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Mitigating employer liability for producers and users of engineered nano materials

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UNIVERSITY of LIMERICK

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**Mitigating Employer Liability for Producers and Users of
Engineered Nano Materials**

by

Eamonn Martin McAlea B.Sc M.Sc

A thesis submitted to the Kemmy Business School, University of Limerick in
fulfilment of the requirements for the degree of

Doctor of Philosophy

Supervisors: Dr. Finbarr Murphy, Dr. Martin Mullins and Dr. Syed A.M. Tofail

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Mitigating Employer Liability for Producers and Users of Engineered Nano Materials

Eamonn Martin McAlea B.Sc M.Sc

Abstract: This thesis presents a series of arguments, tools and techniques to help facilitate the efficient transfer of occupational risk from the community of producers and users of engineered nano materials (ENMs) to insurers, thereby helping secure the promise of an on-going technological evolution for which these materials are paramount. As an emerging technology, there is insufficient data and few guiding analogues or useful metaphors to inform a perspective on their risks for insurers and regulators. In a climate of uncertainty, their utility is threatened by the possibility of over regulation or excessive insurance costs. This work firstly establishes the potential long term economic gains from ENM applications and highlights how such gains could be undermined by over regulation or high insurance costs. Insurance is identified as the primary vehicle to not only facilitate risk transfer, but to also act as a surrogate regulator in the interim, thereby providing a well-tailored template for on-going developments in command and control regulation. A hazard inference system is described that can be used by insurers or regulators to quickly flag an ENM as potentially hazardous on the basis of its physicochemical properties. Available characterisation data for engineered nano materials can be incongruous and there remains a dearth of standardised information on these materials. A Bayesian regression framework is developed that can help insurers and regulators make best use of this characterization data as it stands and as it becomes more available. Finally, an insurance framework is specified that includes a protocol, specified as a mark-up language, for consistently communicating complex risk information from producers and users of engineered nano materials to insurers. This framework also deploys Bayesian methods to account for unpredictable and difficult to measure ENM exposure and hazard levels for the purpose of insurance pricing. The combined contributions of this work provides a clearer perspective for insurers regarding the nature of the occupational risks stemming from ENM production and use, and offers several methodologies that insurers could adopt to aid their risk management needs in this regard.

Declaration of Originality

No portion of this work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

I hereby declare that this thesis describes the results of my own work. In accordance with principled academic observances, I have duly acknowledged the work of others where appropriate.

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Signed _____

Eamonn M. McAlea

Publications, Present and Pending

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Abbreviations

NP	Nano Particle
NF	Nano Fibre
ELI	Employer Liability Insurance
ENM	Engineered Nano Material
NM	Nano Material
NT	Nanotechnology
Sanowork	Safe Nano Worker Exposure Scenarios

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Foreword

Throughout this treatise, reference will be made to the Sanowork project from time to time. The Sanowork project examined the occupational, and in one case environmental, risk linked to six manufacturing processes

involving ENMs based on titanium, zirconium, carbon, polyamide and silver. The companies and materials involved were chosen on the basis that they are fairly representative of the sector at the present time.

Dedicated to my parents and family

1 Introduction

1.1 Overview

In 1959 the Nobel Prize winning physicist Richard Feynman presented his now landmark lecture, ‘Plenty of Room at the Bottom’, in which he elaborated on the possibility of manufacturing everyday objects one atom or molecule at a time (molecular manufacturing). His vision was to scale down industrial robots to the nanometre scale, nano assemblers, where they would construct everyday objects atom by atom from the bottom up. However, fully fledged nano assemblers and robots are still only at the speculative stage. The 3D printer is a precursor to the concept of bottom up manufacturing, now commercially available, which employs a single material, the medium, to build up 3D objects in successive layers. Although Feynman did not coin the term ‘nanotechnology’ (Norio Taniguchi, a professor at the Tokyo University of Science, first used term in 1974) his vision made nanotechnology a buzzword and launched a global nanotechnology race. Since then however, the meaning of the word has shifted. A vastly expanded definition of ‘nanotechnology’ has prompted specialists from a wide diversity of fields to adopt the nanotechnology brand.

Nanotechnology as Feynman originally conceived it, is still very much at the conceptual and basic research phase. This contrasts sharply with the increasing prevalence of engineered nano materials (ENMs) in real world applications. A risk-benefit appraisal of nanotechnology at a holistic level has to be assessed in terms of a wide spectrum of technologies under their respective risk-benefit paradigms. It can be argued that many classes of nanotechnology are inherently safe such as nano electronics in which the nano components are securely embedded in solid structures and substrates. For those more unprecedented forms of nanotechnology that are commercially available, namely ENMs, there is an acute lack of regulatory

oversight and comprehensive risk analysis frameworks. This problem is not unique to ENMs as emerging technologies in general typically evade risk assessment and regulation for considerable periods after they first appear (Salsburg 1981)

1.2 Research Motivation

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. So far the evidence that ENMs may ultimately prove detrimental to human wellbeing 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. Insurers are especially concerned about potential employer liability claims as many are seeing parallels between fibrous ENMs and asbestos fibers in terms of their experience with asbestos litigation, that for many insurers, is still a costly overhead.

With a view to helping secure the long term promise of those technologies that depend on ENMs, this thesis focuses on the issue of ensuring the sustainability of the ENM community through insurance solutions for its member companies. Given that ENMs are more likely to exist in their unbound and most concentrated forms in manufacturing environments, this thesis will furthermore restrict its focus to the insurance problem of gauging and managing the costs of occupational risk of injury or disease attributable to ENMs. In the case of consumer exposure it can be argued that exposure risk is low since ENMs are tightly bound to their host products throughout the consumer stage of their life cycle or exist as part of larger particle aggregates at the micrometer scale and beyond. For environmental exposure, there is no clear consensus on the long term impacts of ENMs. However, there is evidence to suggest that ENMs present in natural water systems contribute to larger aggregate structures composed of various

materials (Lowry and Casman 2008) and may be thus more benign since they can no longer be regarded as isolated nano materials.

1.3 Background

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 characterised by either nano scale structures or behaviours that occur at the nano-scale. 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. Examples of where technologies have rebranded themselves to avail of nanotechnology focussed funding initiatives include nano electronics, more commonly known in the past as submicron electronics. Nano structured materials have traditionally been described as ultra-fine grade materials. Nano biotechnology is synonymous with molecular biology and genetic engineering. Submicron mechanical devices have been popularized as nano machines. In non-specialist literature, the terms ‘nanotechnology’, ‘nano materials’ and ‘nano machines’ 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. As such, it is necessary to assign specific meanings to each of these terms, as shown in Table 1.a.

Table 1.a: Glossary of nanotechnology terms and definitions

Nanotechnology	General term describing any technology with Nano scale features. Observe that many relatively well established technologies already had this feature, e.g. genetic engineering, molecular biology, chemical engineering.
Parent material	Material from which nano particles and nano fibres are derived.
Nano particle/nano crystal (synonymous terms)	Particles of any material type, element, compound, crystal etc. such that all three dimensions are characteristically in the range 1–100 nano metres. Traditionally known as ultra-fine particles (UFP) or macro molecules, the majority of these particles occur either naturally, or as a by-product of human activity. In urban areas, about 70% of all air born particles are nano particles. The remainder are larger particles typically measuring in the 0.01-10 micron range.
Nano Fiber (NF)	Fibres of any material type, element, compound, crystal ect. such that at least two dimensions are characteristically in the range 1-100 nano metres. Examples, asbestos fibres, carbon nano tubes
Engineered Nano Material (ENM)	Nano particles and fibres that are engineered with desired characteristics and functions. They form the ‘building blocks’ of many other nanotechnologies and are incorporated in many conventional manufacturing processes such as plastic and ceramics production to enhance strength and durability for example.
Nano machine/ nano robot	Machine with features whose characteristic length scales can be measured in nanometres. For instance, Rice University has demonstrated a single-molecule car powered by a chemical process and including bucky balls for wheels (Boyd 2006). A Bucky ball is a spherical nano particle (NP) made from 60 carbon atoms.

More in line with the original Feynman vision and the original definition of ‘Nanotechnology’, the development of the nano machine is still at the embryotic stage. However, if realized, the potential benefits would be enormous. All human material needs could be supplied by desktop factories in which swarms of nano machines would churn out the necessities of life, heralding a new industrial revolution and raising the conditions of life for many of the world’s population. When a consumer item was no longer

needed, it could be instantly deconstructed by the same machines and reassembled into something else. Nano machines would therefore be the ultimate recyclers and manufactures. They could be programmed to rid the environment of pollutants and purify water supplies. Potential medical applications would be in the removal of dangerous plaque accumulations in the lining of arteries and organ repair and reconstruction. However, such wonderful possibilities are overshadowed by stark risks. Such machines could be malevolently programmed to wreak havoc on the environment and human populations, not unlike a biological weapon. In parallel with their development, it will therefore be important to develop an effective regulatory environment to mitigate such risks.

Nano materials are particles or fibres that are typically less than 100 nano metres in at least one dimension. Those that are engineered for specific industrial and scientific purposes 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 centimetre (Hussein et al. 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 nano particles, commonly known in this context as ultrafine particles (UFP)¹. The current phase of nanotechnology is largely based on the exploitation of properties that are unique to ENMs.

There are several historical instances of where nano-materials (NMs) have been used. Although they did not understand why their techniques worked, medieval alchemists added color to stained glass by adding gold and silver nano particles, a technique that is still in use today. It's now understood from quantum mechanics that different gold and silver nano particle 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 nano

¹ Ultra-Fine Particles are less than 100 nano metre by definition.

particles and the recipe for the mix is thought to go back to Roman times. Renaissance artists added gold and silver nano particles (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 presents 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 1980's, 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 electro spinning methods that can produce ENMs in bulk quantities. ENMs used as building blocks allow for the construction of mechanical and electronic structures at the nano scale.

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 nano particles 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 circuits. Similar to the way in which asbestos fibres behave, CNTs once inhaled tend to remain in the lungs. Their fibrous nature renders the normal lung clearance mechanisms inefficient. This can lead to fibrosis and lung cancers. It has been estimated

the average person in the industrialized world consumes trillions of nano particles per day as they are contained in many processed foods to modify textures and colour (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 nano particles in the lining of the intestine (Reijnders 2007). Carbon Bucky balls (fullerenes) can be adapted to target malignant tumours. They 'piggyback' anti-cancer drugs and deploy them at tumour sites. This has the advantage of leaving healthy cells intact. Potential side effects of this form of cancer therapy are not known. Nano materials below about 10 nano metres in diameter, once inhaled can easily pass through the lungs directly to the circulation system and other organs. Evidence suggests that smaller nano particles may persist for significantly longer periods than large particles (Han et al. 2014). For instance, one study has shown that 30 nano metre ceria nano particles were found to reside for up to 90 days in rats (Yokel et al. 2012). Recent research shows that nanoparticles less than 100 nano metres in diameter can enter cells, those with diameters below 40nm can enter the cell nucleus and those that are smaller than 35nm can pass through the blood-brain barrier and enter the brain (Dawson, Salvati and 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).

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's difficult for nanotechnology proponents to counter the 'doomsday' scenarios² 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. In this regard, an important lesson can be garnered from the GMO industry's reluctance to debate the public on the

² such as the 'gray goo' scare promulgated by the tabloid press in the 1980's. (Giles 2004)

dangers of introducing engineered genetic strains into the food chain. It assumed the public did not need to know the risks of consuming GMO foods. As a result, an alarmed public, especially in some European states, have agitated for restrictions on GMO food imports and applications of GMO technology to their respective agro sectors.

1.4 Thesis Layout

Chapter 2 catalogs the growing contribution of ENMs to the key economic sectors of energy, manufacturing and raw materials, agricultural, water management and supply, sanitation, commercial infrastructure and healthcare. In this chapter it is emphasized what is at stake in terms of economic development should the ENM industry become compromised in its ability to innovate and develop either from lack of insurance options or stiff regulation.

Chapter 3 examines the symbiosis between regulatory policies, insurance, public perceptions of risk and the legal profession. A case is made that insurers fulfill not only the role of risk underwriter, but also effectively act as proxy regulators. It is argued that if insurance is affordable then so too is regulatory compliance and vice versa. To this end, some underwriting and risk management strategies targeted at the occupational risks associated with ENM production and use are proposed.

Chapter 4 presents a case study of six manufacturing processes that are a fair reflection of the ENM sector at the present time. These process lines were the focus of the Sanowork project that funded the author's research. The first objective was the specification of an ENM hazard inference protocol that qualitatively categorizes an ENM's potential health hazard in terms of a set of key physical attributes. The tool is then validated at a phenomenological level against hazard remediation steps that are described for each of the manufacturing processes. The inference system can be used to create typologies of ENMs in terms of modes of toxicity action. The second objective is to provide a window for insurers or regulators into the

everyday activities of companies engaged in using or producing ENMs and the critical aspects of the manufacturing processes.

Chapter 5 refines the structural alert protocol of chapter 4 by addressing the problem of heterogeneous protocols for measuring ENM physicochemical and toxicity parameters. A central issue concerning the emerging discipline of nano toxicology and its adjunct discipline of nano material characterization is the problem of experimental replication. Practitioners in the field have yet to devise standardized procedures for assessing the potential hazards of nano materials which has led to several inconsistent claims in the literature regarding their toxicity and causative physicochemical features (Sophie et al. 2012). The Bayesian regression methodology developed in chapter 5 resolves this issue by optimally correlating inherently ambiguous physicochemical and toxicity measurements and provides a corresponding confidence measure.

Chapter 6 develops an insurance model that begins with some rudimentary pricing methods before culminating with an extension of the ideas developed in chapter 5 to account for difficult to measure exposure levels. The insurance model also describes a communication mechanism for conveying qualitative and contextual aspects of ENMs to underwriters that go beyond mere numerical measures of risk. This is an important requirement as underwriters need to develop a ‘sense’ of the risks they are assessing which requires them to have access to Meta and contextual data not usually available from quantitative models.

In summary, chapters 2 and 3 identify the lack of targeted insurance options for ENM producers and users as a fundamental threat to the sustainability of the sector while emphasising the potential impact this could have on the wider economy now and in the future. Chapters 4, 5 and 6 then develop a series of tools and risk assessment frameworks to help address this shortcoming

2 Nanomaterials as a New Resource Base

2.1 Overview

The Project on Emerging Nanotechnologies (2010) reports that the number of products containing ENMs already available to consumers has grown by nearly 521% from 212 products in 2006 to 1317 in 2010. The use of ENMs is not specific to any particular industry and new applications can be found across different consumer sectors ranging from food additives, cosmetics, material science (paints, plastics and ceramics), the energy sector (batteries and solar energy) and medicine (targeted drug delivery systems)(Chan et al. 2008; Chen 2008; Huang 2006; Koo, Rubinstein and Onyuksel 2005). It is important to note that the majority of ENM companies are small to medium enterprises and are driving much of the innovation in the sector (Carroll, Anthony et al. 2015). Thus the vitality of this industry may be sensitive to possible regulatory overhauls or issues surrounding its insurability in the future.

