution range for applying Ag nanosol samples

to a loss from the washing step. In order to satisfy the antibacterial condition, the Ag^+ concentration remaining on the surface after washing should be higher than the antibacterial limit. See Fig. 10.20.

In order to calculate upper and lower limits of the amount of diluting water, m_{wD}, to add to a given starting sol at concentration, $\omega_{Ag}{}^{(0)}$, that satisfies both the antibacterial and non-toxic conditions, the following equation was established:

$$m_0\left\{\omega_{Ag^+}^{(0)}\left[\frac{1/\copyright_{Ag^+}^{(0)}-1}{1/\copyright_{Ag^+}^{(3)}-1}\left(\frac{1}{\omega_{Ag^+}^{AntiB}}-1\right)+1\right]-1\right\}>m_{wD}>m_0\left(\frac{\omega_{Ag^+}^{(0)}}{\omega_{Ag^+}^{Tox}}-1\right) \quad (10.1)$$

The ranges of dilution needed to process the samples in a safe but effective "zone" were calculated and are reported in Fig. 10.21. In Fig. 10.21, $\copyright_{Ag^+}^{(0)}$ and $\copyright_{Ag^+}^{(3)}$ are the mass fraction of silver ions with respect to the total amount of silver in the starting sol and in the sol remaining on the surface after the spray coating application and washing, respectively.

Thus, it could be clearly seen that in comparison with the pristine commercial sample Ag1, sample Ag31, derived from Ag1 after an ultra-filtration treatment, showed a higher range of dilution ratio and therefore a higher chance of falling within a "safe" zone, despite the lower concentration of free toxicant Ag^+ ions that ordinarily would have been expected to decrease its antibacterial performance. Furthermore, AgL, obtained at lab scale under more controlled conditions, improved the quality of the commercial sample, despite its higher toxicity. Sample Ag34, where both remediation strategies were applied (silica coating + ultra-filtration), appeared to be the most promising.

In order to find a general descriptor for easily establishing whether a starting sol could be made non-toxic while remaining antibacterial and, more generally, to assess the applicability of soluble nanomaterials whose biological reactivity is driven by the availability of ionic forms, (10.1) was re-arranged in the following way:

$$\frac{1/\copyright_{Ag^+}^{(0)}-1}{1/\copyright_{Ag^+}^{(3)}-1}\left(\frac{1}{\omega_{Ag^+}^{AntiB}}-1\right)+1>\frac{m_{wD}/m_0+1}{\omega_{Ag^+}^{(0)}}>\frac{1}{\omega_{Ag^+}^{Tox}} \quad (10.2)$$

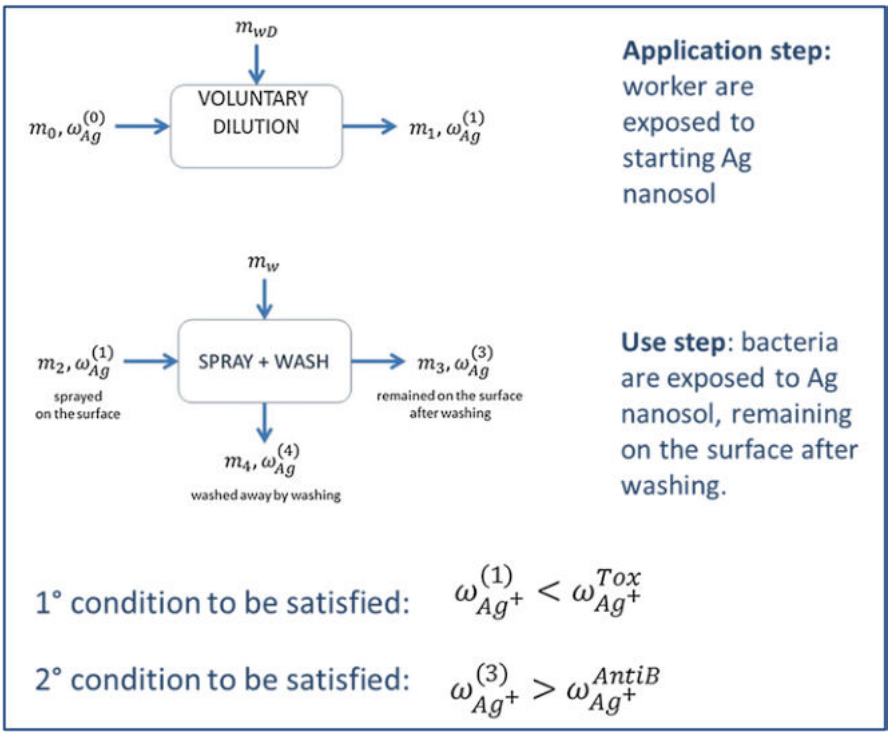


Fig. 10.20 Ag nanosol mass fraction (ω) useful to match the safe range

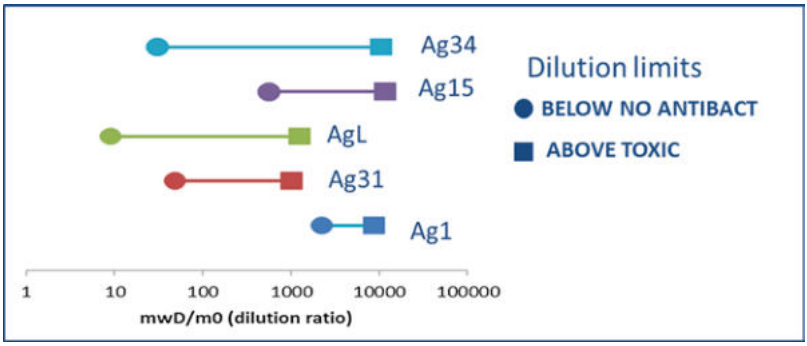


Fig. 10.21 Dilution limits for a safe and effective application of Ag nanosols

Furthermore, a dimensionless parameter, named Quality Index (QI), defined as the ratio between the upper and lower limits established by (10.2) was introduced:

$$\mathrm{QI} = \omega_{\mathrm{Ag}^+}^{\mathrm{Tox}} \cdot \left[\frac{1/\copyright_{\mathrm{Ag}^+}^{(0)} - 1}{1/\copyright_{\mathrm{Ag}^+}^{(3)} - 1} \left(\frac{1}{\omega_{\mathrm{Ag}^+}^{\mathrm{AntiB}}} - 1 \right) + 1 \right] \tag{10.3}$$

Thus, it was possible to find a general criterion to establish if a starting sol could be made non-toxic while remaining antibacterial. If QI is higher than 1 ($\mathrm{QI} \geq 1$), a safe but effective sol can be obtained, while this is not possible when $\mathrm{QI} < 1$. When $\mathrm{QI} = 1$, the range collapses to a point. The larger QI, the larger is the amplitude of the range and, therefore, the easier it is to satisfy both conditions. The quality of the starting sol is considered better when this parameter assumes high values, and for this reason, the parameter was named Quality Index. The more interesting aspect is that the QI depends only on four parameters, all experimentally measurable and sample-dependent, except for $\copyright_{\mathrm{Ag}^+}^{(3)}$ that is also process-dependent:

- Toxicity limit ($\omega_{\mathrm{Ag}^+}^{\mathrm{Tox}}$)
- Antibacterial limit ($\omega_{\mathrm{Ag}^+}^{\mathrm{AntiB}}$)
- Mass fraction of silver ions with respect to the total amount of silver in the starting sol ($\copyright_{\mathrm{Ag}^+}^{(0)}$)
- Mass fraction of silver ions with respect to the total amount of silver in the sol remained on the surface after washing ($\copyright_{\mathrm{Ag}^+}^{(3)}$).

However, the QI does not depend on the starting concentration of silver ($\omega_{\mathrm{Ag}}{}^{(0)}$). This means that it is not important what the concentration of total silver is in the starting sol, but only on the distribution of silver between ions and nanoparticles.

A general rationale to classify silver colloidal samples and identify conditions for safe use, preserving the expected antibacterial activity, was presented. This led to the definition of a Quality Index, representative of the capacity of the sample to be applied and exploited in a safe concentration range. Thus, it was possible for the first time to develop a general approach for the safe design and management of partially soluble nanomaterials for antibacterial applications.

10.4.1.4 CuO (SUN)

CuO commercial nanopowder (PlasmaChem GmbH) is used as active component in the formulation of antimicrobial (preserving) wood coatings. In this case study, its colloidal properties as a function of surface chemistry were assessed in order to provide necessary information for the control of biological reactivity in a Safety by molecular Design approach (SbyD). The following trends were observed: after dispersing CuO in a buffer borate solution at different pH levels, the dissolution of Cu^{2+} ions were detected. The Cu^{2+}/Cu weight ratio was determined by ultrafiltering (10 kDa Millipore filters) the CuO dispersions and analyzing the filtered solutions

by ICP-OES. This gave rise to negatively charged Sodium Citrate and Ascorbate (CIT and ASC), positively charged poliethyilenimmine (PEI), and neutral polyvinylpyrrolidone (PVP).

Four surface capping agents that differed in their charge were investigated. They were added and mixed with nanoparticles in water suspension in order to promote the creation of self-assembled layers of additives on particle surfaces.

Media Composition

Generally, colloidal properties as well as the dissolution behavior were assessed by preparing stock dispersion at 10 g/L in buffer phosphate and diluting at working stock concentration in toxicological tests water or (eco)toxicological relevant media, depending on the concentration used.

Milling Process

Ultrasonic (US) mixing and ball milling (BM) techniques were used to disperse CuO nanoparticles within stock suspensions. Fifteen minutes of US mixing has been compared with 95 h of ball milling in the presence of 3 mm YTZ grinding media. The state of agglomeration was assessed and the effect of milling treatment on breaking agglomerates evaluated.

Every experiment has been followed by characterization of the gained colloidal stability, expressed by zeta potential determination, mean particle size, and fraction of copper dissolved.

The results revealed that copper oxides nanopowder without any stabilizing agent produce suspensions that are only slightly stable in the pH region close to neutrality. At basic pH, these exhibit strong aggregation and subsequent precipitation, leading to poor transport fate mechanisms and adding pollution to soils and sludge instead of superficial waters. On the other hand, acid solutions induce copper dissolution with increasing Cu^{2+} amounts present in the samples. The surface coating experiments revealed that ionic agents (negative citrate/ascorbate and positive PEI) adsorb on the surface, resulting in better dispersions with a significant decrease in the average hydrodynamic diameter in comparison to the pristine sample and PVP-coated sample, the last result being very evident if the electrosteric stabilization of capping agents is coupled with that of ball milling treatment.

An example of the kind of data that can contribute to filling the gap between the synthetic and the biological identities of engineered nanomaterials is presented in Table 10.3 in which Zeta potential data of pristine and modified samples prepared in buffer solution and solubilized in different media are reported. It was found that the pristine sample dispersed in Milli-Q showed a negative zeta potential, despite the expected positive value of copper oxide and metal oxides generally when dispersed in water. The latter observation is supported by the presence of phosphate ions

Table 10.3 Zeta potential data of CuO samples dispersed in different media (MilliQ water, DMEM, and MEM)

	Zeta potential$_{ELS}$ (mV); pH					
Sample	MilliQ	pH	DMEM*	pH	MEM*	pH
CuO_Pristine	−9.1 ± 0.4	6.47	−8.2 ± 0.4	7.97	−10.1 ± 0.5	8.20
CuO_CIT	−18.0 ± 0.3	6.47	−9.7 ± 0.6	7.90	−10.5 ± 0.2	8.20
CuO_PVP	−8.1 ± 2.3	6.52	−9.4 ± 0.8	7.93	−10.1 ± 0.4	8.19
CuO_PEI	+28.3 ± 0.7	6.50	−10.1 ± 0.7	7.92	−10.5 ± 0.9	8.20
CuO_ASC_SYN	−17.4 ± 0.3	6.38	−9.2 ± 0.2	7.93	−9.5 ± 0.2	8.19

* DMEM pH = 7.86, MEM pH = 7.30

(PO_4^{3-}), which are specifically adsorbed onto CuO NPs surface, transferring the negative charge. The modified samples dispersed in Milli-Q water showed values coherent with the charge given by the capping agent, confirming the preferred interaction of the last over phosphate ions. The addition of a neutral PVP coating did not modify the zeta potential of the pristine sample as expected. When the samples were dispersed in cell culture media DMEM and MEM, a negative zeta potential around −10 mV was detected (Table 10.3). Such behavior occurred due to the presence of protein in the media. In fact, weakly negative charged proteins cover the CuO NPs surface, leading to a negative zeta potential ("protein corona" phenomenon) in all samples. This was further confirmed by the zeta potential of DMEM and MEM media (without NPs dispersed) that resulted in −10.6 and −10.9, respectively.

10.5 Conclusion

Addressing safety issues at the early design stage of product development presents new challenges for the development and promotion of nanomaterials that satisfy performance and safety requirements.

The FP7 collaborative project Sanowork and SUN developed "design option"-based risk remediation strategies and integrate them within industrial processing lines. The design solutions were applied to commercial nanomaterials to decrease exposure and/or hazard potential while preserving functional properties. A cost-benefit evaluation of the proposed strategies was performed, focusing on the photocatalytic and antibacterial properties of the samples used in the final products.

The first very interesting result was found by testing the photocatalytic properties of TiO_2 coatings as estimated from the degradation of the pollutant NO_x. It was found that silica remediation not only improved the photocatalytic efficiency of TiO_2, but caused a significant degradation of NO_x at low concentrations where ROS production was also lower.

The second very interesting result was found by comparing toxicity and antibacterial activity of pristine and modified Ag sol samples. The toxicity and antibacterial

properties were, as expected, Ag^+-dependent and suggested a deeper study of the mechanisms involved and the application conditions in order to establish a general criterium for a safe application. Thus, a factor to assess the safety/balance quality of Ag nano sols was developed that determined toxicity and antibacterial limits based on an estimation of Ag^+ ions still available within the application after the washing treatment. It was therefore possible to introduce a general rationale to classify partially soluble nanomaterials that can be exploited in antibacterial applications, opening a new perspective towards the promotion of a safer by-design management of nanomaterials' exposure risk. A systematic investigation on relationships that link pristine properties or properties modified "ad hoc" in a safety by design strategy with risk determinant properties can fill the knowledge gap between synthesis and biological identities, allow a better comparison with biological outputs, improved existing paradigms of toxicity, and provide new solutions for the design of safer nanomaterials.