Adequate availability of energy, housing, water, food, healthcare and sanitation is required to maintain a healthy and therefore productive population. A society's productivity and resource bases have to cover the cost of current needs and fund, both directly and indirectly, the cost of research and innovation to create new resource platforms for future generations; through economic attrition, raw materials, agriculture and non-renewable energy sources are being irreversibly drawn down. ENMs are increasingly playing a significant role in the provision of these fundamental economic inputs and moreover hold the potential to alleviate the pressure on existing raw material, food and energy sources. In view of the pivotal role of energy for economic growth, ENMs are contributing to the direct production of energy in for example solar technologies and indirectly through improvements to net energy output³; for instance, ENM based coatings

³ The production of energy requires the consumption of energy, leaving a net energy balance for all other needs. Energy consumption in relation to production manifest as

enhance the resiliency and lifetimes of steam driven turbine blades and associated gearing and bearing systems for electricity generation.

On the other hand, with the use of ENMs comes an array of human and environmental risks that need to be assessed in relation to the potential benefits. For instance, there is the cost of loss of human/intellectual capital through accidental and prolonged exposure to ENMs with unknown health effects in terms of morbidity rates, mortality rates and changes in cognitive abilities⁴; the expected prohibitive recovery costs of low density distributions of ENMs based on rare elements such as gold and silver embedded in nano enabled products etc.; the potential cost of environmental loss as a result of ENM pollution from landfills etc., possibly manifesting in the losses of agricultural land or areas for human settlement.

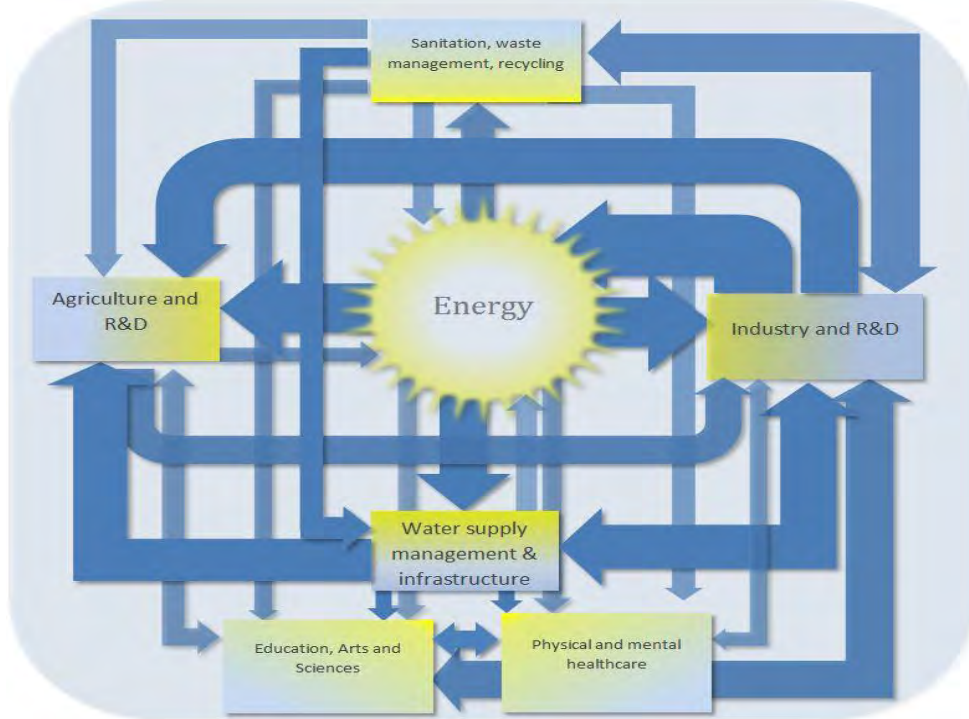
The remainder of this chapter is organized as follows: For each of the economic sectors depicted in Figure 2.a, the author explores the contribution made by the ENMs investigated as part of the Sanowork project and similar ENMs in the context of risks and benefits at a macroeconomic level. This follows with a brief assessment of potentially positive political risk outcomes from the ENM industry and how it may be threatened by unresolved regulatory and insurability issues which are the subject of chapter 3.

construction, maintenance and decommissioning costs aggregated over the entire supply chain for energy producing and distribution systems.

⁴ As an analogy, some evidence indicates that trace element exposure may effect cognitive functions Emsley, C. L., S. Gao, Y. Li, C. Liang, R. Ji, K. S. Hall, J. Cao, F. Ma, Y. Wu, P. Ying, Y. Zhang, S. Sun, F. W. Unverzagt, C. W. Slemenda, and H. C. Hendrie, 2000, Trace Element Levels in Drinking Water and Cognitive Function among Elderly Chinese, *American Journal of Epidemiology*, **151**, 913-920.

2.2 Economic Foci

Figure 2.a: Depicted are the primary sectors of a modern agro-industrial economy and corresponding interdependencies. The blue arrows represent capital transformation relationships in which the thickness of the arrows signifies the expected magnitude of the transformation. In addition to being the sources of new forms of capital, ENMs are expected to play an important role at enhancing the efficiency of existing capital transformation and formation processes.



2.2.1 Energy applications

The International Energy Agency (IEA) has estimated that global energy consumption can be reduced by one fifth as a result of efficiency improvements to energy technology (Christian et al. 2013; Nano-Connect-Scandinavia 2009-2012). Nanotechnology enables large energy and cost savings, especially in the building, transportation and manufacturing industries. Technologies utilizing ENMs for direct energy production; conversion, storage, distribution, and consumption are being rapidly developed and deployed. ENMs indirectly contribute to net energy availability by reducing construction, maintenance and decommissioning costs for energy generation infrastructure; it's important to consider the net power generation after accounting for the investment (input energy) that is

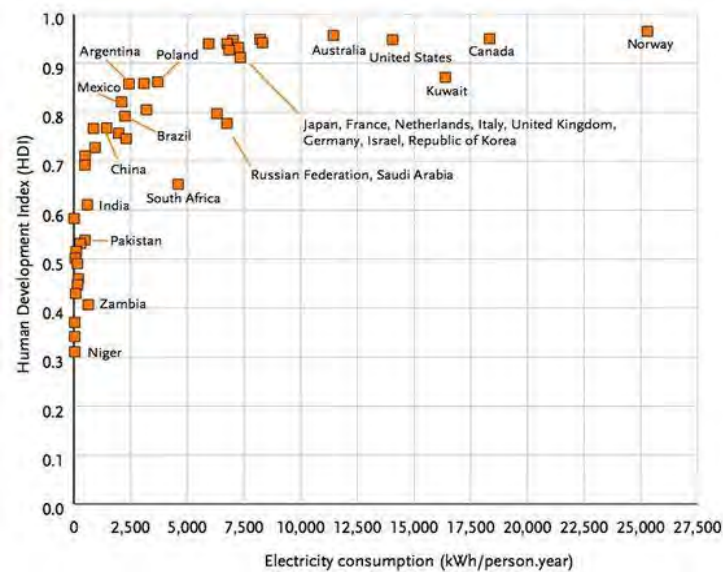
required to bring capacity online, maintain it and eventually decommission it at the end of its life cycle. The latter is mostly due to better use of existing material inputs and reduced hardware attrition and frictional losses from the wear of moving parts, for example, in the gearing and torque transmission systems in wind turbines. For the same reason, energy consumption can be reduced in other economic sectors through ENM applications, particularly in manufacturing, agriculture and construction.

A number of metrics based on physical quantities are available to express economic wellbeing other than monetary based GNP figures which are susceptible to distortion due to the vagaries of currency manipulation, the variation of the money supply with economic cycles⁵ and the base money creation policies of central banks. A more insightful measure of actual living standards is an economy's net energy generating capacity per capita, or simply, the average external usable power available to each member of society (Joyeux and Ripple 2007). This measure expresses itself in other standard of living indices such as available food and water, both potable and for agro-industrial uses per capita, and various commodity basket indices which together determine a region's maximum population carrying capacity⁶. That energy availability per capita correlates with living standards is empirically well established as shown in Figure 2.b

⁵Within debt based monetary systems, the greater part of the money supply is created and enters circulation via loans whose issuance times tend to cluster as a result of competition between lenders. Since most loans from different institutions are similarly structured, it follows that loan repayment schedules will also cluster. The net effect of this dynamic causes the overall money supply to first rise during the issuing periods and then fall as loans are repaid. This periodic rising and falling of the money supply in circulation corresponds to periods of inflation and subsequent deflation accounting for the classic business cycle of 'boom and bust'.

⁶ This assumes that an economy is configured for the maximum transformation of available energy into consumer and capital goods and services.

Figure 2.b: Relationship between human development index (HDI) and per capita electricity consumption 2003-2004.



Source: <http://osqar.suncor.com/2010/12/is-there-a-link-between-energy-use-and-standard-of-living.html>

Specific examples of energy technologies incorporating ENMs that either produce energy or lead to net increases by improving energy efficiencies or by reducing losses include photo voltaics; super-capacitors; nano-electrodes which improve battery capacity and energy delivery (Bruce, Scrosati and Tarascon 2008); improved thermal insulators made from aerogels with nanoscale porosity; light weight nano composites; and low friction lubricants.

Electrical transmission lines suffer approximately 5% losses per 100 miles. Special carbon nano tubes (CNTs) known as armchair nano tubes offer alternative conducting mediums with efficiencies which for example are ten times greater than copper, have greater tensile strength and are much lighter thus requiring fewer supporting towers (Elcock 2007). An additional 7% of electrical distribution losses are attributable to leakage currents to ground via high tension insulators in pylon connectors and connectors in substations. Dielectrics based on polymer nano-composites offer better insulating properties as well as greater breakdown thresholds in the extreme

electric field environments of high voltage transmission systems (Dissado and Fothergill 2004). In the area of renewable energy there are a myriad of applications. For example, the energy harvested by a wind turbine blade is proportional to the square of its length. Ordinarily, the gains from large blades come at the cost of their increased weight, implying higher manufacturing and maintenance costs. ENM based composites with high strength to weight ratios enable larger blades to be constructed with only moderate increases in weight. Hydrogen generation as a means of storing energy is currently limited by the low energy density of hydrogen with respect to volume as determined by safe storage pressures and temperatures. Hydrogen containment mediums based on lightweight ENMs with excellent tensile strengths are set to alleviate these storage limitations (Niemann et al. 2008). Thermo electric applications which convert waste heat to electricity has been traditionally limited by low conversion efficiencies until the application of nanostructures significantly improved performances (Park et al. 2014). Similarly, nano-generators based on piezoelectric ENMs such as zinc oxide nano-wires convert surplus mechanical energy to electricity. Catalytic promotion of energy conversion through chemical reactions can be significantly enhanced by using catalysts with nano-scale features. The high surface to mass ratio of the nano metric forms yield much higher reaction rates for a given catalytic mass since catalytic activity in these instances is largely a surface phenomenon. For example, TiO₂ nano fibres facilitate the electrochemical photolysis of water to produce hydrogen (Mao, Shen and Guo 2012). Substitute materials allow for net improvements to energy supply as a result of cheaper production costs, a major component of which is energy consumption. For instance, grapheme may be used as an alternative to indium tin oxide, an otherwise scarce material, to produce transparent electrodes in solar cells (Wassei and Kaner 2010). Research and development of nuclear energy has experienced a renaissance in recent years, largely due to contributions from China, India, Russia, South Africa and Argentina. The efficiency of nuclear energy generation is constrained by three primary factors: the efficiency of energy extraction from nuclear fuel, the operating lifetime of nuclear energy infrastructure and the costs of waste processing and remediation of associated environmental risks. ENMs

are finding applications that address problems in each of these areas with the aim to improving the overall cost effectiveness of nuclear technology (Shi et al. 2014).

2.2.2 Healthcare

ENM applications offer the possibility of enhanced medical treatments, lifetime extension and reduced medical costs. Examples of applications in this area include: ENM coatings such as those based on zirconium that improve biocompatibility between implants and their hosts, reducing the risk of adverse immune responses (Afzal 2014); silver based solutions that are known to be highly toxic due to presence of un-reacted silver ions are thus recognized for their antibacterial uses. Silver ENM coatings of surgical instruments, wound dressings and ceramic tiles help maintain sterile environments and temper the proliferation of antibiotic resistance bacterial strains such as the MRSA bacterium (Bandow and Metzler-Nolte 2009; Tofail, O'Brien and Craighead 2011). Filtration systems based on polyamide nano fibres can remove reactive compounds and bacterial contaminants from circulating airflows. The photo catalytic properties of TiO₂ nano particle coatings allow for self-cleaning surfaces that breakdown organic contaminants. In addition to health benefits, this also reduces cleaning and maintenance costs. However such materials may be inherently toxic to humans. At a general level, there is the potential cost of lost productivity and healthcare costs from impaired cognitive functions and increased morbidity and mortality following prolonged exposures.

2.2.3 Sanitation/waste management/environment

ENMs have found application in environmental remediation and clean-up operations following hazardous spills etc. For instance, ENMs and dependent technologies have great potential to advance water treatment and aid environmental remediation efforts. Current innovations include ENM based membranes, adsorbents, and catalysts for water treatment or groundwater purification. Such benefits must however be evaluated in the context of the risk these materials may present. In particular, an increased production of ENMs will likely lead to the introduction of these materials into ecosystems, the long term impacts of which are not presently known.

Secondary environmental impacts from ENMs may originate from the industrial wastes that are generated from the manufacture or uses of ENMs (Hillie and Hlophe 2007; Tarabara 2013; Vaseashta 2010; Wiesner 2011). However, it's important to note that even though the effects of ENMs accumulating in the environment remain unknown, there is some evidence to suggest that common ENMs found in the environment only exist as part of larger aggregates and clusters (Lowry and Casman 2008), which may render them more benign than their isolated counterparts.

2.2.4 Agriculture

ENMs are being used in the production of pesticides and fertilizers and as bio sensors for pathogen detection and for monitoring soil conditions: nano particles (NPs) can deliver pesticides to selectively target crop pathogens and deliver fertilizers to key growth centres in plants. Indirectly, as surface coatings to enhance longevity of moving parts subject to wear and attrition from frictional resistances, they may contribute to production efficiency by reducing maintenance, downtime and replacement costs for agricultural machinery (Jie, Jose and Jorge 2013; Khot et al. 2012)⁷.

2.2.5 Water management & infrastructure

Fresh water supplies from tapped sources are limited in relation to an ever expanding global population. Untapped sources constitute about 98% of fresh water supplies such as those locked up in glaciers and the huge snow-melts that flow from the Canadian Rockies to the Pacific Ocean each spring. Difficult to access potable water is a leading cause of childhood mortality and disease across the developing world (Pickering and Davis 2012) and existing infrastructure in many 'developed' regions is in need of upgrade and repair (Cohen 2012); a deficit of water storage, retention and distribution infrastructure such as dams, locks, canal networks and desalination facilities in arid regions mean that extreme weather patterns either render existing flood protection barriers inadequate or create water shortages in times of drought. It's important to note that the lion's share of

⁷ It's important to differentiate the role of ENMs in agricultura from bio tech and genetic engineering that are sometimes included under the umbrella term 'nanotechnologies'.

fresh water in the U.S. for example is used for agriculture (including irrigation) followed by industry which includes a significant use of water as a coolant for electricity generation equipment (thermoelectric), as shown in Figure 2.c

Figure 2.c: Water use in the United States.



Source: <http://water.usgs.gov/edu/qa-usage-freshwater.html>

Approximately seven tenths of the earth's water is locked up in the oceans. Desalination technologies coupled with renewable energy technologies and recent advances in nuclear energy present the possibility to fully exploit this abundant source⁸. ENMs promise to play an invaluable role in desalination methods. For example, the superior separation and transport characteristics of CNTs make them particularly suited for high efficiency desalination systems in terms of energy consumption and maintenance costs (Goh, Ismail and Ng 2013). Indirectly via energy applications described previously, ENMs will contribute to fresh water generation from saline sources. The combination of small quantities of ENMs to cement as well as nanostructured cement materials improve compressive strengths and anti-corrosion properties of concrete, leading to smaller material and energy inputs for construction and maintenance of water management infrastructure for which concrete is a major requirement (Sobolev et al. 2008). Also see section on applications to commercial infrastructure.

For instance, the development of the much safer pebble bed reactor; improvements in breeder reactor designs which utilize so called 'nuclear waste'; and the thorium reactor, considered inherently stable and based on a fuel three times more abundant than uranium.⁸

2.2.6 Manufacturing, mining, mineral exploration

Despite iron being the fourth most abundant element in the earth's crust, the amount of high grade ore that can be commercially mined is limited (Pincock 2010; Sylvester, Brian 2010). To make the mining and processing of lower grade ores economically viable, greater extraction and processing efficiencies principally in terms of reduced energy consumption and hardware attrition will need to be brought online. It's in the area of such efficiency improvements where ENMs are playing an important role, for example in the form of zirconium based coatings to produce harder, sharper and more durable cutting tools for boring machines and pulverisers that require less energy to operate and experience less downtime, maintenance and replacement costs etc. (Wong 2012). For similar applications in the oil exploration industry see (Nabhani and Emami 2012). Similarly, essential rare earth minerals while relatively abundant in the earth's crust remain expensive due to the low availability of ores of sufficient grade that can be cost effectively recovered (Liu et al. 2013). Furthermore, even if it's not possible to enhance the global yield of essential industrial inputs using nanotechnology or other means, the possibility remains that ENM alternatives will eventually replace them (Liggett 2011; Piesing 2013). It's in this context where there is also the threat of resource depletion and the need to develop cost effective recovery methods for low density distributions of ENM forms of already precious metals such as gold, silver and palladium in nano enable products at the end of their life cycles. In short, ENM applications to raw material mining and ENM substitutes for rare but essential industrial inputs could have the same transformational effect on manufacturing and industry as advancements in crop science had on agricultural productivity as exemplified by the development of crop varieties that are able thrive in arid soils.

2.2.7 Domestic housing and associated infrastructure

ENMs are poised for widespread use in the construction industry where they can offer significant advantages for a variety of applications ranging from making more durable concrete to self-cleaning windows. As mentioned previously, widespread use in building materials comes with potential

environmental and health risks when those materials are thrown away. Quoting from (Lee, Mahendra and Alvarez 2010),

nano materials can strengthen both steel and concrete, keep dirt from sticking to windows, kill bacteria on kitchen work surfaces and bathroom interiors, make materials fire-resistant, drastically improve the efficiency of solar panels, boost the efficiency of indoor lighting and even allow bridges and buildings to "feel" the cracks, corrosion and stress that will eventually cause structural failures.

2.2.8 Commercial infrastructure

Exposed infrastructure that may be vulnerable to the elements, such as bridges and canal locks, is already being treated with ENM enabled long lasting paints and coatings, requiring fewer applications (Dubbert et al. 2014; Naganathan et al. 2014; Olar 2011). Quoting from (Dubbert et al. 2014),

Applications of engineered nano materials can also provide breakthroughs in commercial infrastructure by reinforcing mechanical properties, decreasing vulnerability to chemical corrosion and accidental damage, and providing supplementary functions such as anti-bio fouling and hydrophilicity.

Commercial infrastructure consumes large quantities of concrete and asphalt: ENMs can be used to inhibit corrosion of reinforced concrete (Koleva); small amounts of nano-clays added to asphalt pavements increase viscosity and reduce deformation in hot weather, resulting in cheaper maintenance overheads and extended utility from road networks as well as reduced vehicular damage and corresponding passenger and freight transport costs (You et al. 2011). But commercial infrastructure projects that incorporate ENMs could be a significant source of environmental exposure. To exploit the benefits of ENMs while managing potentially crippling backlashes from watchdog groups etc., efforts will be needed to monitor and publicly disseminate the environmental impacts of ENMs that are used in typically high visibility infrastructure projects.

2.3 Political Risk Implications

Much of the foreign policy of western governments has always focussed on key natural resource locations to supply the needs of their respective economies. This gives rise to the potential for conflict among the major governments vying for access to these locations as well as conflict with the host countries themselves that are often the target of colour revolutions and subversive politics instigated by outside interests (Kissinger 1974) . Thus from an insurers perspective, alleviating the scarcity of key raw material and mineral supplies for manufacturing and non-renewable energy sources by the means outlined in the previous sections, offers the prospect of greater prosperity and international stability.

2.4 Impact on Insurers and Regulation

Most of the above applications will have an impact on insurers and will likely be subject to eventual regulation. For example, CNTs, when combined with ceramics and plastics imbue these materials with added strength and durability. This will indirectly benefit insurers and their customers since stronger materials would have in some instances a direct bearing on property related risks and allow for cheaper policies (e.g. nanomaterial enabled fire retardants). Similarly, the health benefits following from medical applications may eventually lead to cheaper health and life insurance.

The majority of ENM producers are small to medium enterprises and are arguably responsible for many of the innovations occurring in the sector (Carroll, Anthony et al. 2015). In the absence of actual risk data, perceived dangers coming from the use of ENMs may exaggerate the real risks and prompt costly but unhelpful regulation or exorbitant insurance costs, reflecting the precautionary principle. The latter would hurt small companies and lead to losses of competition and market share to larger companies with the accompanying decline in innovation and product stagnation. Such issues are examined in the next chapter which explores the roles of regulation and insurance in the ENM industry and their relationship to one another in the context of risk perceptions and evolving legal definitions of injury.

2.5 Summary

At a general level, the long term benefit of ENMs will principally be felt as economic and societal gains and attenuations in political risks deriving from the following sources: reductions in the material needs and maintenance costs of commercial infrastructure, the construction industry and agro-industrial hardware; as facilitators of energy, water and food supplies; as substitutes for difficult to access raw materials; and from healthcare applications. However, such benefits ultimately depend on the availability of ENMs, most of which are currently supplied by small to medium enterprises. One potential scenario playing out that could derail the vitality of these companies and therefore the promise of ENMs as a new resource base would be an onslaught of prohibitive regulatory overheads or insurance costs stemming from a lack of relevant risk data. The potential ramifications of this issue if left unresolved are explored at length in the following chapter

3 Engineered Nanomaterials: Risk Perception, Regulation and Insurance.

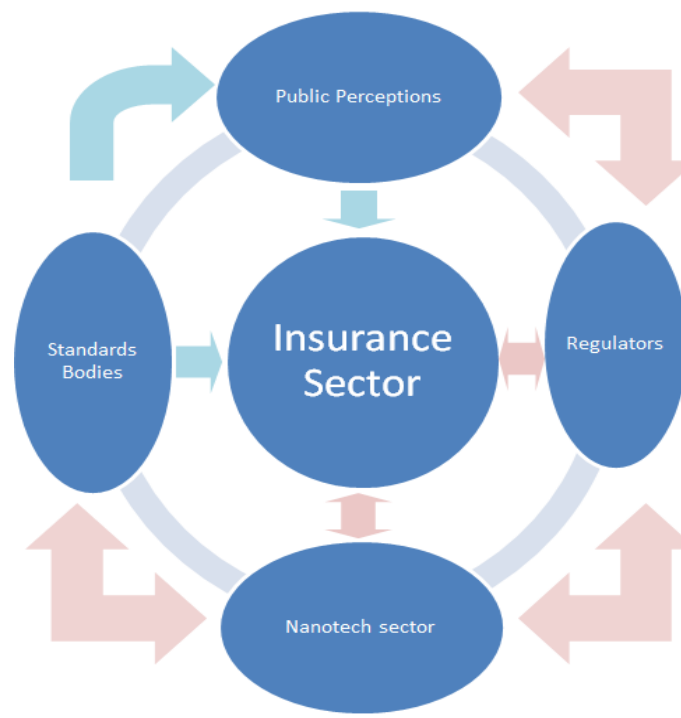
3.1 Overview

Concerns surrounding the health risk of engineered nano materials from public interest groups, the lack of suitable regulation, an environment of legal uncertainty driven by ever changing legal definitions of injury and the lack of specifically tailored insurance products targeted at occupational risk for the ENM sector are putting the industry's long-term economic viability at risk. There is interdependence between risk perceptions, regulation, the legal profession and insurability; in this emerging and fast changing space, regulators are failing to keep pace and hence risk perception among the above stakeholder groups remains a stubborn problem. In the absence of well-developed regulatory protocols, the insurance industry has come to occupy a key role as an effective lobby in terms of improved occupational risk management practice. The failure of regulators and prominent industry participants to create uniform standards for ENMs creates an environment of uncertainty for all stakeholders. The latter not only causes problems in term of risk transfer but may lead to ill-conceived regulatory requirements, potentially exhausting resources and stifling innovation in the sector. In the absence of targeted regulation and standards, the insurance industry will continue to do what it has always done. It will insure uncertain risks based on risk appetite and a careful consideration of worst case scenarios, although in the short term this will likely entail high insurance premiums, reflecting the cost of uncertainty (Shang and Chen 2012). In this regard insurers effectively act as proxy regulators and beacons of assurance to those individuals and groups who share concerns about the human and environmental threats they perceive coming from emerging technologies.

Figure 3.a illustrates how key centres of civic influence and decision-making can mutually effect and benefit one another through multiple self-reinforcing feedback loops. For example, this can happen through the

sharing of risk information and proposals for standard operating procedures (SOPs) etc.

Figure 3.a: Illustrated is the mutual interconnectedness between perceptions of nanotechnology related risk, regulators, Insurers, standards bodies and the nanotechnology industry. It can be argued that insurers play a crucial role in defining and shaping these relationships. For example, the provision of insurance acts as a proxy regulator for official regulators by signaling that the insurability of risks renders them manageable and therefore amenable to regulation. This would tend to have positive impacts on public perception that would only be of benefit to insurers. For example, insurers involved in litigation are sometimes at the mercy of juries whose members' opinions reflect the prevailing views of the wider public in relation to perceived risks. Generally speaking, the effects that insurers set in motion are such that they eventually reinforce and support the positions they have taken (see section 3.3). There are exceptions to the latter however, for instance, insurers' long history with asbestos litigation



It's important to note that the synergistic potential depicted in Figure 3.a may only be effective at managing and insuring short term (acute) exposure risks. Longer term risks (chronic), typified by long latency periods after exposure before injuries would be expected to manifest, present a more challenging problem. However, understanding and managing the short term risks provides a solid foundation for the study and control of chronic risks. Regarding the latter, one promising line of inquiry that will be explored in

this chapter concerns the potential use of ambient nano sized (ultrafine) air pollution particles as reference materials that have characteristics similar to common engineered varieties of particles for which long term exposure risk information is required; epidemiological studies have suggested that these ultrafine particles are a significant contributor to morbidity and mortality rates in the exposed populations (Calderón-Garcidueñas et al. 2008; Robert D. Brook 2004; Schwartz 2000)

In the meantime, insurers will presumably muddle through by employing less than ideal non-actuarial methods for managing long term risks, particularly the kind that accumulate over long periods and then crystallize over short periods as typified by the health risks linked with asbestos exposure. The latter are potentially catastrophic to those insurers who are exposed to them. In chapter 6 a Bayesian based framework is described that can rigorously model these long term risks. Common strategies employed by insurers to help manage catastrophic risk include catastrophe bonds and reinsurance that help insurers divest their balance sheets of over exposed risk positions by sharing them with other insurers or speculative investors. Examples of catastrophic risk include flood and earthquake risks, risks for which many insurers would be too undercapitalized to cover.

3.2 Context and Current Practice

The insurance community, regulators and public interest groups are concerned about the toxicology and exposure risks of ENMs (Allan, Anderson and Petersen 2010; Boholm 2012; Marchant, Sylvester and Abbott 2008; Maynard and Aitken 2007; Stampfli, Siegrist and Kastenholz 2010; Valverde and Linkov 2011). For nanotechnology to flourish there needs to be an understanding of both the short term and, more importantly, long term risks of human exposure to these materials. The benefits of such risk assessments are threefold: Regulators can optimally regulate the sector (in the absence of risk data, regulators may over regulate and consequently stifle innovation and product development). Secondly, insurers will be able to provide employer liability protection at a reasonable cost to

nanotechnology companies. This would help address the concerns of potential investors who regard insurance as a prerequisite. Thirdly, aided with knowledge of long tail risk, nanotechnology proponents can diffuse public anxieties and concerns over this emerging technology. The attitudes of regulators, insurers and public interest groups are inter-related and in order for nanotechnology to be put on a sustainable path all three need to be reassured as to the nature of the long term risk. Even in the absence of risk data and standardized workplace practices, insurers continue to engage with nanomaterial producers and users to help facilitate their risk management needs; insurers are basing their decision to sell policies on risk appetite and statutory reserve requirements to manage maximum loss scenarios (Mullins et al. 2013). That said, there is no reason to believe that this will always be the case, and insurers could in the future become reluctant to underwrite these risk categories (Meder 2010). In this context, this chapter discusses how risk transfer from the nanotech sector to the insurance industry might be facilitated. The author suggests strategies designed to address short and long term risk management in order to facilitate risk transfer across this spectrum.

Manufacturers have risk exposures at all stages of their product life cycles in terms of occupational health, environmental impact, product recall, public liability and patent infringement. Insurers need to employ separate methodologies and paradigms to address each risk category (Robichaud et al. 2005). Many risk categories, such as product recall risk, are at least diversifiable and are therefore easier to insure. Short term risks also tend to be diversifiable and insurable. In the context of nanotechnology, it is the unbound nanomaterials (materials that are either aerosolized, in liquid dispersants or in powder forms) that present the greatest potential for long term aggregate risk to human health. Given that these are most likely to be found in manufacturing environments (Bronikowski et al. 2001; Howard et al. 1992), the focus of this chapter is on the insurability of occupational risk from nanomaterial exposure.

The predominant approach for insurers to calculate premium rates is to use

actuarial methods (Rejda and McNamara 2013). The actuarial method for calculating premiums requires the total value of all premiums contributed by policyholders to equal the expected pay-outs resulting from claims filed, plus a moderate commission for the insurer. The key metrics to be determined are the probability of losses and the expected size of losses. The simplest method for estimating premium rates is to use existing claims data (claims experience) to statistically infer future losses.

Given that nanotechnology is an emerging technology, insurers have limited claims experience for underwriting policies related to it utilizing actuarial methods, partially explaining their hesitance towards the sector. Regulators often fail to recognize nanomaterials as a new class of material and are attempting extensions of existing regulations relating to the parent materials (Valverde and Linkov 2011). However, these attempts are having difficulties in taking account of the idiosyncrasies unique to nanomaterials. Additionally, there is a need for a comprehensible and unambiguous terminology for underwriters to rigorously describe nanomaterials in insurance contracts and for regulators to draft precise regulation concerning the handling and transportation of nanomaterials (Klaessig, Marrapese and Abe 2011).