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Chapter 11
A Bayesian Regression Methodology for Correlating Noisy Hazard and Structural Alert Parameters of Nanomaterials

Eamonn M. McAlea, Finbarr Murphy, and Martin Mullins

Abstract Exposure to ENMs may have associated health risks, but accurate measurement of these risks is difficult due to overwhelming methodological limitations and epistemic uncertainties. This is especially the case for ENM physiochemical and toxicity measurements. A common example of controlling such risks in workplace environments where these materials are produced and used is control banding. It offers a useful framework to categorize health risk but is presently limited by existing quantitative data that is susceptible to ambiguity. With an aim to addressing these issues, this chapter develops a Bayesian regression or QSAR (**Q**uantitative **S**tructure **A**ctivity **R**elationship) model that relates hazard levels (dependent) to physical and chemical attributes (independent) but crucially takes full account of uncertainty in both the dependent and independent data sets. The developed model is applied to recover the marginal probability density distribution of a varied set of physical attribute measurements of cerium oxide nanoparticles that were supplied from a common batch. Each of the measurements in the set was carried out by one of several disparate institutions. It is in the author's opinion that this model is successful because in principle it is able to exploit and objectively incorporate seemingly conflicting data points to produce meaningful regression fits. This is something that is not possible using conventional regression techniques that typically rely on subjective judgments to resolve such conflicts prior to analysis. The danger of the conventional approach is that potentially useful information, usually interpreted as 'statistical outliers', may be disregarded as a result of experimenter bias.

E.M. McAlea (✉) • F. Murphy • M. Mullins
Department of Accounting and Finance, Kemmy Business School,
University of Limerick, Limerick, Ireland
e-mail: Eamonn.McAlea@ul.ie

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11.1 Introduction

A central issue concerning the emerging discipline of Nanotoxicology and its adjunct discipline of ENM characterization is the problem of experimental replication (Kato et al., 2009). Practitioners in the field have yet to devise standardized procedures for assessing the potential hazards of ENMs (Fujita, Onishi, & Xu, 2009). This has led to many inconsistent claims in the literature regarding the toxicity of certain classes of ENMs (Sophie, Carmen, Coralie, Urs, & Morteza, 2012). It may be the case there is a pragmatic limit to the accuracy, and hence exact repeatability, of toxicity and attribute characterization procedures. If so, the results of such procedures will be limited to probabilistic interpretations, analogous to quantum theory where the Heisenberg uncertainty principle placed a fundamental limit on the confidence level of observations (Busch, Heinonen, & Lahti, 2007).

With this in mind, the focus of this chapter is to describe a framework that incorporates marginal probability representations of ENM's physical properties and its corresponding hazard profile—against a range of biomarker and cell lines into a Bayesian-based regression model. The model relates hazard levels to physical and chemical attributes through the application of universal conditional probabilities (in the sense of being independent of any particular material) that are obtained algorithmically from the marginal distributions for an arbitrary number of ENMs. Such a tool can then provide estimates for hazard levels for a known physicochemical characterization and vice versa. Essentially, what the author is proposing is a least squares regression methodology (Geladi & Kowalski, 1986) developed within a Bayesian context that takes full account of the uncertainty in both the dependent and independent data sets.

Producers of ENMs do not have standardized procedures for classifying them in terms of their physical attributes (Geladi & Kowalski, 1986; Leach, 2009) (physicochemical characterization). Material scientists quite often come up with different physical attribute values for the same sample of materials (size, shape, core chemistry, surface chemistry, surface charge, etc.). The requirement to reproduce observations is fundamental to any discipline that needs to stand up to scientific scrutiny, and by itself forms almost the very definition of science (Jasny, Chin, Chong, & Vignieri, 2011). As a corollary, a hypothesis put forward to explain some phenomenon must be falsifiable (Popper, 1935). Specifically, some reproducible experiment must exist that could conceivably refute it; the present difficulties associated with replicating experiments pertaining to ENMs suggest that it may be difficult to negate, and therefore rule out, hypotheses that have been proposed to account for the mechanisms that underlie ENM-specific toxicology. The Bayesian framework described in this chapter should help address such issues and assign more value to potentially ambiguous ENM characterization and toxicity data aggregated from diverse sources.

It is important to note that a lack of consensus among health risk and characterization experts and the consequent dearth of related environmental health and safety (EHS) risk models present challenges to regulators, insurers and public policy

makers, etc. If left unresolved, such issues ultimately pose a wider threat to the nanotechnology manufacturing and research sectors that require unimpeded access to ENMs, access that could become inhibited by a lack of affordable insurance premiums and favourable regulatory/political environments (Mullins, Murphy, Baublyte, McAlea, & Tofail, 2013).

The next section briefly outlines some current approaches for estimating human exposure risk to ENMs. They all have their shortcomings and merits, but in each case their ultimate utility will depend on inputs provided by an understanding of potential toxicity mechanisms at the cellular level. This in turn will be supported by a representation of observational data obtained by in vitro methods. The author submits that the Bayesian formulation described in this chapter offers such a representation. Section 11.3 provides a brief overview of the theoretical underpinnings of Bayesian statistics in conjunction with *the principle of maximum entropy* that is commonly utilized in the application of Bayesian techniques. Having established the necessary background and theoretical prerequisites in Sect. 11.3, Sect. 11.4 develops the chapter's main result; a Bayesian based regression framework. As a demonstration, the framework is applied to the generalization of the simple least squares fit regression methodology in order to accommodate potentially noisy input data, initially assumed to be normally distributed. Insofar as preliminary observations indicate, this implementation appears to exhibit a useful feature that was not anticipated at the outset of its development; better quality data, as defined by data points with smaller variances, is assigned more significance than data points with larger variances. The maximum entropy principle is applied in Sect. 11.5 to the recovery of marginal probability density distributions of ENM physical attribute and toxicity data for which the assumption of normality in Sect. 11.4 is relaxed. This allows for a broader generalization of the least squares fit methodology in which potentially noisy input data, described according to arbitrary marginal probability distributions, may be incorporated into the framework. To address the dependence of multiple biological endpoints on multiple physical attributes values, Sect. 11.6 finishes with a brief overview of the multiparameter generalization of the one-dimensional problems described in Sect. 11.4.

11.2 Current Approaches to Calculating Exposure Risk In Vitro—In Vivo Extrapolation

This approach attempts to predict the effects of a known dose of a particular pathogen at the organism level by extrapolating the effects of a much smaller dose at the in vitro level. However, there are several factors this technique fails to take account of; in particular, cellular dynamics within a living organism differ from those when the cells are held in vitro. An example of this is the phenomenon of cytokine cascades (Tisoncik et al., 2012) that occur only within in vivo environments and are the

source of inflammatory responses.[1] Such an effect could never be inferred at the in vivo level from simply observing responses in vitro assays since it does not occur at this level. In short, much of cellular behaviour in vivo is qualitatively quite different from in vitro behaviour (Hasjim, Lavau, Gidley, & Gilbert, 2010; Lin, 1998). At best, extrapolation can only work on the assumption that in vivo cell behaviour differs only quantitatively from in vitro behaviour; to quote from an EPA study (Richard et al., 2009).

> *The most widely held criticism of this in vitro-to-in vivo prediction approach is that genes or cells are not organisms and that the emergent properties of tissues and organisms are key determinants of whether a particular chemical will be toxic.*

A second cause for concern is that many in vitro studies to date involve pristine nanomaterials interacting directly with the cell cultures. In reality, what typically occurs on exposure is the material will first interact with the host's blood serum protein that forms a corona around the NP before interacting with cells (Monopoli, Åberg, Salvati, & Dawson, 2012). The effect of the corona is to essentially 'tame' the NPs by reducing their surface energies and thus their potential to illicit intracellular damage. In fact, it has been demonstrated that the intracellular behaviours of most NPs, as observed in vitro, that have initially received such coronas are more predictable insofar as they are internalized by cells via the normal endocytosis pathways by which unwanted materials are eventually removed from the organism (Verma & Stellacci, 2010). Lastly, investigators need to consider the typical dose levels that would result from realistic exposure scenarios; in some cases for any observable behaviour to be elicited in vitro, unrealistically large doses of ENM's must be administered and likely far in excess of what would actually be the case in a normal exposure scenario (Kong, Seog, Graham, & Lee, 2011).

11.2.1 In Silica Methods

In the context of toxicology, in silico methods refer to computational simulations of interactions between ENM pathogens and their biological hosts. Presently, exact simulations are impossible due to issues of computational intractability that emerge from the reductionist[2] approach to the problem. For example, simulations of approximate models of entire viruses (Freddolino, Arkhipov, Larson, McPherson, & Schulten, 2006) have already been achieved, but opinions are mixed as to their

[1] Messenger cytokines are invoked as part of the immune response to recruit antibodies from surrounding tissues to the pathogen's location for it to be removed or destroyed. This in turn promotes the production of more cytokines that repeat and reinforce the process in a positive feedback fashion. This dynamic only occurs at the organism level and could never be predicted on the basis of in vitro observations alone.

[2] Reductionism attempts to understand the behaviour and properties of a system in terms of its irreducible subsystems considered in isolation from one another. The individual subsystem descriptions are then *reassembled* to offer a complete understanding of the parent system.

feasibility to replace experimental methods, since the omission of the tiniest detail in a model can have far reaching implications in terms of its predictive accuracy (Andrés, Natalio, Juli, & Amparo, 2009; Joyner & Pedersen, 2011). The dynamics of biological systems, like the majority of natural phenomena, are highly non-linear. The predictive power of models describing non-linear systems is extremely sensitive to small differences between themselves and the reality they are attempting to describe. This is known as the '*butterfly effect*'[3] and it places significant limitations on the accuracy of such simulations (Hilborn, 2004). Invariably, the predictive accuracy of these simulations deteriorates relatively quickly as they advance. For example, weather forecasting and the analysis of stock market movements, being highly non-linear in nature, are particularly prone to this problem; in spite of the availability of the most optimized and advanced computer architectures, weather forecasts are typically only accurate for several days in advance and rarely useful beyond 2 weeks (Teixeira, Reynolds, & Judd, 2007). In light of these considerations, in silico applications to the effects of ENMs may at best only be effective at predicting acute near-term responses to ENMs at the microscopic and cellular levels, predictions that would later be confirmed by in vitro assessments (Werner, 2005).

The limitations imposed by computational intractability and the butterfly effect, while keeping in mind the analogy of weather forecasting, suggest it is doubtful it would be effective at identifying long-term or chronic responses at the macroscopic in vivo level. However, it is precisely such longer-term risks that nanotechnology's major stakeholders, particularly insurers and regulators, are most concerned with (Becker, Herzberg, Schulte, & Kolossa-Gehring, 2011).

For all practical purposes, what is likely to develop in the immediate to near future, will be a paradigm in which experimental and computational methods are used in conjunction with one another. The results from each methodology will be used to check and complement the other (Mukherjee & Byrne, 2013), similar to what currently happens in various fields of engineering.

11.2.2 Pharmacokinetics and Its Application to Long-Term Risk Estimation

Pharmacokinetic approaches for estimating the distributions of biopersistent ENMs are less demanding than attempting to model interactions between ENM pathogens and their host cells at the molecular level throughout an entire organism. With respect to the study of ENMs, they encompass the relatively more tractable problem of modelling at a macroscopic level movements of bulk quantities of non-soluble ENMs throughout the body in accordance with physiological determinants, such as blood flow rates and arterial diameters, etc. (Li, Al-Jamal, Kostarelos, & Reineke,

[3] Hypothetical scenario in which the flapping of a butterfly's wings results in the formation of a hurricane at another point on the earth's surface through rapid amplification of the initially small disturbance by non-linear atmospheric dynamics.

2010; Riviere, 2009). This approach is experiencing increasing levels of sophistication with advances in computer hardware and modelling techniques. Conceptually, long-term exposure risks could be estimated by comparing the expected bulk accumulations of engineered ENMs at different bodily regions along with their in vitro data (for the corresponding cell lines that typify each region) with the expected accumulations and in vitro data for anthropogenic and natural ENMs. Combining this information with the available epidemiological data that correlates with long-term exposure to anthropogenic and natural sources would then provide a baseline from which to estimate the long-term risks from exposure to the engineered sources (Anderson, Ponce-de-Leon, Bland, Bower, & Strachan, 1996; Brook et al., 2004; Cass et al., 2000; Moulton & Yang, 2012; Schwartz, 2000; Schwartz & Neas, 2000; Stone, Johnston, & Clift, 2007; Tiitanen, Timonen, Ruskanen, Mirme, & Pekkanen, 1999).

11.3 Bayesian Statistics

Bayesian statistics begins with the proposition that truly objective probabilities do not exist (Shafer, 1976). Within the Bayesian paradigm, all probabilities reflect an unbiased degree of belief regarding the state of the world, with such beliefs exclusively informed by all currently available information. There are several interpretations of probability, with the most common being that of an absolute and fixed probability that is based on the frequency of past events. By contrast, Bayesian probabilities can be continually modified as new information becomes available, reflecting the way that new information can change perceptions. They do however possess a degree of objectivity, but not in the usual sense; by definition they encode the most unbiased view of the world exclusively on the basis of universally available information. Since it is a probability that reflects the most unbiased belief, it is therefore unique and in this sense objective. In principle, all unbiased observers given the same current information should be able to independently quantify it. Should the contextual background information remain static for long periods, then Bayesian probabilities will themselves remain static and will appear to resemble those that are based on the frequency of past events. In this sense, Bayesian statistics presents a more a general notion of probability that invokes the common frequency-based interpretation only when the known state of the world does not change significantly over an extended period.

11.3.1 Principle of Maximum Entropy

The principle of maximum entropy forms an important adjunct to Bayesian statistics, particularly in its application to estimating prior distributions (Guiasu & Shenitzer, 1985). The natural world, as formed by the collective actions, influences

and interplay of the geosphere, biosphere and Noosphere,[4] is replete with distributions of an infinite variety. From the distributions of molecular speeds in gases[5] to those of species varieties across the planet, to the distribution of wealth and information in the sphere of human activity, one principle always applies: that against the constraints and properties of any system that generates distributions, the most probable one will invariably emerge (Swenson, 1989). The apparent obviousness of this statement masks its potency; it is almost universal applicability across different schools of thought and the depths of its implications in relation to a wide spectrum of phenomena. The probability of a distribution's emergence is known as its entropy and the principle that the most likely one will manifest is known as the '*principle of maximum entropy*'. Of relevance to this chapter will be the need to uncover the entropy of certain marginal probability distributions that are consistent with experimental hazard and material characterization data (see Sect. 11.5). These distributions with the greatest entropy, that deem them most likely to occur in reality, are then selected as inputs to the model.[6]

11.4 Probabilistic Relationships Between Physicochemical Properties and In Vitro Observed Hazard Levels

Described are the results of a hypothetical in vitro experiment in which the effects of zeta potential[7] on ROS[8] levels for one particular cell line are measured for a set of n ENMs. A regression algorithm should extract from the data a parameterized

[4] Noosphere denotes the sphere of human intellect and its effects, through conscious intention, on the physical environment.