Acute or short term risks tend to be diversifiable, non-aggregate and non-*systematic*. Owing to a lack of historical exposure and hazard data, they are not quantifiable at this point. However, by definition, acute risks are a function of short term observations and this will allow for their actuarial estimation in the near future. Policy limits are largely determined by maximum loss scenarios. Severe Acute Risks (SARs), not covered under the general liability policy, can be covered under specially tailored policies. SARs are typified by rare but potentially very hazardous industrial accidents that would have a limited impact on neighbouring businesses and the environment but would be expected to incur large losses for the insured. The release of highly toxic material in a contained and secure laboratory is an example

Chronic or long term aggregate health risk cannot be managed within the

actuarial paradigm. If the nanotechnology sector is unable to transfer this risk type to the insurance sector, then the risk would be carried by the industry itself. Chronic risk is inherently less diversifiable than acute risk as chronic risks are characterised by correlated incidents. For insurers, regulators and public policy makers, they are a real cause for concern. Chronic health risk is an instance of long tail aggregate risk (non-diversifiable and possibly catastrophic risks that accumulate over an extended period).

Quoting from (Chatterjee 2009), '*Carbon nanotubes have been shown to have asbestos-like impacts on mice*', reveals that insurers are aware of the similarities between asbestos fibres and fibrous nanomaterials both in terms of their shape and modes of toxicity action. These parallels are well established in the nano toxicity literature, for example (Kisin et al. 2011; Palomäki et al. 2011; Turci et al. 2012). Hence the concerns insurers have about the chronic health risk from these materials can be understood in terms of their extensive experience with financially burdensome asbestos related litigation (Carmean 1995). As a result of the accumulated health risks to asbestos exposure and the waves of litigation that followed, many of the Lloyds syndicates experienced unsustainable losses. see (Fink 2010) and '*How asbestos brought Lloyd's of London to its knees in the 90s*' [The Telegraph 2011]. The combination of this institutional memory, high levels of risk perception among the lay community (Sheetz et al. 2005) and an absence of robust international regulatory frameworks place the insurance community in a difficult position. This is reflected in present practice whereby the insurance market does not have pricing and selection models for long tail nanomaterial exposure risks. Exposure to nanomaterials is generally neither explicitly included nor excluded from general liability policies. That said, some insurers having been making efforts to remedy this.

Data from research institutions is actively being harvested by insurers for future business opportunities (KIM 2010). Lexington Insurance, beginning in 2010, has been providing a nanotechnology risk coverage product to

companies domiciled in the US (Monica 2010). According to its promotional literature, Lexington works with legal expertise in defining suitable language for the wording of contracts, consults with toxicologists in assessing hazard threats of the relevant materials and provides on-site assessments to observe handling and manufacturing procedures. Laplaya are offering a specific product for nanotechnology companies. Zurich is developing a tool, 'The Zurich Nanotechnology Exposure Protocol', in collaboration with Intertox, a Seattle based health consultancy, to gauge the hazard potential of nanomaterials. Zurich is also represented in the American National Standards Institute's (ANSI) accredited U.S. Technical Advisory Group (TAG). Zurich claims to closely observe regulatory proposals from around the world and 'seeks to inform the debate when a risk management perspective seems needed' (Joseph A. Clark 2009). Lloyds of London is also engaged in the field of nanotechnology and published a 2007 report outlining pre-emptive risk mitigation strategies (2007).

All nanotechnology related risks, currently unknown, are implicitly subsumed under general liability policies (Fink 2010; Ginsberg 2010). This presents litigation risks to both the insurers and the policy holders as 80% of occupational disease claims are challenged in the courts (Levy et al. 2011). For example, general liability insurance in many instances excludes pollutants from coverage, an insurer could argue that exposure to toxic nanomaterials was pollutant exposure and it therefore should not be liable for damages. Within common law jurisdictions the probable outcome of such a dispute has no precedent; it has been argued that the courts would likely side with the insured, refuting the insurer's likely argument that nanomaterials could be considered pollutant (Ginsberg 2010). On the other hand, it has also been argued that such an outcome is not guaranteed (Popovsky 2011). This current state of affairs regarding legal uncertainties ultimately poses a long term threat to the sustainability of the nanotechnology industry.

Despite their current inability to isolate the long term risks attributable to nanomaterials, insurers are adept at using non-actuarial techniques to

manage other categories of long tail risks such as earthquake and flood risks. For instance, they can avail of reinsurance⁹, catastrophe bonds¹⁰ and/or government backed schemes to cover catastrophic loss¹¹. The risks covered by reinsurance are typically only regionally catastrophic and have a degree of diversification at the national and transnational levels that are exploited by judiciously spreading these risks among independent and geographically diverse insurers. Arguably, and assuming that ENM production and use becomes a global phenomenon, the long term risk presented by occupational exposure to ENMs is potentially globally catastrophic to insurers. Therefore the application of reinsurance would not be appropriate as many insurers would be exposed simultaneously. Government schemes and state operated insurers typically try to keep premium rates affordable. In the context of nanomaterial exposure, this could be construed as a subsidy and a socialization of the costs of catastrophic risks should they ever crystallize. Political demands for more regulation and higher insurance premiums for the affected industries could follow, thus undermining their economic impact and competitiveness. In principle, catastrophe bonds could be used but the returns investors would likely seek to offset the potentially large downside of the insured risks would tend to render uneconomic the cost of insuring against them. Essentially, catastrophe bonds represent a form of financial engineering to manage catastrophic risk; it's within a financial engineering context that the author subsequently outlines a potentially more cost effective approach that utilizes financial derivatives to manage the long tail exposure risks presented by ENMs.

The remainder of the chapter is organised as follows; the next section

⁹ To mitigate risks to large loss scenarios, insurers can sell a portion of these risk types to other insurers (reinsurers) and thus reduce the seller's exposure to potentially ruinous losses.

¹⁰ A catastrophe bond (Cat Bond) is an investment product that allows an insurer to transfer risk to investors (Stone, Robert 2012)

¹¹ The Price Anderson act of 1957 provided government insurance for nuclear power operators to transfer the catastrophic component of their operating risk (Dubin and Rothwell 1990)..

provides an overview of the perceived risks in the manufacture and end use of ENMs. In the context of cultural backgrounds and related risk perceptions, the author identifies symbiotic relationships between the concerns of public interest groups, effective regulation for nanomaterials and well-tailored insurance coverage for nanomaterial exposure risks. This is then followed by proposals for nanotechnology companies to manage and communicate short term risks to insurers, regulators and public interest groups using control banding and risk mitigation at source methods. In the absence of historical risk data, the author identifies some existing alternatives for insurers to manage long term risks. Finally, the author proposes a non-actuarial method within a financial engineering paradigm for insurers to hedge against fluctuations in market expectations of the costs of these risks.

3.3 Risk Perception

Insurance companies need to be alert to changes in public perception regarding nanotechnology risk (Currall et al. 2006; Freeman P and Kunreuther H 1996; René Zimmer, Rolf Hertel and Böl 2009; SatterfieldTerre et al. 2009; Sheetz et al. 2005; Sylvester, D. J., Abbott and Marchant 2009). A listed insurer or one that's privately held and seeking to issue debt in the financial markets, would need to consider the public's perception of its nanotechnology related exposure. Regardless of the actual risk levels, such perceptions would have a direct bearing on its market valuation or the cost for it to issue debt. Risk perceptions, on occasion, merit as much consideration as actual risk levels. In the absence of wholly rational and objective analysis, the public assesses the risks of new technologies on the basis of cultural values, societal attitudes and the media, itself a reflector and influencer of attitudes and values (Marchant, Sylvester and Abbott 2008; Schummer 2011; Viklund 2003). It is also worth noting that underwriters themselves are influenced by their cultural backgrounds and the widely held views in the communities they occupy. For example, facilitated by a cultural deference to science and scientists, China's

dominance in nanotechnology is promoted by the state as a national goal (Appelbaum and Parker 2008). To quote from Schummer,

Once nanotechnology is made a national prestige object, the perception of ethical issues changes because it stands for something that is considered intrinsically good, such that any criticism would seem to undermine the cultural basis of values. There is some evidence that nanotechnology is also becoming a national prestige object in other countries, including fast developing ones like South Korea and China.

By contrast, the western public, exposed to the concerns of public interest groups and occasionally alarmist accounts of the hazards of emerging technologies, tend to hold conflicting views regarding the risks and benefits of science and technology. This is no less true for emerging fields such as nanotechnology¹² and genetically modified organisms (GMO).¹³ Such views are explored in Pidgeon et al. 2009 in which differences in perceptions of nanotechnology risks within and between surveyed groups in the UK and US were measured in detail. In particular, it was found that concerns were more differentiated with respect to application rather than nationality, with both groups embracing energy technologies, while being less certain about applications in *'health and human enhancement'*. At the national level subtle differences did exist however; in general, it was found that US participants were to an extent more embracing of nanotechnology than the UK audience which the authors attributed to past regulatory failures in the UK. It could be argued that western ambivalence towards emerging technologies has been influenced by postmodern environmentalism that generally has been more politically received in developed regions. Typified by organisations such as Green Peace, the World Wide Fund for Nature (WWF) and the Campaign for Nuclear Disarmament (CND), environmentalist groups engendered a public wariness of science and technology in general but particularly nuclear technology (Moore 2005).

¹² One such example was the 'Grey Goo' scenario that gained some media attention during the 1980s' (Giles 2004)

¹³ GMO foods have now been banned in a number of countries (Meyer).

Nuclear technology in the context of the cold war and its threat of *Mutually Assured Destruction* (MAD), only served to heighten anxiety in the public mind about the dangers of ‘out of control technology’. To a lesser extent, the debate on the merits and perils of science and technology in western society can be traced back to much earlier times. For example, (Hammond 2004) perceives the monster in Mary Shelly’s *Frankenstein* as representing the unforeseen consequences of the scientist’s supposedly good intentions.

Motivated by alarmist levels of perceived risk, public interest groups can organize to create political pressures that may result in burdensome regulations being imposed on the industry or even having the production of certain nanomaterials banned. This could undermine innovation by diverting research and development budgets to fund compliance with ineffectual regulation. Insurers occupy an interesting position in this regard. In terms of risk management in society, they are one of the key stakeholders. Their ability to manage risk could go some way to allaying the fear of the wider society; to quote from (Stone, Deborah 2002),

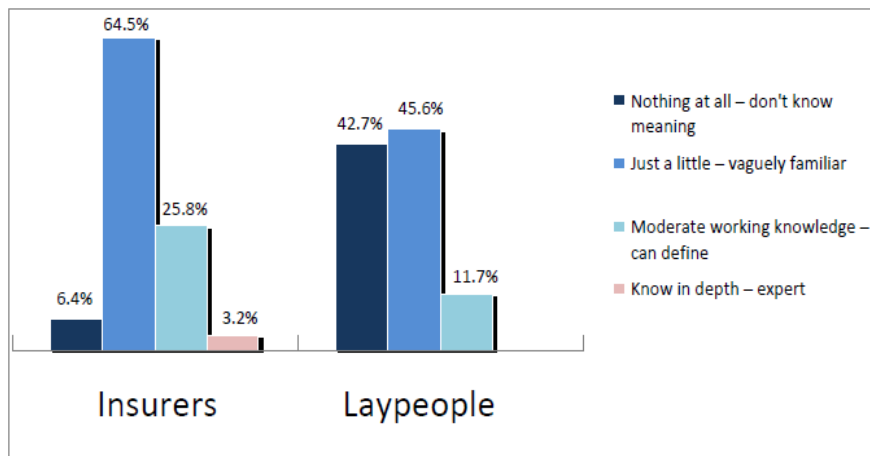
Insurance often pays for services to alleviate harms, rather than paying cash to compensate for losses. By funding services, it stimulates the development of harm-alleviating technologies and occupations that then become part of the societal standard of care. Once these technologies and services are part of the societal standard of care, they also may come to be seen as legitimate, if not morally essential, collective aid. Lack of the services necessary to provide the standard of care then becomes, in effect, an adverse event against which the people believe they are, or ought to be, insured.

The presence of either affordable insurance or effective regulation is in itself an implicit indicator of an understanding of risk. Arguably, there is an intimate relationship between regulation and insurance; each can inform the other.

It’s worth noting that in (Baublyte et al. 2014) it was found that insurers at the time were less concerned in general with nanotechnology risks than experts. The study also revealed that insurers had a basic knowledge of nano

technology, beyond that held by lay groups, but not on the level of experts. This finding is consistent with previous studies (Bostrom and Löfstedt 2010; Priest 2006; Siegrist et al. 2007).

Figure 3.b: Insurers and laypeople awareness of nanotechnology and NMs.



Source: (Baublyte et al. 2014)

For nanotechnology to advance at an optimal rate, the danger of *regulatory overshoot* needs to be addressed. The majority of regulatory proposals are predicated on the ‘precautionary principle’, the EU’s REACH framework proposal¹⁴ being an example. However, the precautionary principle represents a traditional risk management paradigm and would have limited success when applied to an emerging field such as nanotechnology. It could prove to be overly restrictive and expensive, leading to diminished innovation. Some possible pitfalls of ill-conceived regulation are discussed in the following section.

3.4 Emerging Regulatory Response

Regulation if done purposefully can be of general benefit to society. For example, it can enable cheaper insurance costs, provide public assurances

¹⁴REACH is the European Community Regulation on chemicals and their safe use. It deals with the Registration, Evaluation, Authorisation and Restriction of Chemical substances. The law entered into force on 1 June 2007 (Breithaupt 2006).

concerning product safety and accommodate export markets that adhere to strict quality and safety standards such as the EU. If hastily drafted it may be more of a hindrance than a help, particularly as the author will argue, if it reflects the precautionary principle. Compliance costs have to be added to manufacturing costs (Bruno and Claessens 2010). This may inhibit innovation by directing resources to regulatory compliance with no discernible benefit rather than research and development (Crain and Crain 2010). In turn, this contributes to a loss of competition and market share from small and medium enterprises to larger companies. The latter may lead to market monopolization followed by price and wage gouging and declines in product quality. For instance, (Sutton 1975) argues this was the primary motivation behind FDR's new deal initiatives in which the implementation of greater government control of industry and finance favoured large well established companies that did not feel the impact of regulatory compliance to the extent their smaller competitors did. Moreover, being aware of this effect, it is argued that large organizations lobby and influence the legislative process through political donations etc. to deliberately create a regulatory environment that is difficult for small firms to comply with. The relative advantage over smaller companies that regulation brings to larger organizations may be countered by state subsidies to afford small to medium companies a fairer margin of competitiveness, thus averting the threat of monopolization and the decline in innovation that would be expected to follow.

The evidence that monopolization leads to stagnation in innovation abounds. For example Microsoft's domination of the desktop operating system market hampered advancements in computer hardware design for almost a quarter century until the emergence of tablet computing from Apple broke the trend. PC manufacturers had to target a relatively static hardware design patterned on the original IBM PC architecture in order to be compatible with each release of a new operating system from Microsoft as well as being backwards compatible with older operating systems (Economides 2001). Private investors may be swayed from investing in small to medium enterprises if they suspect a sizable portion of their capital

will be consumed by regulatory compliance rather than product development, particularly if such compliance is perceived to offer no economic benefit and has been imposed hastily without adequate forethought and design. For this reason, the prospect of an uncertain regulatory environment could discourage investment from private equity markets.