[5] The direct application of this principle to statistical mechanics leads to Maxwell–Boltzmann statistics for molecular energy distributions in high-temperature gases. In low-temperature environments, it yields the Fermi–Dirac statistics for fermions and Bose–Einstein statistics for bosons.

[6] Numerically, the entropy $H[P(x_1, x_2, \ldots, x_n)]$ of a general discrete multivariate distribution, $P(x_1, x_2 \ldots x_n)$, is given by: $H[P] = \sum_X P(x_1, x_2 \ldots x_n) \log\left(P(x_1, x_2 \ldots x_n)\right)$ in which the summation is taken over all allowable assignments of the vector $X = (x_1, x_2 \ldots x_n)$. Informally, if P is a one of an infinite number of candidate PDFs capable of describing the distribution of a given set of observations, then $H[P]$ is the log of the probability that P is the actual distribution underlying the observation set. Formally, on the basis of existing constraint data, for example in the form of prior moment information or marginal distributions, the most unbiased distribution that could be inferred would be the one with greatest entropy. By contrast, a biased choice of an otherwise consistent distribution would be one informed by considerations beyond the domain of available information (i.e. irrational) and with the entropy of such a choice being sub-maximal.

[7] A ENM's zeta potential is one of several common physicochemical attributes that are used to characterize ENMs. Among others are size, core chemistry, crystalline structure and aspect ratio.

[8] The measurement of biomarkers provides a means to indirectly observe cellular activity in vitro. Unusual or elevated levels normally indicate abnormal cellular behaviour and can be used to infer the potentially toxic effects of a foreign material such as a nanoparticle. There are many varieties

Table 11.1 Results of a hypothetical procedure measuring ROS levels against ZP measurements for a range of n ENMs labelled I_1 to I_n

ROS	Zeta potential	NM id
$\bar{r}_1 \pm \Delta r_1$	$\bar{z}_1 \pm \Delta z_1$	I_1
$\bar{r}_2 \pm \Delta r_2$	$\bar{z}_2 \pm \Delta z_2$	I_2
…	…	…
…	…	…
…	…	…
…	…	…
$\bar{r}_n \pm \Delta r_n$	$\bar{z}_n \pm \Delta z_n$	I_n

model in the form $r(z)$ in which the zeta potential, z, is used to determine the ROS level, $r(z)$. As a first approximation, it can be assumed that $r(z)$ depends on z linearly such that $r(z) = a\,z + b$ in which a and b are best fit parameters that are inferred from the data in Table 11.1. In Table 11.1, r_k represents a ROS measurement for the ENM labelled as I_k, for $k = 1,2\ldots n$, while z_k indicates the corresponding zeta potential for the same ENM. Due to experimental error, repeated measurements for each ENM for both ROS and zeta potential levels will generally yield a range of values clustered around some average values. Table 11.1 summarizes the potential spreads in ROS and zeta potential measurements for each ENM as mean and variance values denoted by $\bar{r}_k$ and $\bar{z}_k$ and by Δr_k and Δz_k respectively.

Typically, a regression analysis, such as one based on the method of least squares, applied to the data in Table 11.1 would utilize only the mean values, $\bar{r}_k$ and $\bar{z}_k$, and ignore the variance (noise) components, Δr_k and Δz_k. Such an assumption is plausible when the expected noise levels are small compared to the average values but may be questionable for larger values. Large uncertainty levels in relation to average values is expected to be a common feature of physical attribute and hazard data for ENMs, particularly for polydisperse[9] materials (Tomaszewska et al., 2013). Arguably therefore, the direct application of conventional least squares regression methodologies is unsuitable for analysing such data sets. To mitigate potential ambiguities and help render the data more informative, the author presents within a Bayesian paradigm a generalized formulation of the common least squares regression algorithm.

with probably the most cited in the literature being reactive oxygen species (ROS), cytotoxicity, cell viability, cytokine numbers and genotoxic effects. Reactive oxygen species (free radicals) result from chemical reactions between cellular components and a foreign substance. They result from normal cellular functions such as metabolism and can have elevated levels when a cell attempts to metabolize a substance that cannot be metabolized such as inorganic non-soluble foreign bodies, for example metallic nanomaterials. Cytokines are messenger molecules that support the immune system. The presence of a pathogen invokes their dispatch by the immune system to signal neighbouring white blood cells in surrounding tissues to come to the infected cell's aid to remove or destroy the offending pathogen (white blood cells are the immune system's vacuum cleaners). Genotoxicity effects measure changes in a cell's DNA structure due to the presence of a pathogen.

[9] A polydisperse ENM is characterized as one having by a diverse range of values over a particular attribute or set of attributes.

Allow $\rho(r_k, z_k \mid I_k)dr_k dz_k$ to denote the joint probability, of measuring both a ROS level in the range $(r_k, r_k + dr_k)$ and a zeta potential in the range $(z_k, z_k + dz_k)$ for the ENM labelled I_k. For ease of notation, the subscript k will be dropped when referring to z_k and r_k in the following analysis: using the Bayes theorem, this joint distribution is decomposed into posterior and prior marginal distributions given respectively by $\rho(r \mid z, I_k)$ and $\rho_1(z \mid I_k)$, or alternatively by $\rho(z \mid r, I_k)$ and $\rho_2(r \mid I_k)$, such that

$$\rho(r, z \mid I_k) = \rho(r \mid z, I_k)\rho_1(z \mid I_k) = \rho(z \mid r, I_k)\rho_2(r \mid I_k) \tag{11.1}$$

The posterior, $\rho(r \mid z, I_k)$, has the following interpretation: $\rho(r \mid z, I_k)dr$ is the probability of measuring a ROS level in the range $(r, r + dr)$ given that material I_k has a known zeta potential of z. In this example, it is assumed that r is influenced exclusively by z and is independent of other aspects of the ENM. It is important to note that this will typically not be the case and a brief overview of an analogous and more general approach involving multiple parameters is presented in Sect. 11.6. The assumption that r is dependent on z only is reflected in $\rho(r \mid z, I_k)$ by dropping its dependence on I_k so that $\rho(r \mid z, I_k)$ is thus given simply by the universal quantity, $\rho(r \mid z)$, that is common to all ENMs (it is important to note that the Bayesian formulation of the least squares regression method being developed here hinges on the assumption that $\rho(r \mid z)$ is of a universal character).

The marginal quantities $\rho_1(r \mid I_k)$, $\rho_2(z \mid I_k)$ and $\rho(r \mid z)$ are related by first integrating over the joint distribution and then employing the Bayesian relation, (11.1), such that

$$\rho_2(r \mid I_k) = \int_0^\infty \rho(r, z \mid I_k)dz = \int_0^\infty \rho(r \mid z, I_k)\rho_1(z \mid I_k)dz = \int_0^\infty \rho(r \mid z)\rho_1(z \mid I_k)dz \tag{11.2}$$

$\rho(r, z \mid I_k)$ provides a complete description of the relationship between ROS levels and zeta potentials for material I_k. Generally, it can be said that if $\text{Max}\,\rho(r, z \mid I_k) = \rho(r', z' \mid I_k)$ then an ROS level of r' and a zeta potential z' would most likely be measured for the material identified as I_k. Alternatively, it may be useful to speak in terms of the expected, or mean, ROS measurements as a function of a known zeta potential. If $\bar{r}(z)$ represents the expected ROS level for a known zeta potential of z then $\bar{r}(z) = \int_0^\infty \rho(r \mid z)rdr$. Unfortunately for these calculations, the majority of experiments do not furnish the joint distributions as they are either exclusively based on characterization or toxicity profiling. At best, they only provide the marginal quantities, $\rho_2(r \mid I_k)$ and $\rho_1(z \mid I_k)$, that are reflected by the variance components Δr_k and Δz_k as shown in Table 11.1.

How to build $\rho(r, z \mid I_k)$ and $\rho(r \mid z)$ *from the marginal quantities* $\rho_1(r \mid I_k)$ *and* $\rho_2(z \mid I_k)$*?*

A first approximation is to assume that $\rho(r \mid z)$ *and* $\rho_1(z \mid I_k)$ are normally distributed about their average values so that $\rho_1(z \mid I_k) \approx N(\bar{z}_k, z_k^2)$. From the hypothetical data in Table 11.1, we construct n such normal distributions for the zeta

Table 11.2 Representation of the error and mean values in Table 11.1 as PDFs that describe the uncertainty in the ROS and ZP measurements

$\rho_2(z \mid I_1)$	$\rho_1(z \mid I_1) \approx N(\overline{z}_1, \Delta z_1^2)$	I_1
$\rho_2(z \mid I_2)$	$\rho_1(z \mid I_2) \approx N(\overline{z}_2, \Delta z_2^2)$	I_2
…	…	…
…	…	…
…	…	…
…	…	…
$\rho_2(z \mid I_n)$	$\rho_1(z \mid I_n) \approx N(\overline{z}_n, " z_n^2)$	I_n

The uncertainties in the ZP measurements are assumed to be normally distributed. Note: the error values are identified with the variances of the respective distributions

Table 11.3 The PDFs in Table 11.2 must all satisfy (11.2)

$\rho_2(r \mid I_1) = \int_0^\infty \rho(r \mid z)\rho_1(z \mid I_1)dz$
$\rho_2(r \mid I_2) = \int_0^\infty \rho(r \mid z)\rho_1(z \mid I_2)dz$
…
…
…
…
$\rho_2(r \mid I_n) = \int_0^\infty \rho(r \mid z)\rho_1(z \mid I_n)dz$

This provides n conditions that $\rho(r \mid z)$ must simultaneously satisfy

potential measurements of each material I_k. These distributions, as shown in Table 11.2, are then inserted into (11.2) to yield n conditions that $\rho(r \mid z)$ must simultaneously satisfy, as shown in Table 11.3.

Since $\rho(r \mid z)$ is also assumed to be a normal distribution in which the mean and variance, given respectively by $\overline{r}(z)$ and $\sigma(z)$, are parameterized by z, such that

$$\rho(r \mid z) = N\left(\overline{r}(z), \sigma(z)^2\right) \tag{11.3}$$

means that the joint distribution for each material is given by:

$$\begin{aligned}\rho(r,z\,|\,I_k)&=\rho(r\,|\,z)\rho_2(z\,|\,I_k)\approx N\left(\bar{r}(z),\sigma(z)^2\right)N\left(\bar{z}_k,\Delta z_k^2\right)\\&=\frac{1}{2\pi\sigma(z)\Delta z_k}\mathrm{e}^{-\frac{(\bar{r}(z)-r)^2}{2\sigma(z)^2}}\mathrm{e}^{-\frac{(\bar{z}_k-z)^2}{2\Delta z_k^2}}\\&=\frac{1}{2\pi\sigma(z)\Delta z_k}\mathrm{e}^{-\left(\frac{(\bar{z}_k-z)^2}{2\Delta z_k^2}+\frac{(\bar{r}(z)-r)^2}{2\sigma(z)^2}\right)}\end{aligned}\tag{11.4}$$

The expressions in Table 11.3 imply that by definition the moments of $\rho_2(r\,|\,I_k)$ should equal the moments of $\int_0^\infty \rho(r\,|\,z)\rho_1(z\,|\,I_k)dz$ for each material. Specifically, conventional least squares regression would only attempt to equate the mean values of the dependent data to the mean values of the independent data points. The more general approach being proposed here, as expressed by (11.5), will attempt to equate all moment values that are available, which in this case happen to be the mean and variance values of the two data sets in Table 11.1. The optimal choices of $\bar{r}(z)$ and $\sigma(z)$ are therefore those that minimize the sum of the squared terms as given in (11.5):

$$\begin{aligned}\text{Sum Probability Squares}&=\sum_{k=1}^{n}\left(\mathrm{var}\left(\rho_2(r\,|\,I_k)\right)-\mathrm{var}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)\right)^2\\&+\left(\mathrm{mean}\left(\rho_2(r\,|\,I_k)\right)-\mathrm{mean}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)\right)^2\\&=\sum_{k=1}^{n}\left(r_k-\mathrm{var}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)\right)^2\\&+\left(\bar{r}_k-\mathrm{mean}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)\right)^2\end{aligned}\tag{11.5}$$

In which

$$\mathrm{mean}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)=\int_{r=0}^{\infty}r\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)dr$$

$$\mathrm{var}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)=\sqrt{\mathrm{mean}\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)-\int_{r=0}^{\infty}r^2\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I_k)dz\right)dr}$$

It is further assumed that $\bar{r}(z)$ and $\sigma(z)$ are linear[10] in z such that for constants a, b, c and d

$$\bar{r}(z) = a + bz \tag{11.6a}$$

$$\sigma(z) = c + dz \tag{11.6b}$$

Inserting (11.1) and (11.2) into (11.5) and minimizing should yield the parameters a, b, c and d that best fit the data in a statistical sense.

Note that is easy to show that (11.5) reduces to a conventional least squares fit expression when all the variances in the above distributions tend to zero so that for each $k = 1$ to n[11]

$$\rho_1(z \mid I_k) \to \delta(\bar{z}_k - z)$$

$$\rho(r \mid z) \to \delta(\bar{r}(z) - r)$$

so that heuristically;

$$\begin{aligned} &\text{mean}\left(\int_{z=0}^{\infty} \rho(r \mid z)\rho_1(z \mid I_k)dz\right) = \int_{r=0}^{\infty} r\left(\int_{z=0}^{\infty} \rho(r \mid z)\rho_1(z \mid I_k)dz)\right)dr \\ &= \int_{r=0}^{\infty} r\left(\int_{z=0}^{\infty} \delta(\bar{r}(z) - r)\delta(\bar{z}_k - z)dz)\right)dr = \int_{r=0}^{\infty} r\delta(\bar{r}(\bar{z}_k) - r)dr = \bar{r}(\bar{z}_k) \end{aligned} \tag{11.7}$$

(See[12])

This implies that in the limit of negligible variances, (11.5) reduces to

$$\text{Sum Probability Squares} = \sum_{k=1}^{k=n} \left(\bar{r}_k - \bar{r}(\bar{z}_k)\right)^2 \text{ in which } \bar{r}(\bar{z}_k) = a + b\bar{z}_k \tag{11.8}$$

In accordance with conventional least squares regression methodology, a and b are then chosen to minimize the sum of the squared terms in (11.8) to provide a best fit to the data points $(\bar{r}_k, \bar{z}_k)$ for $k = 1, n$.

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[10] In general, this assumption is not necessary. It has been introduced for reasons of simplicity and ease of illustration. A linear combination of an arbitrary set of basis functions could equally have been used for nonlinear fits.

[11] A normal distribution tends to a delta function for vanishing variance. That is $N(\bar{x}, \sigma^2) \to \delta(\bar{x} - x)$ as $\sigma \to 0$.

[12] A delta function is defined as $\delta(x) = 0$ when $x \neq 0$ and $\delta(0) \approx \infty$ such that $\int_{-\infty}^{\infty} \delta(x)dx = 1$. It can be shown that this leads to a delta function having the following property: $\int_{z=0}^{\infty} f(z)\delta(x - z)dz = f(x)$ for an arbitrary f. Thus $\int_{z=0}^{\infty} \delta(\bar{r}(z) - r)\delta(\bar{z}_k - z)dz = \delta(\bar{r}(\bar{z}_k) - r)$ when $f(z) = \delta(\bar{r}(z) - r)$.

11.4.1 Example Case

The methodology is demonstrated by the following test case. For numerical expediency, the variance term, $\sigma(z) = c + dz$, was further constrained to be constant such that $\sigma(z) = c$. The least squares problem is then reduced to identifying just three constant a, b and σ such that (11.5) is minimized. Generally, σ provides a measure of confidence regarding the accuracy of the mean fit as prescribed by $\bar{r}(z) = a + bz$, the smaller σ, the more definite the fit.

From a number of trial computations using synthetic data, it has been observed that for small variances in the input data the fits are similar to those produced by the conventional least squares approach in which only the mean data points are considered. However for larger variances, the Bayesian best fit estimates differed significantly from their conventional counterparts. In particular, the algorithm appears to exhibit a useful artefact that was not anticipated at the design stage: It has been observed that more weight is attached to data points with relatively smaller variances. In this way, the algorithm will automatically learn to discriminate between poor and better quality data by assigning more significance to the latter (Fig. 11.1).

11.5 General Marginal Distributions and Maximum Entropy

The Bayesian version of least squares regression based on normal PDFs described in the previous section can be extended to accommodate all varieties of distributions. Marginal PDFs can be constructed without having to invoke the assumption of normality by identifying those unique distributions of maximum entropy that fit the raw experimental data. The usual practice is to summarize such data as a mean and variance as shown in Table 11.1. That is, only the first two moments of the data are quoted to provide a summary of its statistical character. However, in principle any number of moments can be calculated from individual data points and may be employed to identify the unique continuous marginal PDFs of greatest entropy whose moments match those calculated from the data sets. Additionally, the assumption that the posterior quantity, $\rho(r \mid z)$, also has maximum entropy allows for a broader generalization of (11.5) to include any number of moments (in this case the author assumes the first l moments are known for the two classes of marginal distributions, $\rho'(r \mid I_k)$ and $\rho(z \mid I_k)$):

$$\text{Sum Probability Squares} = \sum_{j=0}^{l}\sum_{k=1}^{n}\left(\frac{\text{moment}_j\left(\rho_2(r \mid I_k)\right) - \text{moment}_j}{\left(\int_{z=0}^{\infty}\rho(r \mid z)\rho_1(z \mid I_k)dz\right)}\right)^2 \tag{11.9}$$

in which

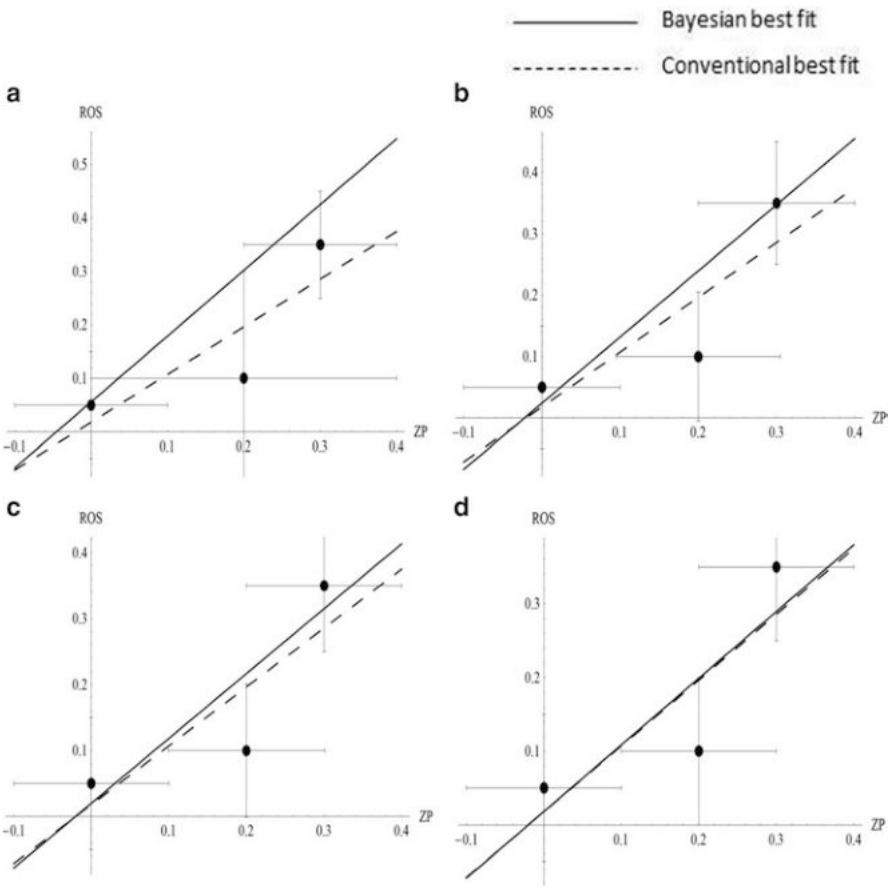

Fig. 11.1 (**d**) shows the neutral scenario in which all the data items share the same uncertainty. In this case, the Bayesian generalization coincides with the conventional least squares regression method that uses only the mean data values. In (**a**) the uncertainty in the second item is twice that of the other two. Here, the Bayesian generalization of least squares regression tends to ignore it in favour of fitting to the other points that are relatively less ambiguous. (**b**, **c**) show the rather slow convergence to (**d**) by tending $\Delta z_2 = \Delta r_2 \to 0.1$ in line with the other data items: $\Delta z_1 = \Delta r_1 = \Delta z_3 = \Delta r_3 = 0.1$. The mean values are $z_1 = 0, r_1 = 0.05, z_2 = 0.2, r_2 = 0.1, z_3 = 0.3, r_3 = 0.35$. **(a)** $\sigma = 0.031, \Delta z_2 = \Delta r_2 = 0.2$, **(b)** $\sigma = 0.031, \Delta z_2 = \Delta r_2 = 0.105$, **(c)** $\sigma = 0.035, \Delta z_2 = \Delta r_2 = 0.101$, **(d)** $\sigma = 0.051, \Delta z_2 = \; r_2 = 0.1$

$$\rho\left(r \mid z\right) \propto \mathrm{e}^{m_0(z)+rm_1(z)+r^2m_2(z)+\cdots+r^n m_l(z)} \tag{11.10}$$

It can be seen from (11.10), which has the general form of any PDF exhibiting maximum entropy, that a normal distribution is just the distribution of greatest entropy matching the first two moments, corresponding to the mean and variance, of a given data set. As in the example from Sect. 11.4, the functions $m_0(z), m_2(z) \ldots m_l(z)$, are assumed to

have a linear form given by $m_0(z) = a_0 z + b_0, m_1(z) = a_1 z + b_1 \ldots m_l(z) = a_l z + b_l$. The constants $a_0, b_0, a_1, b_1 \ldots a_l, b_l$ are then chosen such that they minimize the probabilistic least squares expression given by (11.9).

11.5.1 Example of a Prior PDF Construction

The author illustrates by way of a real-world example the general methodology for determining a prior PDF of maximum entropy describing the distribution of a given discrete data set. The example data is taken from (Roebben et al. 2011) that summarizes the collaborative efforts to date of the *International Alliance for NanoEHS Harmonization* (http://www.nanoehsalliance.org/). This group, comprising a number of institutions with ENM characterization capabilities, seeks to establish and harmonize protocols and procedures for ENM attribute and toxicity measurement. The participants' characterization instrumentation was initially calibrated to produce near identical results for several reference materials (gold, silica and polystyrene nanoparticles) that were considered mono disperse with respect to both size and zeta potential. The aim of the investigation was to highlight the potential variability of physical attribute measurements of non-reference material (cerium oxide NPs) even under conditions of careful instrument calibration informed by certified reference materials. The polydisperse nature of the non-reference materials, a feature common to many ENMs, was attributed as the primary cause of the measurement variability.

To justify the viability of the maximum entropy principle as a means of generating descriptive marginal PDFs, it was first tested by reconstructing a known PDF from its corresponding moment information. An unwieldy mixed model PDF containing two maxima was deliberately chosen to highlight the method's robustness. Such distributions would be typical of ENMs that are polydisperse across various metrics. Figure 11.2 shows how a mixed model normal PDF with two maxima can be rebuilt on the basis of its first four moments. This makes sense since a mixed Gaussian distribution containing two peaks can be encoded with four numbers, two mean values and two variances. The reconstruction examples lend credibility to those distributions that are then built from moment information derived from discrete data sets, as exemplified in Fig. 11.3.

Figure 11.3 depicts one particular set of results obtained by seven members of the group to measure the zeta potential of cerium oxide nanoparticles that were supplied from the same batch. From the seven data points the first seven moments were obtained that provided the maximum information regarding the distribution of the data. The application of the maximum entropy principle to the seven measurements then supplied the corresponding PDF. However, it is important to note that PDFs built from larger data sets would be more indicative of their actual underlying distributions, since for larger sets possible statistical outliers become increasingly insignificant in terms of their influence on the corresponding PDFs. Arguably, for Fig. 11.3 to represent a realistic zeta potential distribution, more measurements would be required.

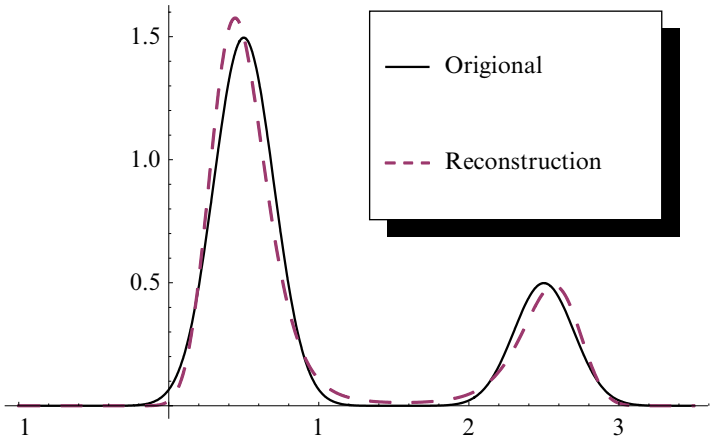

Fig. 11.2 The Max entropy principle for constructing PDFs from their corresponding moments is tested on a known mixed normal distribution containing two maxima. Here the first four moments are first calculated from the known distribution and then used to rebuild it using the max entropy principle

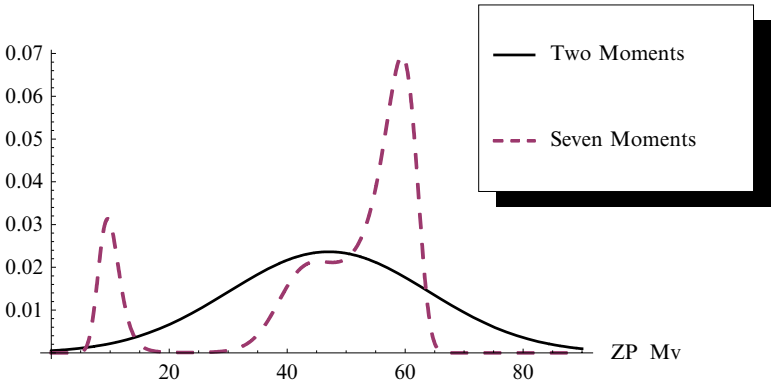

Fig. 11.3 A discrete set of seven data points representing zeta potential measurements in millivolts of cerium oxide NPs taken from the same batch are used to build a PDF describing their distribution. The points are used to calculate the first seven moments that are then used to build the corresponding distribution from the Max entropy principle. The seven data measurements were ZP = 10, 40, 50, 50, 60, 60 and 60 MVs, respectively. To confirm the accuracy of the PDF, the first seven moments were obtained directly from both the discrete data and the PDF and then compared. The first seven moments calculated directly from the discrete data are $1, 47.1429, 2500, 137571, 7.70714 \times 10^6, 4.37186 \times 10^8$ and $2.5045 \times 10\,\hat{}\,10$. While the first seven calculated from the PDF are $1, 47.1345, 2499.45, 137537, 7.70539 \times 10\,\hat{}\,6, 4.37086 \times 10\,\hat{}\,8$ and $2.50397 \times 10\,\hat{}\,10$

The key is for characterization and toxicological personnel not to make assumptions about the distributions of the data sets they collect but to adopt the principle of maximum entropy to discern the actual distributions underlying them. For example, combining two samples of a particular ENM into a common batch that were individually characterized by normal distributions over a particular attribute would now be characterized by a mixed normal distribution over the same attribute (unless aggregation occurred). Such a mixed PDF could easily be uncovered by the principle of maximum entropy as illustrated in Fig. 11.2.