Advances in science and technology generally precede the development of the corresponding regulatory frameworks (Salsburg 1981). It is becoming evident that this is also the case for engineered nanomaterials in which regulators are struggling to keep pace with rapid advances in the field (Marchant, Sylvester and Abbott 2008). Ideally, the cost for a manufacturer adhering to prescribed regulation should offset the potential cost of societal harm, a cost for which the company would be ultimately liable. The present state of the regulatory field for using or producing nanomaterials offers few benefits to either industry or society; so far regulators do not generally consider nanomaterials as requiring special attention. Presently, there are no industry definitions to unambiguously and rigorously characterise nanomaterials, in spite of attempts at promoting such a standard by insurers and regulators (Hunt 2004) Failure to rigorously describe ENMs may conceal potential hazardous properties¹⁵. Experiments performed on laboratory animals have revealed that certain classes of nanomaterials, upon entering the alveoli of the lung, are small enough to then pass directly to the bloodstream and induce inflammatory responses in other organs (Kayat et al. 2011; Vu et al. 1996). Owing to quantum effects that dominate at the nanoscale, the behaviour of nano particles is in general difficult to predict and is not intuitively accessible (Roduner 2006).

The lack of a descriptive terminology was highlighted when Continental Western Insurance Group attempted to insert an exclusion clause stipulating that physical injury resulting from exposure to carbon nano tubes would not

¹⁵ For example, a ENM's typically high surface area in relation to its volume can cause it to be more reactive and prone to induce inflammation in exposed hosts than its parent material.

be covered as part of their general liability coverage (Gorman 2008). This proved unworkable as the definition of what constituted a ‘carbon nano tube’ was ambiguous and could not be uniquely identified with specific manufacturing processes. In effect, the clause became practically meaningless. The exclusion clause was rescinded within a year of its introduction. Here we see how a regulatory shortcoming and a lack of a suitable contractual vocabulary have impacted upon the provision of insurance. Due to a lack of suitable nomenclature and definitions, regulatory authorities do not distinguish nanomaterials from their chemically identical bulk forms. In the U.S for instance, although the EPA has proposed rules (the NMSP –National Materials Stewardship Program) to address nanomaterials as a distinct category, they are not yet considered distinct from their chemically identical bulk forms (Valverde and Linkov 2011). That said however, a more recent effort from the European Commission’s Joint Recent Centre is currently underway to develop a more precise concept of nanomaterials (Birgit et al. 2014)

It’s useful to consider the reciprocal relationship between regulation and trust in society. In (Aghion et al. 2010) it is argued that trust in society negatively correlates with regulation. This conclusion roughly follows from the argument that highly civic societies require only minimum regulation while the populations in less civic societies typically demand more regulation usually as a result of corruption, past regulatory failings and bribery among business and government elites. The article also asserts that existing regulation tends to reduce trust, resulting in demand for further regulation. This observation suggests from the outset that a cautious and prudent approach be taken to the regulation of nanomaterials, and for regulators and legislators to closely engage with the public in order to avoid a potentially costly and unending series of regulatory reforms.

Misguided regulation can also be the source of opportunistic litigation; in view of the high number of asbestosis litigation cases in recent years, it has been argued a large portion involved plaintiffs suffering from conditions not directly attributable to asbestos. Current statutory retroactive exposure limits

are comparable with ambient levels. Trial lawyers are easily exploiting these statutes by arguing that past employers failed to maintain asbestos levels within regulatory limits, limits that are now being imposed retroactively. In practice such limits would have been difficult to achieve, if not impossible (Carroll, Stephen J., Deborah R. Hensler, Allan Abrahamse, Jennifer Gross, J. Scott Ashwood, Elizabeth M. Sloss and Michelle White. 2002).

A growing realization that prevailing risk management practices are not well suited to nanotechnology is beginning to surface (Monica, Heintz and Lewis 2007). Driven from the 'bottom up' by a number of stakeholders (e.g. insurance companies, standards bodies, nanotechnology companies and public interest groups), an alternative approach may lie in the development of a new nanomaterial specific regulatory framework that would include a nanomaterial specific nomenclature necessary for drafting precise regulation and providing insurers with a necessary policy language. In the first instance, this would take the form of technical standards, working definitions and practices being adopted on a voluntary basis in order to determine what is most effective. Under this 'self-regulatory' approach, a solution would evolve and emerge within an environment of changing requirements rather than being rigidly, arbitrarily and bureaucratically imposed from the 'top down' (Barandiaran 2007; Marchant, Sylvester and Abbott 2008; Renn, O. and Roco 2006b).

3.4.1 The precautionary principle versus the risk of lost opportunity

In light of the great benefits ENMs could and are bringing to society, as elaborated in chapter two, it's vital that this technology gains and maintains full public acceptance and support and remains free of potentially cumbersome regulation and legislation. The latter can be facilitated through schools and universities and through media promotion and direction to *engineer consent* among lay communities expressing concern about the increasing pervasiveness of ENMs. Here the author examines the benefits of societal acceptance and the potential for current developments in nano material research to inspire new generations of researchers and developers.

The cost of lost opportunity following a failure of the public to embrace the emerging field of engineered ENMs and all that it promises is arguably the greatest risk to society regarding this technology. This is where influential policy makers must be particularly vigilant with respect to misapplications of the precautionary principle, especially for example as mere conciliatory gestures to public interest groups voicing groundless or exaggerated claims purporting to the dangers of ENMs.

As an illustrative case study, it's useful to consider the implications for present day living standards had the proposal to send a man to the moon not received the groundswell of public support that it did. Some commentators have lambasted the excessive costs of space travel and the relatively high casualty figures, contending that the funds invested over the years could have been more effectively allocated 'down here' to address more pressing needs as opposed to 'up there'. However, a case can be made that much of our present standard of living is arguably a legacy of the products and technologies that were spun out of the breakthroughs needed to "land a man on the moon and return him safely to the earth"¹⁶, particularly the development of advanced materials needed to address the extreme thermal and radiation environments of manned space flight. Familiar technologies that can trace their origin to the moon program include bio-monitoring technology, so beneficial in today's hospitals, especially in neo natal wards; cooking foil; Teflon; telemetry based navigation and long distance telecommunications (e.g. GPS); high temperature resistant steel alloys and ceramics; cordless power tools; heat insulators; Infrared based thermometers; large scale integrated circuits; freeze dried food; memory foam; scratch resistant lenses; smoke detector; water filtration systems used to kill bacteria in space (Riley 2012).

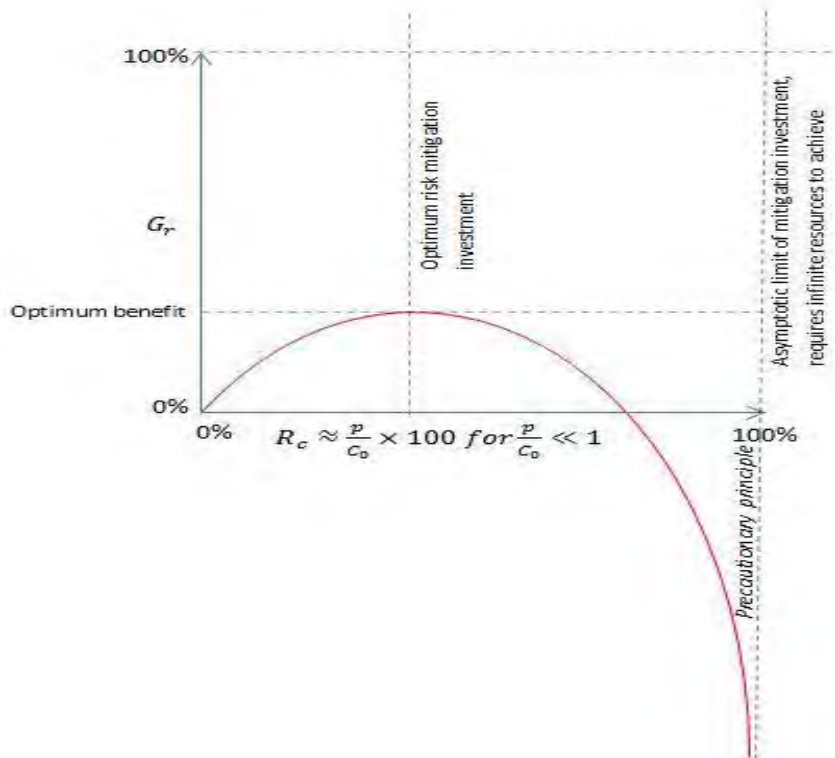
Economic and educational policies that promote and support programs to achieve scientific breakthroughs to solve big problems tend to engender a

¹⁶ For instance, on a purely cost accounting basis, it has been estimated that each dollar invested in the Gemini, Mercury and Apollo space programs has generated 7 dollars (adjusted for inflation) in new capital formation by 1970 Schee, J., *The Economic Impacts of the U.S. Space Program*, *Business Administration Department, Rutgers University*.

positive societal outlook, especially among young people regarding their futures. Despite large initial outlays, such policies generally produce economic and cultural dividends valued at many times the original investment. In the midst of the cold war and conflict in south East Asia, the moon program inspired optimism in a somewhat dejected public. By achieving a monumental technological feat in a relatively short period, the moon program helped foment the view that human beings could solve seemingly insurmountable problems. It also compelled many of that generation's young people to follow a career in science and engineering whose contributions account for a significant portion of today's GDP figures. Thus a consideration of applying the precautionary principle in relation to ENMs' production and use must be cognitive of the potential ramifications in terms of a loss of optimism, positive outlook and inspiration among those considering a career in science or engineering, with the associated losses of productivity and innovation.

ENMs offer the potential for the same kind of economic transformation and arresting of societal malaise that was stimulated by the technologies that drove the moon program and the space race in general. Assuming the present rate of population growth and living standards are to be maintained, agro-industrial and energy outputs based on current methods of production may fail to provide for the needs of future generations. Given that Western society today is generally more risk averse in regard to emerging technologies than it was in the future orientated 'heady days' of the 1960s (Furedi 2007), suggests that arbitrary regulatory enforcement including misuse of the precautionary principle regarding ENMs' use and production could lead to future energy, water and food deficits. In summary, the precautionary principle viewed as an extreme risk mitigating measure can be said to lie toward the far right of the graph in Figure 3.c beyond the optimum point denoting maximum societal benefits, such that society experiences a net economic loss as a result of its adoption. The notion of the existence of an optimum risk (loss) prevention strategy is examined at an abstract level in the following subsection.

Figure 3.c: The Y axis represents the total aggregate of economic gains, G_r , as a result of a total societal investment, R_c , targeted at capital loss reduction as depicted on the X axis. The general qualitative form of the relationship between gains and investment is postulated to be one in which there exists an optimum investment strategy beyond which further efforts produce no discernible gains and in fact lead to a net loss if the loss mitigation measures are carried out to the extreme.



3.4.1.1 Abstract cost-benefit analysis of regulation-risk control

Arguably, all forms of risk cannot be removed in their entirety from economic activity: Figure 3.c illustrates qualitatively the idea that 100% risk reduction is not possible for a society as such a policy would consume all available capital including the investment portion needed for growth. Thus, attempting to remove all risk would lead to social decline and eventual collapse if such a policy was not soon aborted¹⁷. More specifically, consider

¹⁷ Adoption of the precautionary principle can be viewed as an excessive investment in risk control, leading to net losses in the aggregate.

the cost of all forms of capital loss per capita in an economic region. The author will qualitatively illustrate how such an aggregate would be expected to vary in relation to the total cost of loss prevention measures per capita: Let C_0 denote the average cost of all forms of loss per capita in an economy that doesn't employ any loss mitigation strategies. Let $C(p)$ denote the average cost of all forms of loss per capita when the same economy employs loss mitigation strategies which cost an average amount p per capita to implement. Note by definition that $C(0) = C_0$. The relative average savings or gain, G_r , per capita as a result of employing loss mitigation strategies is then given by, $G_r = \left(\frac{C_0 - C(p) - p}{C_0} \right) \times 100$. One would expect G_r to be a maximum for some optimum value of p and decline for values of p beyond this value, reflecting the principle that infinite expenditure would be required to eliminate all risk (see appendix 8.9 for a mathematical exposé of this notion). The advantage of expressing G_r as a relative and therefore dimensionless quantity is that it removes dependency on the many units, and their associated ambiguities, used to measure capital such as monetary values or physical measures based on standardized market basket indices etc. Denote R_c as p expressed as a percentage of C_0 , that is $R_c \approx \frac{p}{C_0} \times 100$, referred to as the relative cost of risk (loss) control. The impossible scenario of 100% risk reduction corresponds to the case in which $p = \infty$, $G_r = -\infty$ and $R_c = \infty$ and makes a graphical representation of the relationship between G_r and R_c rather unwieldy. To address this, R_c is redefined so as to fit on a finite scale such that $R_c \approx \frac{p}{C_0} \times 100$ when $\frac{p}{C_0} \ll 1$ but equal to 100 when $p = \infty$. A suitable candidate for R_c that simultaneously satisfies the latter boundary conditions is provided by $R_c = \left(1 - e^{-\frac{p}{C_0}} \right) \times 100$

In the context of insurance for a company using or producing ENMs, p can roughly be identified with the annualized cost of providing safety measures demanded by an insurer in order to avail of a premium rate given by $C(p)$ to cover occupational injury and disease linked to ENM exposure. Regarding

the actions of the insurer as a form of soft regulation, p can be also be viewed as the annualized cost of regulatory compliance.

Compliance with well-designed regulation can make it cheaper for insurers to provide coverage. As a legal prerequisite for insurance, insureds must take all possible precautions that are known to reduce the risk of loss. Adhering to effective regulation would therefore constitute a precondition for affordable coverage (Freeman P and Kunreuther H 1996). If there is a failure to adequately insure the nanotechnology sector then the actual cost of adverse events falls back on the State and ultimately on the citizen. It's the opinion of the author that such an outcome would further reduce the tolerance of the general public towards the risk posed by this new technology.

It's in the context of regulatory issues where the benefit of insurance for companies that either use or produce ENMs may be most acutely felt: as mentioned above, the provision of insurance would be expected to be contingent on the insured adhering to particular set of standards stipulated by the insurer. Thus in the absence of enforced regulation, insurance provided on the condition of adherence to safe working practices would provide a layer of soft regulation that by definition has to be affordable since affordability is one of the prerequisites of insurability (see section 3.6). The self-regulatory effect of insurance therefore brings to the ENMs' industry as a whole the benefits of regulation while averting the potential perils of enforced regulation. This perspective is echoed by (Hester et al. 2014);

NM applications thus present a potential test case for framing new models of 'soft law' voluntary governance as a substitute for traditional command and control type regulation. An approach based on anticipatory ethics, future oriented responsibility, upstream public engagement and lifecycle risk management which we refer to as Anticipatory Ethics and Governance [AEG] may offer a solution. It adopts a future care orientation by encouraging the internalisation of responsibility to avoid or reduce the risk of harm before it happens rather than retrospectively imposing responsibility and liability after the harm is done. The overarching

objective of an AEG approach is to contribute to the long term sustainability of NT [nano technology].

Beyond acting as regulatory substitute, insurance brings other benefits: From a holistic perspective, insurance helps preserve the economic value added by group collaboration. A company is more likely to stay intact and solvent because of insurance availability, thus preserving the social capital or network value that emerges from collaboration between the individuals which it employs.

3.5 Legal Issues

Seemingly innocuous legal outcomes can affect major socioeconomic changes. For example, the threat posed by monopolies to economic vitality during the early history of US Republic was kept in check by state level chartering laws for corporations (Cray 2007). For instance, some states placed limits on the lifetimes of corporations, prohibited them from owning stock in other companies and required them to function in the public interest such as in the building of roads and bridges. These restrictions were effectively lifted by a series of court rulings during the latter half of the nineteenth century in which corporations became increasingly recognized by the courts as legal persons. With fewer restrictions, the rise of the major industrial cartels and monopolies soon followed, resulting in the undermining of small and medium enterprises, wage gouging, long working hours and in many cases hazardous working conditions. The response was the formation of workers unions and populist uprisings, respectively accompanied by industrial discordance and social unrest.