It is important to note from (11.9) that the distinction between the number of moments being calculated for each marginal distribution and the number of materials being examined is an artificial one: specifically, (11.9) suggests that it may not be strictly necessary to distinguish each ENM; in principle, they could be logically combined and treated as a single ENM at the cost of requiring higher moment marginal PDFs to describe the properties of the logically composite ENM. In practice, this suggests groupings of similar ENMs that are technically difficult to isolate for toxicity analysis may be treated as single entities. They would however require relatively higher moment PDFs to describe the combined toxicity and physical attribute data of the ENMs in each group; to compensate for the loss of distinction among the individual ENMs forming a group, a greater number of moments would be required to generate general mixed model marginal distributions reflecting the individual characteristics of each ENM. Heuristically, a measure of the information encoded by (11.9) can be defined as the product of the number of moments calculated for each marginal distribution and the number of ENMs being examined. This suggests the results of a regression analysis for scenarios in which this magnitude is maintained should be similar. For example, the profile for $\rho(r\,|\,z)$ obtained from minimizing (11.11),

$$\text{Sum Probability Squares} = \sum_{j=0}^{l\times n}\left(\text{moment}_j\left(\rho_2(r\,|\,I)\right) - \text{moment}_j\left(\int_{z=0}^{\infty}\rho(r\,|\,z)\rho_1(z\,|\,I)dz\right)\right)^2 \tag{11.11}$$

in which the previous n ENMs are now logically combined and designated as a single ENM, labelled I, should be commensurate with the solution for $\rho(r\,|\,z)$ obtained from minimizing (11.9).

This observation has important practical implications in regard to the commonly held opinion among investigators that ENMs must be well characterized for toxicological profiling. It suggests this requirement may not be as stringent as previously thought and a broader classification of ENMs may be permitted in terms of the spreads of physical attribute measurements for obtaining the dependency of toxicity on physical attributes. This would thus mitigate the need to sub classify, with the attendant technical difficulties, similar ENMs according to narrowly defined physical attributes prior to toxicity testing. Profiling groupings of related ENMs by aggregating a relatively large number of moderately accurate measurements to produce higher moment marginal PDFs would compensate for forgoing the more accurate but technically challenging individual characterizations. Given the current

issues surrounding ENM metrology, the latter approach may be more technically feasible than aiming for precise characterizations to distinguish similar ENMs. In any case, such characterizations could prove to be somewhat transient given the propensity of ENMs to alter their surface characteristics in response to subtle environmental changes.

In this section, the author demonstrated how in principle real but seemingly conflicting data points can produce optimal data regressions using the Bayesian generalization of least squares fit. Additionally, the structure of (11.9) suggested that utilizing a large number of moderately accurate observations to calculate an extensive set of moments for similar ENMs could compensate for a general lack of more precise measurements to differentiate them. Such measurements in any case could prove to be somewhat transient given the susceptibility of narrowly defined ENMs to lose their characterizations from environmental change. In particular, materials that have been in transit for long durations prior to toxicity profiling are especially prone to this problem due to changes in temperature, humidity, etc.

11.6 Multidimensional Problem

The observed responses in terms of biomarkers to the presence of a pathogen such as an ENM depend not only on the pathogen but also on the type of cell (cell line) under observation. For example, the biomarker response of a lung cell will generally be different from that of a heart cell. Quantitatively, the toxicity profile of a particular ENM cannot be uniquely described in terms of a single number or scalar. Instead, an array of quantities are required, one for each biomarker of interest per cell line. The toxicity profile or hazard signature will become increasingly specific to the ENM in question by increasing the number of biomarkers and cell lines used to profile it. Similarly, the measurement of an increasing number of physical attributes should become increasingly specific to each material and provide it with a unique physicochemical signature. The goal in nanotoxicology is to essentially map physicochemical signatures to hazard signatures by developing hypotheses that explain hazard signatures in terms of physicochemical signatures and then testing these hypotheses through in vitro assessments. However, the data from these procedures is expected to contain a relatively high degree of uncertainty compared to mean values and thus may be considered too ambiguous to be useful using conventional regression methodologies.

What is required therefore is a multidimensional version of the example described in Sect. 11.5 that will correlate multiple hazard values with multiple physical attribute data. This problem is formulated as identifying the multivariate joint distribution— $\rho\left(h_1, h_2 \ldots, z_1, z_2 \ldots \middle| I_k\right)$, in which h_1, h_2 denotes a list of hazard metrics taken

from the hazard tensor[13] for material I_k and $z_1, z_2, \ldots$ is a corresponding list of physical attribute metrics such as aspect ratio, size, zeta potential, etc.

Tackling the multidimensional case should proceed analogously to the analysis of the two-dimensional problems examined in Sect. 11.4 but will likely be more computationally demanding as the solution will require the numerical evaluation of multiple multidimensional integrals, etc. The challenge here is to identify computational short cuts and those parts of the regression algorithm amenable to parallelization on the latest multicore/processor architectures.

11.7 Conclusion

Enhanced fidelity is required for the growing but disparate body of ENM characterization and toxicity data obtained at the in vivo level. Failure to address this issue will limit the utility of existing data due to its presently somewhat ambiguous and conflicting nature. The viability of longer-term risk models at the organism level and in vivo–in vitro extrapolation techniques depend, as a starting point, on the judicious interpretation of ENM toxicity profiling as determined in vitro.

Ultimately, positive responses towards ENMs and their associated industries from public policy makers, regulators and insurers depend on the availability and credibility of such risk models. Should these criteria not be meet then the disciplines of ENM characterization, toxicity profiling and subsequent risk analysis may face a potential crisis of confidence within the wider scientific community and key stakeholder groups.

The Bayesian regression framework outlined in this chapter offers the potential to add clarity to existing and forthcoming in vivo and physical attribute data and to automatically over time attach more significance to better quality data. This will provide a dependable foundation for higher risk models and related subsequent work. The key is in the determination of marginal distributions describing physical

[13] Let $h_{i,j}$ denote a measure of hazard defined by in vitro methods in which the cell lines used in the experiments are enumerated with the index i and the observed biomarker with the index j. The entries in the matrix are assumed to be normalized deviations from unperturbed levels of the same biomarkers for each cell line that together form a control experiment. The deviations $h_{i,j}$ are normalized with respect to their corresponding unperturbed levels in the control experiment. This means the entries in the matrix are dimensionless quantities and should all be equal to zero when the presence of a ENM does not elicit a response in any of the cell lines. A benign material can therefore be described by a hazard tensor in which all the entries are equal to zero. $h_{i,j}$ is referred to as the hazard tensor, **H**, given by

$$\mathbf{H} = \begin{pmatrix} h_{1,1} & h_{1,2} & \ldots & \ldots \\ h_{2,1} & h_{2,2} & \ldots & \ldots \\ \ldots & \ldots & \ldots & \ldots \\ \ldots & \ldots & \ldots & \ldots \end{pmatrix}$$

and toxicological characterization data that can be estimated using the principle of maximum entropy. This is particularly crucial for ENM samples that are non-homogeneous or polydisperse with respect to certain attribute metrics. ENM samples that are non-homogeneous over particular attributes can be described by mixed model PDFs over the same attributes. It has been argued that such distributions are readily recoverable from sufficiently sized measurement sets by employing the principle of maximum entropy. Such scenarios would not easily be handled by conventional regression methods. A feature of (11.9) indicated the possibility of exploiting large numbers of moderately accurate measurements from commonly accessible characterization techniques to compensate for the lack of more precise characterizations likely involving greater technical challenges and expense. As a corollary, this offers the possibility of circumventing the problem in which ENMs that have been initially sharply defined using advanced measurement techniques are at risk of losing their characterizations due to subtle changes in their environments prior to toxicity testing, thus rendering uncertain the sought after relationship between toxicity and physical attributes. In such scenarios, there is no benefit to be gained from overly precise physical or toxicity profiling. This leads to the conclusion that it may be better to use a large number of moderately accurate measurements within the Bayesian regression framework to uncover the relationships between physicochemical and toxicity data.

The formulation of the multidimensional case follows in a manner similar to the simplified example presented in Sect. 11.4. A multidimensional scenario involving many variables, possibly leading to computational issues, will require numerical short cuts to make the necessary calculations achievable within reasonable time frames.

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Chapter 12
Organisational Risk Management of Nanomaterials Using SUNDS: The Contribution of CENARIOS®

Tobias Widler, Christoph Meili, Elena Semenzin, Vrishali Subramanian, Alex Zabeo, Danail Hristozov, and Antonio Marcomini

Abstract The CENARIOS®-Standard is the first certifiable risk management system (RMS) and monitoring system designed specifically for the needs of companies concerned with nanomaterials. The rapidly evolving field of nanotechnology is characterised by a high level of uncertainty in environmental health and safety research, economic and social impacts, as well as the risk perception of the technology. Companies dealing with nanotechnology can better address this uncertainty by embedding practices like risk monitoring, risk analysis, risk communication, and crisis management into their organisational culture. Monitoring developments in the fields of toxicology, occupational safety and health, as well as societal and perception risk constitute a fundamental part of the CENARIOS® RMS. As part of the project SUN (Sustainable Nanotechnologies), a questionnaire based on the CENARIOS® Certification Standard is being implemented as a stand-alone module and is linked to the SUN Decision Support System (SUNDS). As risk management in SUNDS Tier 2 is quantitatively linked to risk assessment results, organisational risk management—an essential component in addressing complex and uncertain risks that cannot be evaluated quantitatively—is assessed using a separate web-based questionnaire. The module covers a representative selection of the specific requirements stipulated in the certification standard and thereby enables interested enterprises to assess their level of fulfilment (in terms of the exigencies of the certification standard) in an independent and inexpensive manner. The stand-alone module provides a simple and low-threshold means to evaluate the status of a company's organisational risk management for nanomaterials. Existing gaps that need to be

T. Widler (✉) • C. Meili
The Innovation Society, St. Gallen, Switzerland
e-mail: tobias.widler@innovationsgesellschaft.ch

E. Semenzin • V. Subramanian • A. Zabeo • D. Hristozov • A. Marcomini
Department of Environmental Sciences, Informatics and Statistics, University Ca' Foscari Venice, Venezia, Italy

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addressed in order to comply with the CENARIOS® certification standard are highlighted. If corresponding action is taken, the CENARIOS® stand-alone module may thus contribute to enhancing the safety of facilities and firms producing, processing, or handling nanomaterials.

12.1 Voluntary Risk Management Measures for the Sustainable Use of Nanotechnologies

12.1.1 Interdisciplinary Challenges of a Key Technology

Experts consider nanotechnologies as one of the key technologies of the twenty-first century. Nanotechnologies offer a vast range of opportunities and provide enterprises, researchers, and economies with excellent opportunities for growth, innovation, and development (National Nanotechnology Initiative, 2000). Due to their unique properties, nanomaterials are increasingly applied in industry and consumer products all over the world. Countless cosmetics, varnishes, plastics, electronic components, and medical devices contain nanomaterials (European Commission, 2012a). Nanomaterials have the capacity to considerably improve material properties compared to bulk materials. Due to their extremely small size, nanomaterials possess a comparatively large specific surface, entailing an increased reactivity (Bhushan, 2010). Other properties that may alter at the nano-scale include, but are not restricted to, magnetic, optical, and pyrophoric properties or quantum effects (see, for instance, Edelstein & Cammaratra, 1998).

However, there is also considerable concern among experts and laypeople that the unique properties of nanomaterials come at a cost, namely the incidence of corresponding novel hazards (see, for instance, Siegrist, Keller, Kastenholz, Frey, & Wiek, 2007). Indeed, safety research and research on nanomaterial toxicity have shown that there is a substantial potential for health and environmental concerns (Colvin, 2003; Wiesner, Lowry, Alvarez, Dionysiou, & Biswas, 2006). Arguably, the most prominent example is the case of Carbon Nanotubes (CNT), which made it into headlines of newspapers and magazines due to surmised asbestos-like effects (see, for instance, Poland et al., 2008). Such headlines and the partly negative media coverage have surely contributed to an ambiguous public perception of nanotechnology.

As a consequence of these concerns and to ensure the sustainable use of nanotechnologies (for a definition of sustainable nanotechnology, see Subramanian, Semenzin, Hristozov, Marcomini, & Linkov, 2014), efforts in risk analysis, risk management, and risk communication are much needed (Maynard et al., 2006). The corresponding need for action has been identified and stressed by countless stakeholders. For instance, regulators (such as the European Commission (EC) or the United States Environmental Protection Agency (EPA))[1] have started to gradu-

[1] c.f. European Commission (2012b) and EPA (2015).

ally implement nano-specific requirements and decrees, albeit at varying degrees and relying on vastly differing approaches. Such requirements may encompass labelling and declaration obligations, minimum safety standards for handling and manufacturing, and various forms of substance registration. Occupational safety and health experts have been investigating the development of measurement methods, the assessment of available protective measures, and the adaptation of standards and methods for exposure control, among others (for an overview, see Savolainen et al., 2010 or Wohlleben, Kuhlbusch, Schnekenburger, & Lehr, 2014). As for the private sector, many companies have committed themselves to safety research, dialogues, and voluntary measures. Notably, research has shown that the overarching participation of various stakeholders in voluntary risk measures may contribute to the success thereof (Hansen & Tickner, 2007; National Nanotechnology Initiative, 2015).

12.1.2 Risk Management by Nanotechnology Companies

Under the majority of the legal frameworks, the responsibility of safely handling any given material (including nanomaterials) lies with industry and trade. The existing regulatory gaps and the rapid development in the field of nanotechnology call for a proactive risk management by the industry (Meili & Widmer, 2010). In order to tackle the risk management of nanotechnologies and, above all, the risks associated with manufacturing or processing of nanomaterials, a number of voluntary measures may be taken by enterprises.

Voluntary measures are usually unilateral commitments that complement or go beyond existing regulatory frameworks. Examples of nano-specific voluntary risk management measures include the Precautionary Matrix provided by the Swiss Federal Office of Public Health (to be completed by enterprises; see Höck et al., 2013 for details), TÜV SÜD's CENARIOS® standard (TÜV SÜD Industrie Service, 2008), the Environmental Defence Fund and DuPont's NanoRisk Framework (http://business.edf.org/projects/featured/past-projects/dupont-safer-nanotech/), and Codes of Conduct on Nanotechnologies, e.g. by BASF or the Swiss Retailer Association (Meili & Widmer, 2010). The adequacy, drawbacks, and advantages of such codes have been discussed in Bowman and Hodge (2009).