In this context it is important to understand how the legal system could impact upon the ENM industry. In accordance with principles of common law, there is an obligation towards all workers involved in the production of ENMs to insure their safety. In many jurisdictions, such obligations have been codified under statute. For instance, there is the Control of Substances Hazardous to Health (COSHH) in the UK, so that employers are legally required to protect workers against occupational risks. Paraphrasing from (Hester et al. 2014), It is in the arena of the legal system where the interests

of ENM Stakeholders will be determined. In the past the courts have been forced to resolve claims based on limited and/or uncertain scientific knowledge. Defendants and plaintiffs require a resolution even in the absence of scientific data which is tolerated by the law in the interests of practicality. If ENM related litigation ensues, the courts and the law will be the instruments which will ultimately shape and determine the future development of this technology. 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 ENM industry to gain a better understanding of how it is perceived by the legal system.

3.5.1 Employer liability insurance

Liability may arise under common law, under contract or under statute. Traditionally, and before the advent of employer liability insurance, plaintiffs bore a heavy burden of proof under common law that required them in the courts to exhaustively demonstrate employer liability. The outcomes of these challenges more often than not fell in favour of the defendant. The impetus to create a more equitable balance in the outcomes of such cases between employer and employee has its origins in Bismarck's Germany of the 1870's (Guyton 1999) . The workers compensation reforms introduced by Bismarck became known as the Prussian model and in the years to follow was the template for a series of legislative developments in Britain and the United States that introduced similar schemes. In the early twentieth century United States, demands for fairer treatment of workers began primarily with the trade unions that formed around the emergence of large industrial cartels such as the steel mills and car factories of Pittsburgh and Detroit in which workplace accidents were a common occurrence. There was clearly a need for legislative action that would promote more equitable outcomes for injured workers seeking compensation. Due mostly to lobbying efforts by the unions, what emerged as a solution was the mandatory employer liability insurance (ELI) that had to be held by all companies employing more than a certain number of people. ELI circumvented the need of the plaintiff to seek redress in the courts, which for most plaintiffs was a financially burdensome proposition and usually

beyond their meagre resources. Compensation via ELI now became merely a formality for most injuries. ELI also benefited employers in that once an injured worker was compensated he could not subsequently bring suit against his employer for the same injury. Provided a workplace injury was reported with minimum delay, it was relatively straightforward for a worker to establish to the satisfaction of his employer and the insurance carrier the cause of the injury was work related and not the fault of the worker. Injury was defined as either a permanent physical impairment that rendered the plaintiff unable to secure gainful employment or caused temporary or reduced loss of earnings. The definition in some jurisdictions expanded to include less tangible qualities such as 'pain and suffering' both physiological and physical. However, seeking redress for an occupational disease or an increased risk of developing an occupational disease was and still is, at least until relatively recently, a more complicated affair. From a legal perspective, occupational disease is defined separately from occupational injury(Levy et al. 2011).

Claimants have historically faced mounting difficulties in the courtrooms when attempting to establish liability under common law for what they claimed were occupational diseases. The source of these difficulties mostly stemmed from plaintiffs basing their arguments on tenuous links between alleged toxic exposure and the onset of an illness that may have developed long after the alleged exposure took place. In many cases, such arguments were easily countered by defendants' legal representatives, being typically much better resourced and informed than those acting on behalf the plaintiff. For example, in the case of asbestos exposure, there was generally long dormant period between exposure and the onset of mesothelioma or related conditions. Defendants usually countered with the argument that such conditions were equally attributable to exposure in other workplace environments or even non-occupational exposure. It should be noted that insurance companies are generally not altruistic as they have a duty to their shareholders. Their actions in regard to claimants are based solely on what is the most cost effective path for them to pursue. Although they have an obligation under most jurisdictions to act in good faith, insurers still reserve

the right to challenge any and all claims made against them. The reason they settle most injury claims without contest is that it is simply the cheapest option, since the alternative would entail legal and administrative expenditures likely in excess of simply settling a claim without question or delay. Likewise, an insurance company will challenge a claim if it determines such a challenge to be in its best interest, particularly if the claim is large or it is for occupational disease. As mentioned previously, historically 80% of claims for occupational diseases have gone to court due to insurers' knowledge of similar cases in which claimants were unable to legally establish that liability lay with their employers.

There have been a series of attempts to create fairer outcomes for claimants (Pierce 1985). The result has been that legal definitions of injury, while invariably lagging scientific and technological advancements, are constantly being redefined, oftentimes by judges sympathetic to the plights of plaintiffs who have clearly suffered loss but are unable to establish liability within existing legal frameworks. Such redefinitions manifest through case law in which courts establish new precedents by finding in favour of plaintiffs on the basis of increasingly vague notions of injury. A few precedents have already been set by court rulings finding in favour of plaintiffs solely on the basis of enhanced risk. For instance, quoting from (Klein 1999),

Only two appellate courts, both in asbestos cases, appear to have upheld enhanced risk awards. See Jackson v. Johns-Manville Sales Corp., 781 F.2d 394 (5th Cir. 1986); Gideon v. Johns-Manville Sales Corp., 761 F.2d 1129 (5th Cir. 1985).

In these cases, the traditionally rigorous definition of injury was relaxed and equated with previous asbestos exposures merely having enhanced the risk of the onset of disease. Should such isolated rulings become more frequent and show signs of broadening to include exposures to substances other than asbestos, then it would be in the interest of employer liability carriers for ENM producers or users to avoid courtrooms at all costs, since the previously assured outcomes that typically favoured the defendants may not

be as dependable as previously thought. (Klein 1999) in fact argues that recovery for enhanced risk claims will become de facto in the future in response to the present inability of toxic tort systems to keep pace with increasingly nebulous concepts of injury in an environment of rapid technological change. In support of the latter, (Ree 2004) convincingly argues that an increased risk of future is harm represents a present loss every bit as tangible as manifest injury which tort systems will eventually have to accommodate.

The author argues that it would be therefore prudent of employer liability carriers for ENM producers or users to include a definition of injury that equates with a measure of increased risk, in accordance with current scientific consensus, of developing a debilitating condition later in life as one that can be claimed for without contest. In doing so they would preempt and circumvent likely future developments in tort systems that otherwise would not be to their advantage. To add a further layer of protection, it would also be necessary to stipulate the proviso that compensated workers cannot subsequently bring suit against employers whose insurance carriers facilitated said compensation, in line with the normal provisos of employer liability insurance. It's within this proposed contractual framework and definition of injury that the author proposes a quantitative model for calculating a fair market premium per exposed worker in chapter 6.

3.6 Insurability

There are several definitions of what constitutes insurable risk using traditional actuarial methods. Common to all these definitions is the recognition that for risks to be insurable they must, at the very least, share the following traits¹⁸:

- (1) The risks are diversifiable

¹⁸ It should be noted that the majority of risks faced by companies and organizations are not insurable, such as operational and foreign exchange risk (Vivian, Darius and Palmgren 2000).

- (2) The risks are quantifiable
- (3) The risks are fortuitous
- (4) The cost of risk is affordable.
- (5) The risks are non-catastrophic

The following outlines some proposals being considered by the nanotechnology sector to address severe acute health risks. A framework is described for managing these risks using control banding (CB) and ‘*risk mitigation at source*’ (RMS) risk management methods. In order not to distort general liability premiums that cover more benign risks, the adoption of such a framework by nanotechnology companies could form a condition for coverage under specialized policies to cover SARs. Validating the effectiveness of either CB and/or RMS methods will depend on the availability of exposure and toxicity data and a means of calculating acute risk from these data sets. The target sector is predominantly those companies who either use nanomaterials as additives in otherwise conventional manufacturing process and companies that exclusively produce such additives. Initially, such proposals would enable underwriters to qualitatively assess acute risks. When combined with exposure and hazard data, the framework could be extended to provide a quantitative assessment and a framework for the conception of more advanced models. (see chapter 6)

3.6.1 Control banding

Control banding is a set of protocols designed to minimize the threat of worker exposure to potentially hazardous materials. The materials are identified with different categories depending on initial estimates of their toxicity and exposure levels. Within each risk category are prescribed a set of actions that can affect a reduction in exposure risk. There are strong parallels between the nanotechnology and the pharmaceuticals/biotechnology industries. Control banding, devised by the FDA in the 1980’s for managing occupational risk in pharmaceutical companies, is currently being adapted to manage nanomaterial exposure risks (Paik, Zalk and Swuste 2008). The effectiveness of a control banding

system can only be validated when actual toxicity and exposure measurements have been made after its implementation. If the actual measurements are not commensurate with the initial estimates then the risk remediation action categories need to be redefined. This iterative process of adjustment and subsequent testing is repeated until the system is stable and no longer requires any further changes. In the case of nanomaterials, this will require external expertise in the fields of nanomaterial exposure detection and nanotoxicology to assess hazard levels (Meng et al. 2009; Methner, Hodson and Geraci 2009).

Whilst CB tools are not being primarily designed for underwriters they can, in many instances, help to categorize both exposure and hazard. The resultant risk location can then be used to rank the acceptability of certain risks or can be associated with certain production processes in the ENM sector so that an insurance premium can be applied to specific scenarios.

CB is used to categorize risk levels as a surrogate marker of exposure and hazard. The main components and information required for a CB approach are:

- i) the severity score, which is estimated on the basis of known or suspected hazardous properties. In the case of ENMs, these hazardous properties can include surface chemistry, surface area, particle shape, size and morphology, solubility, carcinogenicity/reproductive toxicity, mutagenicity, dermal toxicity and if it acts as a sensitizer (respiratory or dermal); and
- ii) the probability score (i.e. the exposure probability or emission potential), which includes the estimated amount of material used, dustiness/mistiness, number of employees with similar exposure, frequency of operation and duration of operation.

In the absence of quantitative data, representing an effective strategy of risk communication to insurers by using a generally accepted risk ranking, the CB approach can be adapted to become a tool to suggest behavior-based risk management (RM) practices. In particular, the bands related to the exposure can surrogate for the lack of field measurements.

While in theory it is possible to obtain some form of quantitative information related to ENM exposures, current analytical instruments are generally inadequate in establishing an appropriate quantitative workplace personal exposure measurements, especially using unconventional metrics such as surface area (Abbott and Maynard 2010). Thus, exposure represents a weak link in terms of the estimation of possible health outcomes. A minimum set of data that should be reported for all ENM exposure studies has been proposed by a group of scientists concerned with exposure assessment and characterization (Clark et al. 2012). This set of data includes, but may not be limited to, both nano-specific (e.g. physico-chemical characteristics of airborne released and measured particles, emissivity and flow dynamics) and non-nano-specific information (e.g. on processes, description of sites, and presence of risk management tools put in place).

The reliability of information contained in a CB approach and the subsequent usability of such information by underwriters largely depends on the expertise of industrial hygienists who are usually in charge of application of such a scheme. Such professionals are typically more familiar with exposure parameters than the hazardous properties of newly synthesized chemicals that usually lack safety information. Indeed, emission potential parameters alone do not predict worker exposure potential. That said, they are a good starting point in disclosing the likelihood that ENMs become airborne during production. Currently, the toxicity potential of many ENMs are substantially unknown. Such a lack of information has been overcome by the application of the precautionary principle that does not represent a proactive strategy but instead is quite a conservative approach marred by uncertainties.

3.6.1.1 Standardization

There are control-banding tools available for risk management that can be adopted by the insurer but with some modifications (ANSES 2010; Brouwer

2012; Groso et al. 2010; Paik, Zalk and Swuste 2008; Van Duuren-Stuurman et al. 2012; Zalk, Paik and Swuste 2009). The current lack of standardization in the safety issues posed by nanotechnology development is a significant obstacle to the effectiveness of CB as an underwriting tool. Recently, the International Standards Organization (ISO) has made efforts to define both nanomaterial characteristics and provide nanomaterial characterization methodologies in this regard (ISO 2011). ISO/TS 12901-2:2014 “Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach” is intended for use by competent personnel, such as health and safety managers, production managers, environmental managers, industrial/occupational hygienists and others with a responsibility for the safe operation of facilities engaged in production, handling, processing and disposal of ENMs. We also see the development of ISO/TS 12901-2:2014 is applicable to engineered materials that consist of nano-objects such as nanoparticles, nanofibres, nanotubes and nanowires, as well as their aggregates and agglomerates (NOAA).

3.6.1.2 Categorizing exposure and hazard

In the CB approach, both exposure and toxicity potential need to be segmented into discrete categories. The exposure assessment can be performed by scoring different factors such as the physical state of the materials/products containing ENM (e.g. as an aerosol, dry powder, liquid form and so on), quantity (experimental or mass production), emission potential (cleanroom environment or open space and the emissivity of the ENM), frequency and duration of use. The overall score can then be used to determine the level of exposure potential. Similarly, toxicity levels can be assigned with the help of a scientific literature review and lab analysis (that is, *in vivo* and *in vitro* tests) as well as applying scores to parameters such as chemical composition, particle shape, size, surface charge, solubility, aggregation and agglomeration of nanomaterials. Typically, nanotechnology manufacturers familiar with data reporting on quantitative exposure levels can check whether such levels are within the Occupational Exposure Limits (OELs), should they exist. This has implications in terms of the implementation of the CB approach by insurers for it is along the toxicity

axis of a two dimensional toxicity-exposure CB, that any movement is liable to have consequence in health and safety concerns.

3.6.2 Risk mitigation at source - safety by design

Risk management comprises the selection of a strategy or strategies that are designed to avoid, prevent, reduce, transfer or self-contain risks. This may include the development of “safety by molecular or process design” approaches, applied to single nano-phases or to more critical process steps such as waste treatment and disposal. Such an approach to safety by design has the chance to form a preventive and robust RM measure to prevent risks rather than address them when they occur. Such an approach becomes an effective and sustainable RM tool only if supported by a sound and practical risk assessment (RA) in conjunction with performance evaluation of the ENMs and process.

Some progress has been made by collaborative efforts involving private companies and public institutions to create nanomaterials that are inherently safe¹⁹ (Riediker M 2012). Such goals represent a ‘holy grail’ within the field since their realization would render all other forms of safety control, and associated costs, unnecessary. The predominant approach is to modify the surface features of existing engineered nanomaterials to make them more benign. Modifying a nano particle’s surface characteristics to reduce its hazard and exposure levels, but without compromising its intended industrial functions is known as Safety by Design, as mentioned above. An alternative acronym is Risk Mitigation at Source (RMS). For example, a material’s tendency to become aerosolized, and thus its ability to present a greater exposure risk, can be reduced by alterations to promote aggregation into larger particles. The aggregated particles may also present a smaller hazard threat if inhaled, since their surface to volume ratio has been reduced. Similar to control banding, the effects on exposure and hazard levels need to be validated by specialists in exposure technology and nano

¹⁹ See also www.sanowork.eu

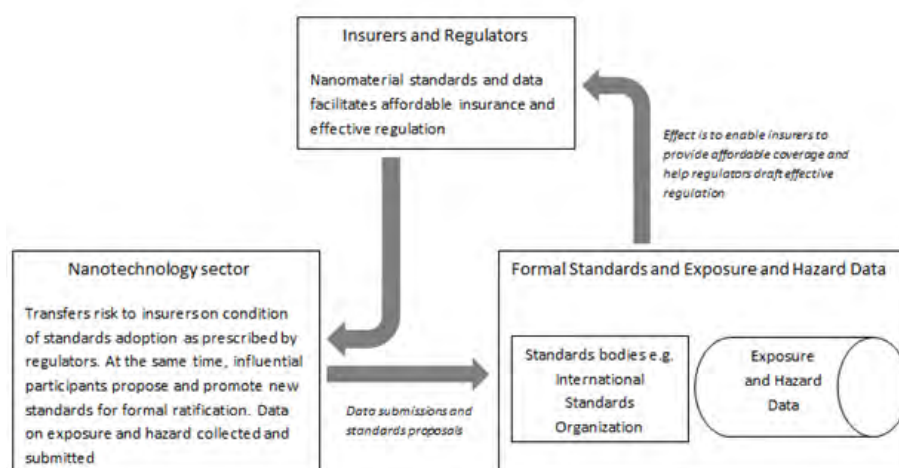
toxicology.