Other voluntary measures include "Control Banding" and "Safety by design" (also referred to as "Safe-by-design") (Hristozov et al., 2016; Oksel et al., 2015). Both are examples of risk management approaches with the potential to substantially contribute to the sustainable use and safe handling of nanomaterials and which could, under certain circumstances, contribute to the insurability of nanotechnologies (McAlea, Mullins, Murphy, Tofail, & Carroll, 2014). These approaches have been investigated with great effort and are often jointly pursued by researchers, occupational safety and health specialists, regulators, and companies. The FP7-funded project NANoREG represents an example of an interdisciplinary and overlapping safe-by-design approach. In nuce, and with regard to nanomaterials,

safe-by-design aims to decipher the interactions of nanomaterials with biological systems in order to predict their toxicity and, ultimately, change nanomaterial properties in a way that they exert no or reduced toxicity while maintaining their functionality (Lynch, Weiss, & Valsami-Jones, 2014). Control Banding is employed by both research institutes and manufacturers of nanomaterials as a means to control risks associated with the handling of nanomaterials (Groso, Petri-Fink, Magrez, Riediker, & Meyer, 2010). It can be harnessed to support the insurance industry in categorising exposure to and hazards of nanomaterials (Bergamaschi et al., 2015; Mullins, Murphy, Baublyte, McAlea, & Tofail, 2013). In fact, the risk matrix (described in Sect. 12.4) that forms part of the CENARIOS® risk management system (RMS) shares some features with the Control Banding approaches described elsewhere, for instance in ISO/TS 12901-2:2014. Both approaches encompass the grouping of occupational settings in categories that present similar hazards and/or exposure and incorporate professional judgment and monitoring.

12.2 The CENARIOS® Risk Management System

CENARIOS®, the first certifiable risk management and monitoring system designed specifically for the needs of companies concerned with nanomaterials, was launched in 2008 by TÜV SÜD (Germany) and The Innovation Society, St. Gallen (Switzerland). CENARIOS®—referring to 'Certifiable Nano specific Risk Management and Monitoring system'—is a voluntary organizational RMS that includes systematic processes to identify, scrutinise, document, and manage potential risks that the manufacturing and handling of nanomaterials entail. The aim of CENARIOS® is to minimise the risks of manufacturing or processing nanomaterials or products that contain nanomaterials (TÜV SÜD Industrie Service, 2008). According to the Certification Standard, the risk topics covered by CENARIOS® include (1) risks for employees producing and handling nanotechnology products (for both manufacturers of basic nanomaterials and downstream users of nanomaterials or -products), (2) risks to the environment and the surroundings of the company/plant (production-related environmental risks), and (3) consumer risks that may arise from the use of the nanotechnology products that are covered by the management system. Importantly, CENARIOS® does not cover other types of risks that may have to be taken into account by firms, such as investment risks or risks resulting from corporate mismanagement, as the system is not designed to account for these types of risks (TÜV SÜD Industrie Service, 2008). Moreover, it is important to note that CENARIOS® is not a product certificate. The certification exclusively refers to the RMS.

The requirements companies must fulfil in order to qualify for a CENARIOS® certificate are stipulated in the CENARIOS® certification standard (hereafter referred to as "the standard"). The standard relates to existing standards and guidelines for risk assessment and risk management, but, more importantly, it includes new tools that have been tailored to account for the complex risks that emerge from

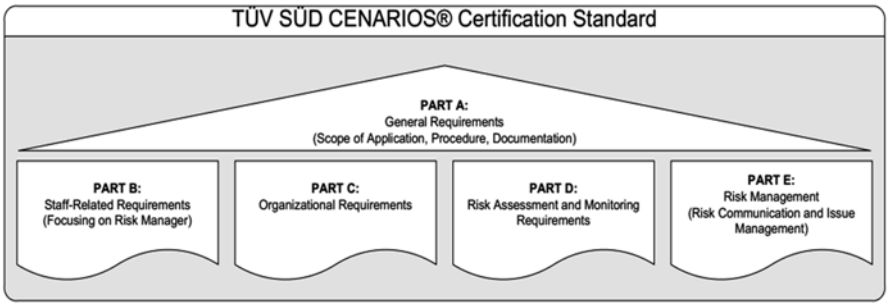

Fig. 12.1 Overview of the five parts of the CENARIOS® certification standard. *Source*: CENARIOS® Certification Standard, TÜV SÜD Industrie Service (2008)

the high uncertainty and market dynamics of nanotechnology (TÜV SÜD Industrie Service, 2008). Certification is carried out by TÜV SÜD, an independent certifying body, in the course of an audit. Re-certification under CENARIOS® needs to be done on a regular basis, i.e. once a year. Re-certification includes a review of the documentation and an assessment of the risk management processes (Meili & Widmer, 2010).

The CENARIOS® certification standard comprises five parts (c.f. Fig. 12.1):

1. Part A: General requirements
2. Part B: Staff-related requirements
3. Part C: Organisational requirements
4. Part D: Risk assessment and monitoring requirements
5. Part E: Risk management

In the following sections, the five parts of the standard (as stipulated in TÜV SÜD Industrie Service, 2008) will be described in more detail.

12.2.1 Part A: General Requirements

Part A of the standard summarises the requirements the RMS has to meet in general and is complemented by requirements for approaches to cover the risks of nanotechnology. The RMS under CENARIOS® (like any given RMS) should include the following elements:

1. Risk analysis
2. Risk assessment
3. Risk reduction
4. Risk control
5. Risk monitoring
6. Risk treatment

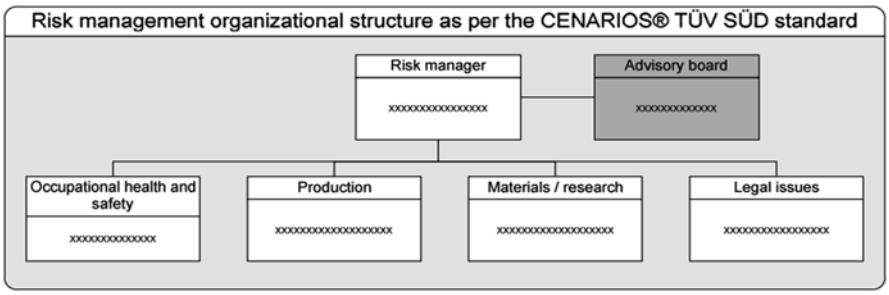

Fig. 12.2 Proposed organisational structure of a risk management system. *Source*: CENARIOS® Certification Standard, TÜV SÜD Industrie Service (2008)

More information on generic RMS can be found in the standards ISO 31000 and in the series ONR 49000. The general requirements of a RMS shall not be addressed in more detail here; instead, the specifics of CENARIOS® will be briefly described. One of the key elements is the establishment of a strategy on how to analyse and estimate the consequences of (adverse) events of nanotechnologies, such as workers' exposure to nanomaterials, in light of the scarcity of reliable data available. To qualify for a CENARIOS® certificate, the RMS must include at least a semi-quantitative approach for an estimate of the consequences (see Part D). The risk treatment system under CENARIOS® must include both risk communication and crisis/issue management. More specifically, risk communication should be based on a pro-active approach, which means that it should include upstream crisis communication, communication during crisis, and downstream communication (Part E).

With regard to the integration of CENARIOS® into the corporate culture and other existing RMS, it should be mentioned that CENARIOS® is designed as a stand-alone system, which can, however, be linked to existing management systems such as ISO 14000 (ff), ISO 31000 (ff) or quality management systems (QMS), such as ISO 9000 (ff). Therefore, in the course of certification, links to and interfaces with existing QMS have to established and stipulated. Figure 12.2 shows the proposed organisational structure of the risk management under the standard (TÜV SÜD Industrie Service, 2008).

12.2.2 Part B: Staff Requirements

The staff requirements listed in Part B of the CENARIOS® certification standard are based on the Austrian Standards Institute's (ON) rule 'ONR 49003', which itself is a guideline on the practical use of ISO 31000. Part B of the certification standard deals with the minimum requirements for risk managers, occupational safety and health managers and experts, production managers, materials/research managers, legal issues managers, and, last but not the least, the advisory board. The

requirements cover, among other things, education, work experience, training, and the exchange of information among different managers involved in CENARIOS® (TÜV SÜD Industrie Service, 2008).

12.2.3 Part C: Organisational Requirements

Part C addresses the requirements associated with the organisational structure of companies. It includes

1. Organisational requirements (such as the scope of the application, the integration of CENARIOS® into corporate culture, the consideration of framework conditions, the definition of responsibilities)
2. Implementation-related requirements (including the documentation of the process and the integration into existing QMS)
3. Documentation requirements

The requirements in Part C are destined to facilitate the smooth implementation of the RMS and follow rule ONR 49002-1. Potential interfaces with other management systems (e.g. ISO 9001, ISO 16949) include management responsibility, resource management, the risk management process, and system monitoring. Importantly, the organisational requirements of the standard stipulate that evidence of the integration of CENARIOS® into existing QMS must be furnished by companies (TÜV SÜD Industrie Service, 2008).

12.2.4 Part D: Risk Assessment and Monitoring Requirements

Part D describes the requirements within the scope of risk assessment and risk monitoring and entails the most comprehensive nano-specific characteristics of CENARIOS®. It is designed to provide for the uncertainties that persist in the field of nano-safety research, but also in other fields such as risk perception, regulatory changes, etc.

Generally speaking, risk analysis should provide answers to several aspects that can be roughly summarised with the following questions (TÜV SÜD Industrie Service, 2008):

- What events may occur?
- What are the consequences of these events?
- What are the underlying causes (i.e., the root causes)?
- What is the frequency of occurrence of these events?

There are tools at hand to answer most of these questions (and to perform the necessary steps in the course of answering these questions). In fact, the process of establishing an answer to the majority of these questions can be routinely performed

by an expert in risk assessment, and nano-specific approaches to tackle some of the questions listed above have been established. For instance, Hristozov et al. (2014a) describe a nano-specific quantitative approach for ranking exposure scenarios. Quantifying the possible consequences of nanotechnologies, on the other hand, is a highly intricate issue which is also addressed in SUNDS Tier 2. While a few well-characterised nanomaterials or nano-enabled products may be assessed with fully quantitative methods, to date the consequences of less well-studied nanomaterials—let alone emerging nanomaterials—may only be estimated based on experience with and analogies to other technologies and on the assessment and categorisation of relevant findings. Performing fully quantitative risk assessment of those nanomaterials or of nano-enabled products for which no comprehensive dataset is available does thus not seem feasible at this time (Marchant, Sylvester, & Abbott, 2008).

To bypass this problem, the CENARIOS® certification standard requires risk assessment to be performed in a semi-quantitative way. Semi-quantitative risk assessment allows for the provision of a surrogate for the variable "consequences of an event", on which limited information and very little (if any) experience from practical cases is available. Semi-quantitative risk assessment—as opposed to fully quantitative methods—explicitly takes this uncertainty into account. It also allows for the linking of subjective assessments to more objective experience (Meili & Widmer, 2010). Control Banding is another suitable approach to be used in the process of risk analysis and assessment (Groso et al., 2010 and ISO/TS 12901-2:2014), although it is not explicitly included in the standard.

In order to perform risk analysis in accordance with the CENARIOS® certification standard, a database reflecting the current state of the art in science and technology is needed as a basis. Once established, the database and the underlying source list should be updated continuously (c.f. Sect. 12.3). The database (respectively items therein) have to be evaluated with regard to (TÜV SÜD Industrie Service, 2008):

1. Their transferability of information ('can findings be generalised and transferred to humans?'): Database entries should be categorised with regard to their applicability to human beings. For example, findings from in silica or in vitro studies can generally not be transferred to humans directly, while findings on humans (such as controlled human exposure studies, if available) are of direct relevance.
2. The consistency of information ('does the findings match with existing information?'): Findings must be evaluated with regard to their consistency with other findings. If inconsistent findings are presented, as might be the case if previously unknown effects are found, the deviations from previous findings should be addressed and put into a context by the study authors.
3. The reliability of the data source ('what is the quality of a source of information?'): Study authors as well as the publication in which the study was published need to be assessed. Evaluation criteria include the peer-review process, the journal impact factor, or conflicts of interest.

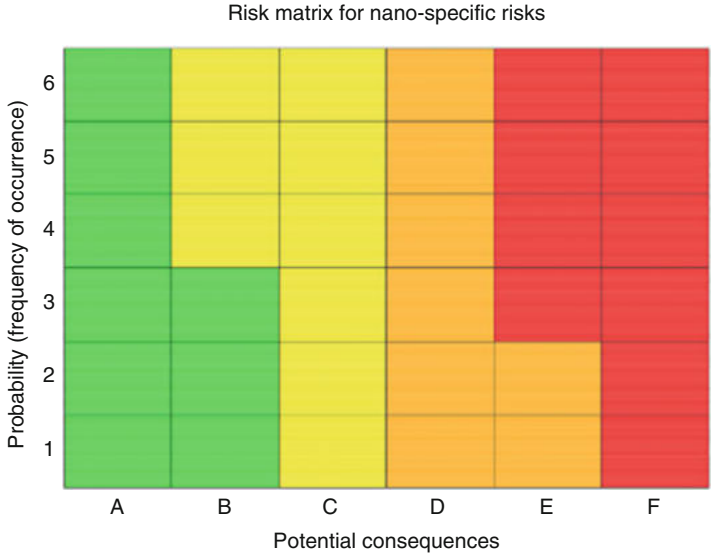

Fig. 12.3 Risk matrix for nanotechnology-specific risks. *Source*: CENARIOS® Certification Standard, TÜV SÜD Industrie Service (2008)

If the overall availability or quality of information is found to be inadequate for risk assessment, further tests may have to be performed to augment the level of knowledge.

The probability of events is determined similar to standard risk assessment and is either based on general experience or substantiated by qualified event reports or expert estimates. Altogether, the steps involved in risk management under CENARIOS® allow for the definition of a nanotechnology-specific risk matrix, as illustrated in Fig. 12.3. The RMS must be updated periodically and risks must be re-assessed.

12.2.5 Part E: Requirements Related to Risk Treatment and Risk Communication

In Part E of the standard, guidance and minimum requirements regarding risk treatment and communication are provided. To some extent, this part of the standard is based on ON Rule ONR 49002-3. It specifies the requirements the risk communication and crisis management must fulfil. These include: identification of issues that may lead to a crisis and of worst case scenarios, elaboration of contingency plans and procedures in case of crisis, and establishing plans on how the company may regain control during and after a crisis. Suitable risk treatment measures must be

developed, taking into account all legal, official, and contractual requirements, among others. These may include preventive and mitigating measures, measures of risk compensation, or insurance, to name a few (TÜV SÜD Industrie Service, 2008).

Risk communication encompasses three phases: Upstream crisis communication, communication during a crisis, and downstream crisis communication. Upstream crisis communication refers to the proactive communication intended to prevent a crisis from occurring. Upstream crisis communication may include measures such as resources planning, defining roles and responsibilities, and providing guidance and training. Communication during crisis is intended to ensure the rapid alert of the crisis management team, the assessment of the situation, and limiting the impacts of the crisis. Downstream crisis communication aims to prevent the crisis from entailing any repercussions and negative associations with the company. It includes the attendance of victims, the analysis of the circumstances that led to the crisis, as well as drawing conclusions with regard to necessary improvements (TÜV SÜD Industrie Service, 2008).