As mentioned previously, Insurers to a large degree function as proxy regulators by stipulating demands for safe work practices and standard operating procedures (SOP). If the employer fails to comply with such requirements to protect its workforce, its insurance costs will be likely high or possibly unaffordable. A strong case can be made that the development of effective risk mitigation strategies offer an economic opportunity as well as assisting in the responsible development of ENMs and its downstream dependents.(Schulte et al. 2014)

The economic burden of insurance could encourage companies to adopt a proactive behavior towards RM procedures, demonstrating that safety practices have been put in place and proven to be effective to reduce emission and exposure and/or to reduce the toxicity (if any) of a given ENM. Adhering to a common CB or/and RMS scheme could allow a collective of nanotechnology companies, especially start-ups, to transfer acute occupational risk at a reasonable cost to insurers. From an underwriting perspective, larger collectives would allow for greater risk diversification and thus smaller premium payments for each member. The development of either or both of these methods would require the close involvement of insurers and regulators. In the longer term, the collective could communicate the schemes to a wider audience through its submission to standards bodies for formal ratification as *standard operating procedures* (SOPs). In Figure 3.d we see how this process might unfold as a positive feedback loop. The process is initiated by the insurance sector by its provision of insurance to the collective. In turn this facilitates the generation of risk data from the syndicate's day to day operations that are now possible from the provision of insurance. The risk data, harvested by insurers and regulators and communicated to standards bodies for formal ratification and to inform the wider public, will ultimately lead to cheaper insurance, thus enabling greater efficiencies for nanomaterial producers and users. The process then repeats itself indefinitely. It is important to note the critical role of insurers by their willingness to initiate the process. Such a strategy is echoed by the International Risk Governance Council (IRGC). The latter

recommends a corrective and adaptive approach that takes into account the level and extent of available knowledge of nanomaterials so that a societal balance of the predicted risks and benefits can be achieved. (Renn, Ortwin and Roco 2006a) More recently, ISO standards provide a pragmatic approach for the control of occupational exposures to ENMs (ISO 2011)

Figure 3.d: Depicted is a hypothetical scenario in which exposure and hazard data along with proposals for industry practice – e.g. SOPs and product standards- are provided by the nanotechnology sector to be considered for formal ratification by standards bodies.



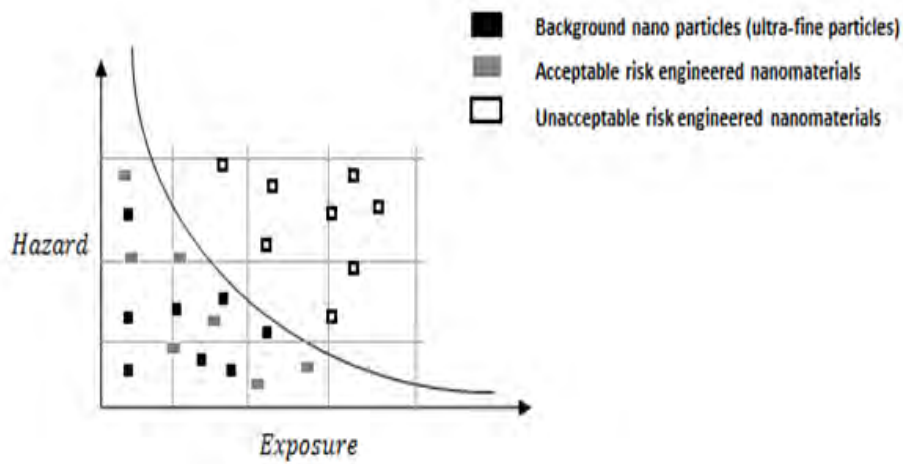
CB and RMS methods can only be validated on the basis of short term observations that by definition only provide a measure of the short term risks. However, the adoption of these methods as conditions for insurance should help promote and sustain what is still a relatively young industry. Improved knowledge of the longer term risks should follow as a result. In the meantime, other methods will need to be devised for managing longer term risks. In the next section we briefly outline some possible strategies to enable the insurability of the cumulative long term health risks from exposure to engineered nanomaterials.

3.6.3 Managing long tail risks

Determining the long tail risk residing in engineered nanomaterials can be addressed in two ways: Firstly, a monitoring program could be set up to log

the exposure histories of effected workers together with periodic health assessments. Such a program would need to be executed over a period of many years before yielding any conclusive evidence. The drawback is the cost and the difficulty of establishing cause and effects relationships between ever changing nanotechnologies and occupational health. Secondly, nanomaterials are naturally occurring and form a major component of air pollution (Calderón-Garcidueñas et al. 2008; Robert D. Brook 2004; Schwartz 2000). Correlating morbidity and mortality rates in exposed populations against air quality measurements could provide a baseline to calibrate the risks of exposure to engineered nanomaterials. To form a baseline, the properties and exposure levels of naturally occurring nanomaterials would need to be compared with engineered nanomaterials. This concept is expressed in Figure 3.e in which the proximity of toxicity and exposure profiles for engineered nanomaterials are compared to those of ambient anthropogenic materials that are assumed to present an acceptable health risk. It is from similar approaches that the emerging field of nanotoxicology has drawn much of its inspiration (Günter Oberdörster 2010; Stone, V. Napier Univ., Edinburgh Johnston, H. ; Clift, M.J.D. 2007; Xia et al. 2006). The drawback is that this concept is at the early stages of development.

Figure 3.e: Depicted is a conceptualization of a long term risk assessment of exposure to ENMs. Natural and anthropogenic sources are depicted in black. There is epidemiological data linking these sources with human health levels and mortality rates.



In the absence of long term and catastrophic risk assessment capabilities, insurers still retain a number of options for managing these risk scenarios. As mentioned, these include reinsurance, catastrophe bonds and, if available, state guarantees, each of which the author argued was unsuitable for managing the long term health risks presented by nanomaterials. However, there still may be some flexibility for insurers to manage such risks by carefully balancing their asset portfolios.

Insurers are free to invest premium streams in excess of statutory capital reserves in whatever way they deem fit. Such investment choices offer a potential means of managing long term risks. In choosing assets in which to invest premiums, insurance risk managers could employ in-house hedging strategies to mitigate insolvency risk. They have a responsibility to ensure the asset portfolios under their management are sufficiently diversified (Cummins 2000). Portfolio diversification is best achieved with assets that are anti-correlated; put options are naturally anti-correlated with their underlying securities and would lend themselves as natural choices for inclusion in such portfolios.

As an exploratory concept, the author suggests that an index based on a basket of listed companies that either produce or use nanomaterials would reflect (price in) the market's perception of the total cost of nanomaterial related risk to these companies. Since there is more reliable data on short term than on long term risk, the market's estimates of short term diversifiable risks would be relatively stable and would not significantly change the share prices of the index members in the near term. On the other hand, changes in the market's estimates of long-tail aggregate risks would likely register as quasi-discontinuous movements in the index, with the shifts being commensurate with changes in the markets' estimate of the cost of such risks. This collective market knowledge or *wisdom of the crowd* (Surowiecki 2005) could be exploited by an insurance portfolio manager in the following way: A financial derivative included in an insurer's portfolio, such as a suitably chosen put option based on the index described above, could offset changes in the insurer's exposure to long term risks from companies comparable to the index's members. By design, such a derivative would have the property that its change in value be commensurate with the corresponding changes in the value of the insurer's long term liabilities linked to these risks (Figure 3.f). Such a strategy would therefore help shield an insurer from sudden shifts in its nanomaterial related long tail risk exposure and enhance the robustness of its balance sheet.

3.6.3.1 Index construction

Insurance contracts stipulate fixed premium rates over their lifetimes. It follows therefore that over the life of a contract its value to an insurer will generally not be constant as it will vary in response to data relating to the covered risks being updated and refined. When the risks covered by a sufficiently large portfolio of contracts are uncorrelated, changes in the discounted expectations of individual claims would tend to cancel and would be expected to have only a marginal effect on the value of the portfolio in question.

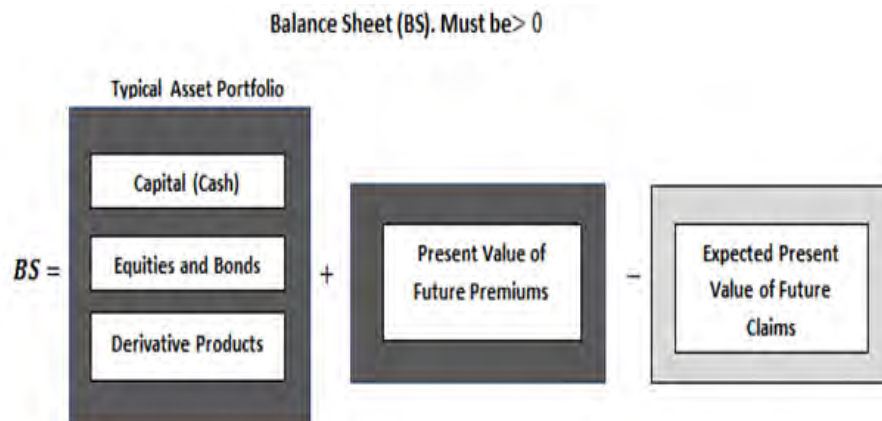
In order to exploit an index to cost effectively mitigate insurance portfolio losses from changes in expectations of non-diversifiable or aggregate risks, the index described above would need to reflect the total market

capitalization of companies, or similar companies, whose total risk exposure was covered by the insurance portfolio in question. The reason for the latter is explained as follows: Firstly, it will be assumed that each of the covered companies is listed or is similar in size and scope to one that is listed. Let $n_i S_i$ be the total capitalization of company i that has a share price of S_i and consists of n_i outstanding shares. The index is defined by $I = \sum_{i=1}^M w_i S_i$ in which $w_i = \frac{n_i}{N}$, $N = \sum_{i=1}^M n_i$ and M is the sum of the number of listed companies in the portfolio and the number of listed companies that are comparable to those companies in the portfolio that are unlisted. The total capitalization of the group is equivalently given by NI . Uncorrelated movements in each of the S_i would tend to cancel, suggesting that I should have a relatively lower volatility than each of its members, causing it to respond only marginally to market information pertinent to individual companies but not to the group as a whole. However, for correlated movements in each of the index members, for example upon the release of market data that was relevant to the whole portfolio group, this would not generally be the case; specifically, such a measure would tend to move against changes in the market's expectation of costs that were common to the group as a whole. That is, $-N \Delta I \approx \text{discounted change in market's expectations of future costs to the group}$.

Thus, the inclusion of N identical put options P_I , each written on I , should help to absorb losses in the aforementioned portfolio owing to changes in the expected costs of non-diversifiable or aggregate risks. That is, $N \Delta I + N \Delta P_I$ would be expected to remain relatively steady even in response to systemic market events that would otherwise affect potentially large variations in the portfolio's valuation if it didn't include the aforementioned set of put options. It might be argued that the use of index option is moot in this example since the same objective could be achieved with a set of individual put options written on the stocks of each of the portfolio members. However, owing to the lower volatility of the weighted index thus

described, utilizing index options would be expected to be a more cost effective²⁰ strategy.

Figure 3.f: When the expected present value (EPV) of future claims cannot be accurately estimated, an insurance risk manager can select specialized derivative products in an asset portfolio to hedge against movements in the EPV of future claims. This can happen when new risk information about future insured events becomes available.



3.7 Summary

Nanotechnology's continued development depends on the affordability of engineered nanomaterials. The costs of nanomaterial production and use will depend on the affordability of regulatory compliance and employer liability insurance. Public sentiment will drive political forces that could adversely influence the quality of nanomaterial regulation. There is a need to diffuse anxieties among public interest groups and to offer regulators an effective framework to define safety standards for the production and use of nanomaterials. Simply extending current regulatory frameworks to include engineered nanomaterials could expose nanotechnology companies to additional risk in the form of unnecessarily high compliance cost (at the expense of innovation) and exploitive litigation. An effective framework

²⁰ The value of a vanilla option increases with the volatility of the underlying asset.

should promote affordable insurance and regulatory compliance and allow standards-bodies to draft a vocabulary of clear and unambiguous industry definitions and conventions. Such a vocabulary will lend further precision to the wording of future regulatory statutes and provide a much needed policy language for insurers to continually refine their insurance products.

A collaborative process was described in which such a framework evolved as an iterative process involving nanotechnology companies, insurers, scientists and public standards bodies. In this sense, the *fittest* solution would emerge as opposed to the imposition of a potentially ill-fitting extension of existing regulations for hazardous materials. Short term risk reduction strategies based on control banding and RMS methodologies were described. Their adoption could serve both as prerequisites for affordable insurance against short term risks and as candidates for industry standards to address future regulatory compliance. Collaborative efforts to achieve similar goals are already underway, as exemplified by the ‘NanoSafe’ Project, a collaborative effort between companies, universities and government bodies.

In general, long tail risks are not insurable using orthodox actuarial techniques. In the present absence of a capability to manage occupational long tail risks for nanomaterials, a financial engineering approach was outlined in which insurers could hedge their exposures to changes in the perceived costs of these risks.

Common to the interrelated requirements of insurers, regulators and the public relations efforts of proponents of nanotechnology, is the need for comprehensive occupational risk assessments, especially long term assessments. A rigorous understanding of these risks will provide for affordable insurance and regulation and allow nanotechnology proponents to diffuse concerns raised by its detractors.

4 A Qualitative Hazard Inference System and Case Study Validation

4.1 Overview

This chapter develops a theoretical inference framework that can operate on an arbitrary set of ENM physicochemical attributes to produce a hazard score. The motivation for such a framework is that it may help circumvent the intractable nature of an ENM risk assessment on a case by case basis given the vast and growing number of ENMs currently available. The hazard score reflects potential contributions from each of the attribute values to known modes of toxicity action. The system is highly intuitive and as such could be used by non-specialists. It is based on certain patterns of toxicity that have been identified with particular physicochemical properties of ultrafine materials (Donaldson et al. 2012). It's reasonable to suppose therefore that such toxicity patterns would be appropriate indicators of potential ENM hazards. In section 4.3, outputs from Sanowork are used to partially validate the scheme but only at a phenomenological level due to gaps in the data set.

These physicochemical 'flags' or *Structural Alerts* form the essence of the hazard inference system. In terms of their potential to illicit harm, the most significant attributes of an ENM are its parent material's status as a carcinogen, mutagen or if it presents a reproductive hazard. The next consideration would be the parent material's solubility and chemical reactivity in the target biological medium, which for example in the case of inhalation exposure would be the lungs. If the parent material appears benign in terms of the aforementioned properties, it's still possible for the ENM to present a health risk due to its nano specific properties. The most significant of these are its morphology, size and surface charge. Considerations of these key properties would provide an approximate sense of a ENMs hazard potential and moreover, would be accessible to non-specialists.