12.3 Nano Risk Monitoring System: The Challenge of Monitoring Nano-risks

Nanotechnology is a broad and interdisciplinary field which is undergoing rapid development and evolution. Manufacturers and processors of nanomaterials and products containing nanomaterials not only have to keep pace with the short cycles of innovation, but are also challenged by regulatory changes and a high level of uncertainty regarding the possible effects (Meili & Widmer, 2010). Moreover, companies also need to keep track of societal trends, since these have the capacity to impact both regulation and their own business. A risk monitoring system dedicated to nanotechnologies should thus be able to comprise all of these dynamics and, importantly, make the information available for risk assessment. Only if it does are companies able to respond to changes in a proactive manner (Meili & Widmer, 2010).

The risk monitoring described here aims to anticipate risks. It not only considers health, safety, and environmental risks, but also societal risk (public perception, risk debate, and media coverage), regulatory risks (changes in regulation) and liability risks (product liability risks)—also referred to as “soft risks”. Continuous updates of the risk monitoring ensure that the risk assessment is provided with up-to-date findings from science, society, and regulation (Meili & Widmer, 2010).

Over the last couple of years, nanotoxicology has emerged as one of the hot topics in nanotechnology, which has led to a soaring number of papers being published. However, in many cases the design of nanotoxicology studies is flawed, and many authors draw erroneous conclusions from their observations (Krug, 2014). Hence, a careful assessment of available studies by suitable personnel—be it internal or external—is a crucial part of the risk assessment and monitoring.

The monitoring of societal risks should include a source list containing representative key-opinion leaders, such as media (online media, newspapers, and pertinent magazines), non-governmental organisations (NGO), and competitors. Moreover, the increasing importance of social media such as Facebook and Twitter should be accounted for, particularly by firms concerned with consumer products. Monitoring societal risks allows companies to closely follow the perception of nanotechnologies. Additionally, companies should pursue a transparent and pro-active communication strategy (see also Part E of the certification standard, TÜV SÜD Industrie Service, 2008).

The methodology of the comprehensive monitoring can also be harnessed by other stakeholders. In 2014, for instance, reinsurance company Gen Re adopted a similar approach for the monitoring of nano-specific risks in a reinsurance context (Widler, Meili, & Wieczorek, 2015). This adds to the list of examples how direct and reinsurers—often in collaboration with researchers—are addressing the chances and risks that come with development of nanotechnologies (c.f. Bergamaschi et al., 2015, Mullins et al., 2013).

12.4 CENARIOS® Stand-Alone Module as a Part of Sunds

12.4.1 Developing the CENARIOS® Stand-Alone Module

As a part of the "Sustainable Nanotechnologies" (SUN) project (a more detailed description of the project is contained in Hristozov et al., 2014b), funded by the European Commission's seventh research framework programme (FP7), a tool based on decision analytic techniques to facilitate decision-making on nano-manufacturing is under development. The tool, dubbed "SUN Decision Support System" (SUNDS), will be devised as a user-friendly software tool, enabling users to estimate nano-related risks for workers, consumers, and ecosystems along the entire life-cycle of nano-products (Malsch, Subramanian, Semenzin, Hristozov, & Marcomini, 2015). SUNDS is designed as a two-tiered framework comprising of tools of differing data requirements and analytical complexity to assess environmental, economic, and social risks and benefits (including uncertainty estimation (Subramanian et al., 2016)). A stand-alone module on the CENARIOS® system complements the two tiers by facilitating users to evaluate their organisational risk management practices. The module, called CENARIOS® stand-alone module, allows pertinent companies to assess their level of fulfilment of the requirements of the CENARIOS® certification standard in an independent manner.

In the process of CENARIOS® certification (as is the case in the course of any comparable certification of a RMS), an audit is performed by an expert of the certifying body, in this case TÜV SÜD (Meili & Klein, 2008). The aim of the audit is to assess the RMS with regard to the exigencies of the CENARIOS® certification standard. Needless to say that within the duration of the audit (usually involving a 2- or

3-day visit on site), not every single requirement listed in the certification standard can be verified by the auditor. To elude this problem, auditors rely on questionnaires covering the key features of the certification standard.

Similarly, the CENARIOS® stand-alone module is based on a questionnaire which covers the crucial aspects of the standard. Based on the topics and issues highlighted in the certification standard and based on the documentation of a previous certification, the questionnaire was edited, shortened, and ultimately transferred into a reduced questionnaire. Although underpinned by experience and by the emphases of the standard, the process of selecting the relevant questions remains—to some degree—subject to the authors' judgement, an issue that was accounted for by applying the principle of multiple assessors.

The online questionnaire comprises one section for each part of the standard. Each section is dedicated to an overarching question. The level of fulfilment is assessed by confirming or declining statements addressing specific requirements of the standard:

1. By means of what organisational structure is the functioning of the RMS ensured? (addressing Part A of the standard by means of four statements catered to specific requisites)
2. Is the risk manager qualified to ensure introduction, establishment, and operation of the risk management process? (Part B, six statements)
3. Are organizational requirements met and sufficiently documented? (Part C, seven statements)
4. How are the risk assessment and the risk monitoring designed and what areas are covered? (Part D, eight statements)
5. Does the company have at hand a structured process for a systematic analysis, assessment, and treatment of crisis? (Part E, six statements)

The number of statements thus amounts to a total of 31. Like the two tiers of SUNDS, the CENARIOS® stand-alone module is implemented as a web-based tool. Users can access the tool by creating an account on http://sundss.com/cenarios. A draft of the tool is depicted in Fig. 12.4. The tool encompasses the following features:

1. Introduction: General information on CENARIOS® and on the tool itself, disclaimer.
2. Questionnaire: 31 statements regarding the fulfilment of key features of the standard, to be affirmed by ticking "Yes", declined by ticking "No", or to be left unanswered if they are "Not applicable". Upon ticking the "No" box, hints on how to fulfil the exigencies and where to find more information are provided to the user.
3. Evaluation/results: The results of the questionnaire are summarised and presented graphically in the form of a radar chart (also referred to as 'spider web chart'), in which the score on each axis represents the percentage of statements valued with "yes" out of those which are applicable for each part. The statements are not weighted individually. Additionally, a list of all the hints provided while answering the questionnaire is included in the final section.

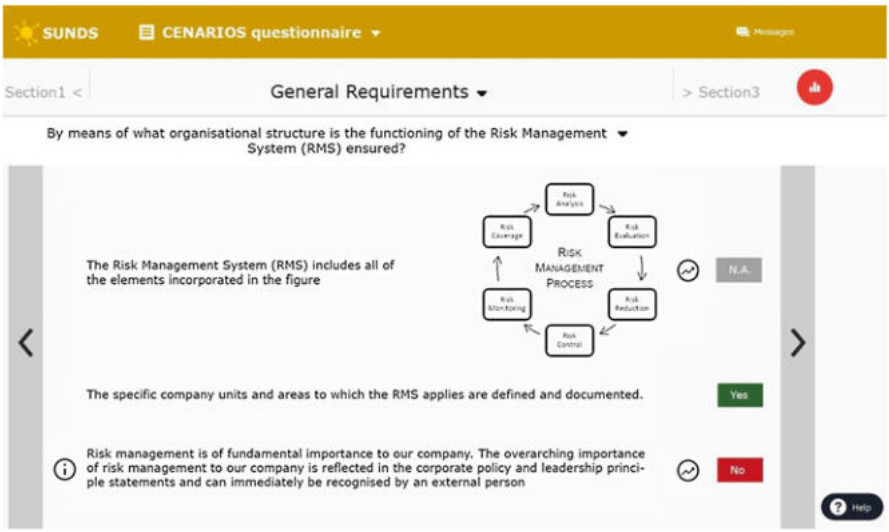

Fig. 12.4 Screenshot of the beta version of the CENARIOS® stand-alone module

12.4.2 The Contribution of the Cenarios® Stand-Alone Module to Organisational Risk Management in Sunds

The CENARIOS® stand-alone module provides a facile and low-threshold means to evaluate the status of a companies' organisational risk management for nanomaterials (in relation to the CENARIOS® Certification Standard). Entities that use the SUN Decision Support System are also referred to the stand-alone Module. Upon completion of the CENARIOS® questionnaire, users are then provided advice on how to improve their organisational RMS. Gaps that need to be addressed in order to comply with the standard are highlighted. The stand-alone Module thus complements SUNDS' Tier 1 and Tier 2.

Schematically, the interplay between SUNDS Tier 1 and Tier 2 and the CENARIOS® stand-alone Module as well as the contribution of the module to the organisational risk management of nanomaterials could be described in the following way:

1. An enterprise which produces processes or sells nanomaterials or plans to do so seeks the support of SUNDS to ensure the sustainable use of nanomaterials. Competent personnel complete SUNDS Tier 1 and Tier 2.
2. The company uses a certified RMS or wants to establish such a system. While using SUNDS, the responsible person is referenced the CENARIOS® stand-alone Module.
3. The person in charge of the maintenance or installation of the RMS completes the questionnaire of the stand-alone Module, using information contained in the organisation chart, the RMS documentation, the QMS documentation, etc.

4. Upon completion of the CENARIOS® stand-alone Module, a graphical representation of the current state of the RMS with regard to the requirements of the standard is displayed, and suggested measures on how to improve the RMS are listed.
5. Together with other competent personnel that needs to be involved in the RMS (according to Parts A to C of the standard), the person issuing the questionnaire discusses the results thereof, the measures suggested therein, as well as the need for action. If the advisory board (or any corresponding board entitled to take such a decision) decides to introduce the CENARIOS® RMS, it will contact TÜV SÜD, go through all the requirements of the standard, and implement the suggested measures as well as other tasks that need to be performed in order to qualify for a CENARIOS® certificate.
6. Together with TÜV SÜD, CENARIOS® is implemented. The company takes all necessary measures to fulfil the requirements of the certification standards. Experts of the TÜV SÜD certification unit perform an audit. If no need for amendments to the RMS is detected, the company is awarded the CENARIOS® certificate by TÜV SÜD. The company may then apply for re-certification on a periodic basis. Corresponding audits will be performed by TÜV SÜD, and re-certification will be granted if all requirements are fulfilled.

In this context, it is of utmost importance to note that under no circumstances completing the questionnaire and/or achieving a high score gives the issuing company the right to a valid CENARIOS® certificate. That said, it seems clear that by addressing the gaps highlighted by the stand-alone module (in conjunction with other gaps evident from the Certification Standard), a company can prepare itself in the best possible manner for a certification.

More specifically, achieving a high score in the stand-alone module—if the questionnaire is completed factually and in good faith and fair dealing—may indicate that the company's RMS is compatible with CENARIOS®, which might be the case, for instance, if it is based on ISO 31000. In such a case, CENARIOS® could be introduced with comparably little adjustments, since it could be linked to the existing RMS (the corresponding steps and requirements are contained in Part C of the Certification Standard). Contrarily, reasons for achieving a low score might be that the company relies on a RMS which is construed in a different manner, or that the company does not currently operate a (certified) RMS. In this case, CENARIOS® would have to be implemented as a stand-alone RMS, and the corresponding audit and consulting might be more costly and time-consuming.

12.5 Conclusions

To summarise, the CENARIOS® certificate provides a means of organisational risk management for companies which manufacture or process nanomaterials. The CENARIOS® stand-alone module, which has been devised as a part of the

FP7-projects SUN and which is linked to SUNDS, provides companies interested in establishing a nano-specific RMS with a low-threshold means to assess the state of their RMS or organisational scheme with regard to the standard. The stand-alone module elucidates the need for action in order to comply with the CENARIOS® Certification Standard.

Upon successful audit and after achieving certification, the CENARIOS® RMS fosters the safety of facilities and firms producing, processing, or handling nanomaterials. Apart from evaluation of health, safety, and environmental impacts, the implementation of CENARIOS® may also catalyse the risk transfer to the insurance industry, as it clearly demonstrates a company's dedication to the proactive tackling of nano-related issues, including health, safety, and societal concerns. By analogy with adhering to a Control Banding scheme, this could allow certified companies to transfer risks to insurers at reasonable costs, as has been suggested by McAlea et al. (2014). In conjunction with other SUNDS tools, the CENARIOS® stand-alone module may thus contribute to the sustainable use of nanotechnologies.

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Appendix A: Search Criteria

F. Murphy et al. (eds.), *Managing Risk in Nanotechnology*, Innovation, Technology, and Knowledge Management, DOI 10.1007/978-3-319-32392-3

Table A.1 Search criteria (referenced from Table 5.1)

Mnemonic	Search query
CELAC+nano	(AFFILCOUNTRY (costa rica) OR AFFILCOUNTRY (el salvador) OR AFFILCOUNTRY (guatemala) OR AFFILCOUNTRY (mexico) OR AFFILCOUNTRY (honduras) OR AFFILCOUNTRY (nicaragua) OR AFFILCOUNTRY (panama) OR AFFILCOUNTRY (cuba) OR AFFILCOUNTRY (puerto rico) OR AFFILCOUNTRY (haiti) OR AFFILCOUNTRY (argentina) OR AFFILCOUNTRY (bolivia) OR AFFILCOUNTRY (brazil) OR AFFILCOUNTRY (chile) OR AFFILCOUNTRY (ecuador) OR AFFILCOUNTRY (colombia) OR AFFILCOUNTRY (paraguay) OR AFFILCOUNTRY (peru) OR AFFILCOUNTRY (uruguay) OR AFFILCOUNTRY (venezuela) OR AFFILCOUNTRY (dominican republic) OR AFFILCOUNTRY (barbados) OR AFFILCOUNTRY (belize) OR AFFILCOUNTRY (bahamas) OR AFFILCOUNTRY (antigua AND barbuda) OR AFFILCOUNTRY (dominica) OR AFFILCOUNTRY (grenada) OR AFFILCOUNTRY (guyana) OR AFFILCOUNTRY (jamaica) OR AFFILCOUNTRY (saint kitts AND nevis) OR AFFILCOUNTRY (saint lucia saint vincent AND the grenadines) OR AFFILCOUNTRY (suriname) OR AFFILCOUNTRY (trinidad AND tobago)) AND (TITLE-ABS-KEY (scanning probe microscopy) OR TITLE-ABS-KEY (nanoscience) OR TITLE-ABS-KEY (nanoparticle) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanomanipulation) OR TITLE-ABS-KEY (nanoindentation) OR TITLE-ABS-KEY (nanoimprint lithography) OR TITLE-ABS-KEY (nanofiltration) OR TITLE-ABS-KEY (nanofibers) OR TITLE-ABS-KEY (nanocrystals) OR TITLE-ABS-KEY (nanobiotechnology) OR TITLE-ABS-KEY (molecular electronics) OR TITLE-ABS-KEY (microfluidics) OR TITLE-ABS-KEY (microfabrication) OR TITLE-ABS-KEY (mems) OR TITLE-ABS-KEY (gold nanoparticles) OR TITLE-ABS-KEY (electrospinning) OR TITLE-ABS-KEY (electron beam lithography) OR TITLE-ABS-KEY (chitosan,technology) OR TITLE-ABS-KEY (carbon nanotubes) OR TITLE-ABS-KEY (atomic force microscopy) OR TITLE-ABS-KEY (nanotribology) OR TITLE-ABS-KEY (nanorobotics) OR TITLE-ABS-KEY (nanomachining) OR TITLE-ABS-KEY (nanofluidics) OR TITLE-ABS-KEY (nano-integration) OR TITLE-ABS-KEY (nanosensors) OR TITLE-ABS-KEY (nanochips) OR TITLE-ABS-KEY (nanodevices) OR TITLE-ABS-KEY (nanomagnetism) OR TITLE-ABS-KEY (nano-optics) OR TITLE-ABS-KEY (nanoelectronics) OR TITLE-ABS-KEY (nanophysics) OR TITLE-ABS-KEY (nanoscale fullerenes) OR TITLE-ABS-KEY (nanoscale thin films) OR TITLE-ABS-KEY (quantum wells) OR TITLE-ABS-KEY (quantum wires) OR TITLE-ABS-KEY (quantum dots) OR TITLE-ABS-KEY (nanoclusters) OR TITLE-ABS-KEY (nanocrystalline materials) OR TITLE-ABS-KEY (nanocomposites) OR TITLE-ABS-KEY (nanoprobes) OR TITLE-ABS-KEY (nanofabrication) OR TITLE-ABS-KEY (nanolithography) OR TITLE-ABS-KEY (nems) OR TITLE-ABS-KEY (nanoelectromechanical systems) OR TITLE-ABS-KEY (nanotextiles) OR TITLE-ABS-KEY (nanotoxicology) OR TITLE-ABS-KEY (nanostructure) OR TITLE-ABS-KEY (nanomedicine) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanobiophysics) OR TITLE-ABS-KEY (nanorods) OR TITLE-ABS-KEY (nanoparticles) OR TITLE-ABS-KEY (nanowires) OR TITLE-ABS-KEY (nanotubes) OR TITLE-ABS-KEY (nanotechnology))

EU + nano	(AFFILCOUNTRY (austria) OR AFFILCOUNTRY (belgium) OR AFFILCOUNTRY (bulgaria) OR AFFILCOUNTRY (czech republic) OR AFFILCOUNTRY (cyprus) OR AFFILCOUNTRY (denmark) OR AFFILCOUNTRY (estonia) OR AFFILCOUNTRY (finland) OR AFFILCOUNTRY (france) OR AFFILCOUNTRY (germany) OR AFFILCOUNTRY (greece) OR AFFILCOUNTRY (hungary) OR AFFILCOUNTRY (ireland) OR AFFILCOUNTRY (italy) OR AFFILCOUNTRY (latvia) OR AFFILCOUNTRY (lithuania) OR AFFILCOUNTRY (luxembourg) OR AFFILCOUNTRY (malta) OR AFFILCOUNTRY (netherlands) OR AFFILCOUNTRY (portugal) OR AFFILCOUNTRY (poland) OR AFFILCOUNTRY (romania) OR AFFILCOUNTRY (slovakia) OR AFFILCOUNTRY (slovenia) OR AFFILCOUNTRY (spain) OR AFFILCOUNTRY (sweden) OR AFFILCOUNTRY (united kingdom) OR AFFILCOUNTRY (croatia) OR AFFILCOUNTRY (iceland) OR AFFILCOUNTRY (macedonia) OR AFFILCOUNTRY (montenegro) OR AFFILCOUNTRY (turkey) OR AFFILCOUNTRY (albania) OR AFFILCOUNTRY (bosnia) OR AFFILCOUNTRY (faroe) OR AFFILCOUNTRY (israel) OR AFFILCOUNTRY (liechtenstein) OR AFFILCOUNTRY (norway) OR AFFILCOUNTRY (serbia) OR AFFILCOUNTRY (switzerland)) AND (TITLE-ABS-KEY (scanning probe microscopy) OR TITLE-ABS-KEY (nanoscience) OR TITLE-ABS-KEY (nanoparticle) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanomanipulation) OR TITLE-ABS-KEY (nanoindentation) OR TITLE-ABS-KEY (nanoimprint lithography) OR TITLE-ABS-KEY (nanofiltration) OR TITLE-ABS-KEY (nanofibers) OR TITLE-ABS-KEY (nanocrystals) OR TITLE-ABS-KEY (nanobiotechnology) OR TITLE-ABS-KEY (molecular electronics) OR TITLE-ABS-KEY (microfluidics) OR TITLE-ABS-KEY (microfabrication) OR TITLE-ABS-KEY (mems) OR TITLE-ABS-KEY (gold nanoparticles) OR TITLE-ABS-KEY (electrospinning) OR TITLE-ABS-KEY (electron beam lithography) OR TITLE-ABS-KEY (chitosan,technology) OR TITLE-ABS-KEY (carbon nanotubes) OR TITLE-ABS-KEY (atomic force microscopy) OR TITLE-ABS-KEY (nanotribology) OR TITLE-ABS-KEY (nanorobotics) OR TITLE-ABS-KEY (nanomachining) OR TITLE-ABS-KEY (nanofluidics) OR TITLE-ABS-KEY (nano-integration) OR TITLE-ABS-KEY (nanosensors) OR TITLE-ABS-KEY (nanochips) OR TITLE-ABS-KEY (nanodevices) OR TITLE-ABS-KEY (nanomagnetism) OR TITLE-ABS-KEY (nano-optics) OR TITLE-ABS-KEY (nanoelectronics) OR TITLE-ABS-KEY (nanophysics) OR TITLE-ABS-KEY (nanoscale fullerenes) OR TITLE-ABS-KEY (nanoscale thin films) OR TITLE-ABS-KEY (quantum wells) OR TITLE-ABS-KEY (quantum wires) OR TITLE-ABS-KEY (quantum dots) OR TITLE-ABS-KEY (nanoclusters) OR TITLE-ABS-KEY (nanocrystalline materials) OR TITLE-ABS-KEY (nanocomposites) OR TITLE-ABS-KEY (nanoprobes) OR TITLE-ABS-KEY (nanofabrication) OR TITLE-ABS-KEY (nanolithography) OR TITLE-ABS-KEY (nems) OR TITLE-ABS-KEY (nanoelectromechanical systems) OR TITLE-ABS-KEY (nanotextiles) OR TITLE-ABS-KEY (nanotoxicology) OR TITLE-ABS-KEY (nanostructure) OR TITLE-ABS-KEY (nanomedicine) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanobiophysics) OR TITLE-ABS-KEY (nanorods) OR TITLE-ABS-KEY (nanoparticles) OR TITLE-ABS-KEY (nanowires) OR TITLE-ABS-KEY (nanotubes) OR TITLE-ABS-KEY (nanotechnology))
CELAC + nano-safety	*Like above* + AND (TITLE-ABS-KEY (nanosafety) OR TITLE-ABS-KEY (safety) OR TITLE-ABS-KEY (risk) OR TITLE-ABS-KEY (nanorisk) OR TITLE-ABS-KEY (toxicology) OR TITLE-ABS-KEY (nanotoxicology) OR TITLE-ABS-KEY (toxicity) OR TITLE-ABS-KEY (nanotoxicity) OR TITLE-ABS-KEY (ehs) OR TITLE-ABS-KEY (nano environmental health AND security))

(continued)

Table A.1 (continued)

Mnemonic	Search query
CELAC+EU+nano	(AFFILCOUNTRY (costa rica) OR AFFILCOUNTRY (el salvador) OR AFFILCOUNTRY (guatemala) OR AFFILCOUNTRY (mexico) OR AFFILCOUNTRY (honduras) OR AFFILCOUNTRY (nicaragua) OR AFFILCOUNTRY (panama) OR AFFILCOUNTRY (cuba) OR AFFILCOUNTRY (puerto rico) OR AFFILCOUNTRY (haiti) OR AFFILCOUNTRY (argentina) OR AFFILCOUNTRY (bolivia) OR AFFILCOUNTRY (brazil) OR AFFILCOUNTRY (chile) OR AFFILCOUNTRY (ecuador) OR AFFILCOUNTRY (colombia) OR AFFILCOUNTRY (paraguay) OR AFFILCOUNTRY (peru) OR AFFILCOUNTRY (uruguay) OR AFFILCOUNTRY (venezuela) OR AFFILCOUNTRY (dominican republic) OR AFFILCOUNTRY (barbados) OR AFFILCOUNTRY (belize) OR AFFILCOUNTRY (bahamas) OR AFFILCOUNTRY (antigua AND barbuda) OR AFFILCOUNTRY (dominica) OR AFFILCOUNTRY (grenada) OR AFFILCOUNTRY (guyana) OR AFFILCOUNTRY (jamaica) OR AFFILCOUNTRY (saint kitts AND nevis) OR AFFILCOUNTRY (saint lucia saint vincent AND the grenadines) OR AFFILCOUNTRY (suriname) OR AFFILCOUNTRY (trinidad AND tobago)) AND (AFFILCOUNTRY (austria) OR AFFILCOUNTRY (belgium) OR AFFILCOUNTRY (bulgaria) OR AFFILCOUNTRY (czech republic) OR AFFILCOUNTRY (cyprus) OR AFFILCOUNTRY (denmark) OR AFFILCOUNTRY (estonia) OR AFFILCOUNTRY (finland) OR AFFILCOUNTRY (france) OR AFFILCOUNTRY (germany) OR AFFILCOUNTRY (greece) OR AFFILCOUNTRY (hungary) OR AFFILCOUNTRY (ireland) OR AFFILCOUNTRY (italy) OR AFFILCOUNTRY (latvia) OR AFFILCOUNTRY (lithuania) OR AFFILCOUNTRY (luxembourg) OR AFFILCOUNTRY (malta) OR AFFILCOUNTRY (netherlands) OR AFFILCOUNTRY (portugal) OR AFFILCOUNTRY (poland) OR AFFILCOUNTRY (romania) OR AFFILCOUNTRY (slovakia) OR AFFILCOUNTRY (slovenia) OR AFFILCOUNTRY (spain) OR AFFILCOUNTRY (sweden) OR AFFILCOUNTRY (united kingdom) OR AFFILCOUNTRY (croatia) OR AFFILCOUNTRY (iceland) OR AFFILCOUNTRY (macedonia) OR AFFILCOUNTRY (montenegro) OR AFFILCOUNTRY (turkey) OR AFFILCOUNTRY (albania) OR AFFILCOUNTRY (bosnia) OR AFFILCOUNTRY (faroe) OR AFFILCOUNTRY (israel) OR AFFILCOUNTRY (liechtenstein) OR AFFILCOUNTRY (norway) OR AFFILCOUNTRY (serbia) OR AFFILCOUNTRY (switzerland)) AND (TITLE-ABS-KEY (scanning probe microscopy) OR TITLE-ABS-KEY (nanoscience) OR TITLE-ABS-KEY (nanoparticle) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanomanipulation) OR TITLE-ABS-KEY (nanoindentation) OR TITLE-ABS-KEY (nanoimprint lithography) OR TITLE-ABS-KEY (nanofiltration) OR TITLE-ABS-KEY (nanofibers) OR TITLE-ABS-KEY (nanocrystals) OR TITLE-ABS-KEY (nanobiotechnology) OR TITLE-ABS-KEY (molecular electronics) OR TITLE-ABS-KEY (microfluidics) OR TITLE-ABS-KEY (microfabrication) OR TITLE-ABS-KEY (mems) OR TITLE-ABS-KEY (gold nanoparticles) OR TITLE-ABS-KEY (electrospinning) OR TITLE-ABS-KEY (electron beam lithography) OR TITLE-ABS-KEY (chitosan,technology) OR TITLE-ABS-KEY (carbon nanotubes) OR TITLE-ABS-KEY (atomic force microscopy) OR TITLE-ABS-KEY (nanotribology) OR TITLE-ABS-KEY (nanorobotics) OR TITLE-ABS-KEY (nanomachining) OR TITLE-ABS-KEY (nanofluidics) OR TITLE-ABS-KEY (nano-integration) OR TITLE-ABS-KEY (nanosensors) OR TITLE-ABS-KEY (nanochips) OR TITLE-ABS-KEY (nanodevices) OR TITLE-ABS-KEY (nanomagnetism) OR TITLE-ABS-KEY (nano-optics) OR TITLE-ABS-KEY (nanoelectronics) OR TITLE-ABS-KEY (nanophysics) OR TITLE-ABS-KEY (nanoscale fullerenes) OR TITLE-ABS-KEY (nanoscale thin films) OR TITLE-ABS-KEY (quantum wells) OR TITLE-ABS-KEY (quantum wires) OR TITLE-ABS-KEY (quantum dots) OR TITLE-ABS-KEY (nanoclusters) OR TITLE-ABS-KEY (nanocrystalline materials) OR TITLE-ABS-KEY (nanocomposites) OR TITLE-ABS-KEY (nanoprobes) OR TITLE-ABS-KEY (nanofabrication) OR TITLE-ABS-KEY (nanolithography) OR TITLE-ABS-KEY (nems) OR TITLE-ABS-KEY (nanoelectromechanical systems) OR TITLE-ABS-KEY (nanotextiles) OR TITLE-ABS-KEY (nanotoxicology) OR TITLE-ABS-KEY (nanostructure) OR TITLE-ABS-KEY (nanomedicine) OR TITLE-ABS-KEY (nanomaterials) OR TITLE-ABS-KEY (nanobiophysics) OR TITLE-ABS-KEY (nanorods) OR TITLE-ABS-KEY (nanoparticles) OR TITLE-ABS-KEY (nanowires) OR TITLE-ABS-KEY (nanotubes) OR TITLE-ABS-KEY (nanotechnology))