As a means of highlighting the system's potential efficacy, it is explored in the context of six manufacturing case studies that were the focus of the Sanowork project. The case studies are based on various states of ZrO₂, TiO₂, multi-walled carbon nanotubes (MWCNT), polyamide and silver. They were chosen because of their industrial and societal relevance due to the fact that they are currently being mass-produced by a number of manufacturers around the World. The materials are tested in a pristine state and in a remediated state in order to validate the efficacy of the system. The remediation strategies are based on the inference system's underlying hypothesis regarding the dominant contributing factors to ENM hazard. It follows from this hypothesis that modulating both the emission potential and the hazard properties enables risks to be controlled at the ENM level. This perspective formalizes the proposed strategies for risk mitigation as described in section 4.3.

4.2 Measuring ENM Hazards

In vivo toxicology procedures, the ideal way to measure hazard levels, are expensive and ethically problematic. The cheaper and faster options, *in-vitro* methods, have been criticized for their unrealistic use of high dose levels (Krug 2009) and of being unreflective of actual environments at the organism level²¹. Extrapolating from toxicity measured at the *in-vitro* cellular level to the human scale ideally requires animal studies as an intermediate step. Notwithstanding the obvious cost and ethical implications, animal to human risk extrapolation entails many assumptions regarding the similarities between animal and human physiology. For instance, subtle differences in human and animal enzymes may vastly affect the way the respective metabolisms respond to the presence of an ENM. Measuring ENM hazards and understanding the mechanisms which underlie them is fraught with many issues, not least of which is cost. Obtaining this

²¹ In one proposal to make *in vitro* tests more indicative of the reality of the target *in-vivo* environments, nano materials are first coated in blood serum proteins before being subject to *in vitro* testing (Monopoli et al. 2012).

information requires expensive, expert directed in-depth investigations to establish rigorous and verifiable protocols for determining an ENM hazard profile. Carrying out a separate analysis for each new ENM that comes on the market could impose a substantial and even unaffordable burden on ENM producers, the majority of which are small and medium enterprises.

This limitation stifles innovation and presents a threat to the entire industry in the event that toxicological profiling becomes mandatory. Availing of the outcomes of existing research from the toxicological literature may offer a cheaper alternative. Quoting from (Bergamaschi et al. 2015)

However this often requires careful interpretation and extrapolation of data by experts as the available literature data may not necessarily be tailored to extract hazard data for the particle in question.

Additionally, there can be variability within what is supposed to be the same material. This variability may originate from numerous and oftentimes subtle environmental factors that accumulate changes in an ENM between the time of production and its subsequent analysis. The latter is indicative of the problem of standardizing measurement procedures for both physicochemical and toxicity profiling. This makes it difficult to map toxicological profiles to physicochemical profiles. Chapter 5 addresses this issue to an extent within a Bayesian paradigm as Bayesian methods readily lend themselves to these kinds of problems.

4.2.1 ENM hazard inference

At a general level, it can be argued that hazards presented by foreign objects derive, in a majority of cases, from two principle sources: either from interference with metabolic pathways or from interference with the immune system. If these interference mechanisms are understood then potential hazards can be qualitatively ranked and moreover steps can be taken to reduce them.

The immune system comprises an arsenal of mechanisms to guard against the entry of foreign bodies. For example, particles that enter the deep recesses of the lungs, the alveolar region, will immediately come under

attack from macrophages, a specialized class of white blood cell, to engulf the foreign object and attempt to dissolve it with enzymes. If this fails, the macrophage will, under normal circumstances, carry the object to the upper lung regions where it will be expelled along with the macrophage by either a coughing or sneezing action. One way of compromising this mechanism is through the morphology of the object. If the object exceeds a certain length, as in the case of fibrous ENM, the macrophage may have difficulty ingesting it. Moreover, if the macrophage fails to break the object down into manageable components, it will suffer impaired mobility and may be unable to reach the higher lung regions where it can be expelled. The immune system will treat an immobilized macrophage as a foreign body, stimulating a cascade of secondary responses that may lead to prolonged bouts of inflammation and internal scarring, otherwise known as fibroses, a thickening of the lung tissue that reduces lung capacity. In this example, the toxicity of a fibrous material derives from the way its fibrous shape impairs the normal functioning of an immune response. An ENM's length may therefore be used to flag it as potentially hazardous. The above description is the primary toxicity mechanism underlying asbestosis. In the study (Hamilton et al. 2009), the pulmonary toxicity of a TiO₂ based nano material changed dramatically as the shape of the material is altered into one that a macrophage has difficulty processing. Where an inhaled object deposits in the lung is largely determined by its effective aerodynamic diameter (EAD). Larger particles tend to settle in the higher lung regions where they can be easily expelled. In the context of macrophage action, the hazards of fibrous ENMs can therefore be ranked according to their lengths and by the inverse of their EADs. The obvious remediation steps then naturally suggest themselves: Either reduce fibre length, which for example can be achieved through ball milling operations (see section 4.3), or modify its surface features to increase its effective aerodynamic diameter. It is important, however, that these modifications do not impact an ENM's intended functional properties. A third option exists that can reduce a fibrous ENM's hazard via inhalation. So far the strategies described have either been about preventing inhaled fibres reaching the alveolar or if they do, insuring that the alveolar macrophages are able to remove them by

reducing the fibre length. The third strategy would be to reduce the probability of inhalation in the first instance. This can be achieved by inducing fibrous ENMs to agglomerate into larger and heavier clusters so that the chance of becoming airborne and subsequently inhaled by an exposed worker is reduced. The latter also has the advantage that ENM clusters have large radii and are less likely to enter the alveolar if inhaled. Agglomeration can be achieved through freeze drying and spray drying procedures that are discussed in section 4.3 as part of the Sanowork case study. On the basis of the above discussion, one possible suggestion for scoring an ENM's hazard in the context of impaired macrophage action might be

$$\begin{aligned}
 & \textit{HazardScore}(\mathbf{ImpairedMacrophageAction}) \\
 & \equiv \frac{\textit{Fibre length}}{\textit{EAD} \times \textit{agglomeration state}} \quad \textit{Eq}(3.1)
 \end{aligned}$$

It should be mentioned however, that the outputs from the Sanowork project were of insufficient fidelity for Eq (3.1) to be meaningfully applied. Similarly, the hazard contribution from other ENM properties has to be assessed in the context of other modes of toxicity action. For instance, an ENM's surface charge may compromise the integrity of cell membranes it comes in contact with, leading to lysis (spilling of cellular contents). As an example of metabolic interference, an ENM's intrinsic reactivity coupled with a high surface area density may lead to copious production of reactive oxygen species that can induce oxidative stress, triggering cells to die prematurely. In this case a property of the parent material, the intrinsic reactivity, and a nano specific feature, a high surface area density, combine to produce an ENM specific hazard. If an ENM is composed of a material which is soluble in a target environment, then it will lose its nano specific features upon entering such an environment by dissolving into its constituent compounds. Hence, soluble ENMs can be risk assessed on the same basis as their parent materials since they should behave similarly in an exposed host. ENMs may also act as Trojan horses by transporting biological contaminants. ENM surfaces can absorb airborne and ground molecules e.g. bacterial endotoxins (Esch et al. 2010), which are able to induce inflammatory responses, (Bianchia et al. 2014; Dostert et al. 2008).

Such biological contaminants have a high propensity to induce inflammation.

Table 4.a summarizes ENMs physicochemical characteristics which are appraised from the literature and are known to strongly influence a material's toxicological profile (Structural Alerts/flags). The specific question underlying the use of a hazard inference scheme is to identify potential hazards without carrying out any toxicological testing. For example, since a fibrous shape of sufficient length is known to increase the pathogenicity of a material, a fibrous ENM can be immediately flagged as potentially hazardous without requiring toxicological testing.

Table 4.a: The relationship between structural alerts and physicochemical features relevant in terms of hazard and biological effects.

Structural Alert	Physico-chemical characteristics	Hazard/Effects Consequences
Size distribution: nanometric (1-100 nm range)	<ul style="list-style-type: none"> • Large surface area • High surface-to-volume ratio • Large amount of less coordinated and more reactive atoms/ions exposed at the particle surface 	<ul style="list-style-type: none"> • Potential for translocation • Increased deposition along the respiratory tract, in particular gas-exchange region • Different cell penetration routes and retention in many cells and organs to a larger extent than larger particles • Enhanced surface reactivity • Foster dissolution of the materials thus lead to the release of potentially toxic ions
Bulk material classified as a carcinogenic, mutagenic or toxic for reproduction (CMR) or sensitizer	<ul style="list-style-type: none"> • It cannot be excluded that the NM is a CMR or skin/respiratory sensitizer until tested 	<ul style="list-style-type: none"> • Potential for repeated dose toxicity, carcinogenesis, mutagenesis, sensitisation and/or reproductive toxicity
Purity/Contaminations	<ul style="list-style-type: none"> • Presence of reactive Transition metals used as catalysts • Amorphous carbon • PAHs etc. • Biological contaminants (e.g. endotoxins) 	<ul style="list-style-type: none"> • Potential for ion driven cytotoxicity/ inflammation/Oxidative stress, leading to acute toxicity, repeated dose toxicity (e.g. fibrosis), sensitisation and/or carcinogenicity • Enhanced inflammatory

		potential (<i>in vivo</i>)
Intrinsic reactivity of the material	<ul style="list-style-type: none"> • Photo-reactivity • Chemical reactivity • Presence of surface defects • Importance of surface reactivity relative to surface area 	<ul style="list-style-type: none"> • Potential phototoxicity (<i>infrequent</i>) • Potential for inflammogenic effects and/ or genotoxicity leading to acute toxicity, repeated dose toxicity, and/or carcinogenesis • Modulated by the interactions with biomolecules
Intrinsic acidity/basicity	pH alterations away from the normal range (for tissues/biological systems)	<ul style="list-style-type: none"> • A substantial pH deviation away from the normal range of the biological environment at the site of deposition could cause local effects such as skin irritation/ corrosion, or cell death within the lungs leading to inflammation/ oedema/ fibrosis.
Surface charge	<p>Propensity to agglomerate or aggregate in various fluids</p> <p>Zeta-potential as proxy for particle charge giving an idea of the level of agglomeration/ aggregation of the material</p>	<ul style="list-style-type: none"> • Potential for translocation • Reduced reactivity (i.e., agglomeration into large particles, will decrease the biologically accessible surface area) • Biological membrane and protein interactions (<i>charged biomolecules</i>) • Uptake by cells • Potential for cytotoxicity/ inflammation leading to acute toxicity, repeated dose toxicity
Solubility	<ul style="list-style-type: none"> • Release of ions in different matrices • Bio-durability <p><i>(Note: the bio-durability of carbon nanotubes has been shown to depend on many parameters such as their structure mono or multi-wall, the presence of surface defects, their functionalization etc.)</i></p>	<ul style="list-style-type: none"> • Cell uptake and release of toxic ions inside cells • Potential for ion driven cytotoxicity/ inflammation/ Oxidative stress/ leading to acute toxicity <p><i>(Note: soluble particle that does not release toxic ions or other components could result in the overall progressive reduction/removal of dose as the particle dissolves ultimately removing any toxic stimulus (if caused) or be intrinsically non-toxic. However, a particle that is soluble but releases toxic/reactive ions or other components may generate localised or even systemic toxicant accumulation and, hence, toxicity).</i></p>

		<ul style="list-style-type: none"> • Bio-persistence of the dose
Morphology and size/ classification as a High Aspect Ratio Particle (HARP)	<ul style="list-style-type: none"> • Aerodynamic diameter • Aspect ratio • Fibrous aspect/bundle-like spherical morphology 	<ul style="list-style-type: none"> • Potential for impaired clearance, lung and pleural retention • Potential for cytotoxicity/ inflammation/ oxidative stress leading to acute toxicity, repeated dose • toxicity (e.g. Fibrosis) and/ or carcinogenicity

Source: (Bergamaschi et al. 2015)

In (Bergamaschi et al. 2015), a number of questions are put forward to sift out the presence of structural indicators of potential hazards. These are:

1. *Is the median particle size in the upper or lower portion of the 100nm size range?*
2. *Is the bulk material classified as carcinogenic, mutagenic or toxic for reproduction (CMR) or sensitizer?*
3. *Is the nanomaterial reactive? (because: a) contaminated with reactive contaminants, or b) intrinsically reactive for the presence of chemical groups or photo-reactive)*
4. *Is the nanomaterial highly acidic / basic?*
5. *Does the nanomaterial have a charged surface?*
6. *Is the nanomaterial soluble? If so, does dissolution lead to the release of toxic or reactive components such as ionic species?*
7. *Is the nanomaterial a High Aspect Respirable Particle (HARP)?*

Affirmative answers to the questions in the above list are to be viewed as suggestive of potential toxicity rather than definitive. That is, an affirmative answer suggests the material in question may present a hazard and should be monitored accordingly for the effects it could induce, as detailed in Table 4.a. The hazard score in this case is simply the sum of affirmative answers and represents a more general notion of hazard that is less context dependent than that suggested by Eq (3.1) for example. As such, since the scheme is qualitative in nature, it suggests a possible range of hazards. However, viewed as a screening tool, its value lies in identifying those materials that may warrant further testing in order to provide numerical

hazard data which for instance might be required to satisfy regulatory or insurance requirements.

The other component contributing to ENM workplace risk are exposure levels which the scheme thus far described does not explicitly address. Although as mentioned previously, emission potential can be reduced at the material level by producing ENM clusters through freeze and spray drying techniques, or maintaining ENMs in wet states until the time of their application. Moreover, threshold doses need to be established for the possible effects outlined Table 4.a to manifest in order to determine the relevancy of such thresholds to realistic exposure scenarios.

4.3 Sanowork Case Study

The Sanowork project examined the occupational, and in one case environmental, risk linked to six manufacturing processes involving ENMs based on titanium, zirconium, carbon, polyamide and silver. Processing line 1 (PL1 and PL# generally) consisted of an environmental remediation operation to recover zirconium ENM precursors from waste water before discarding. PL2 produced ceramic pebbles formed from zirconium NP powders that were compressed in a mould before a high temperature treatment was applied to form the ceramic. PL3 produced water filters made from polyamide nano fibres (NFs). PL4 produced TiO₂ NFs for photo catalytic applications. PL5 spray coated ceramic and glass surfaces with solutions containing TiO₂ and silver NPs to create self-cleaning and antimicrobial properties. PL6 mixed CNTs with a polymer compound to imbue it with enhanced mechanical and fire retardant properties.

Such applications and manufacturing processes are fairly representative of the ENMs industry at the present time. As such, their detailed descriptions provided by the Sanowork deliverables and descriptions of risk remediation strategies where risks have been identified would form a very effective case

study for concerned parties outside the scientific communities, such as regulators and insurers in particular.

The occupational risks posed by the various ENMs that were studied under the Sanowork project were hypothesized to originate from three principle modes of toxic action: the cytotoxicity of reactive and soluble ENM components, as in the case of unreacted ions present in silver NPs; from the fibrous nature of the ENM, as in the case of carbon or titanium NFs and MWCNTs and in particular how this can impact the efficiency of macrophages to remove the material from the lung; and oxidative stress and cytotoxicity induction by highly redox reactive and low solubility NPs such as zirconium and titanium dioxide NPs. Thus, the proposed remediation strategies were designed to interfere with the assumed modes of toxic action to affect an overall reduction in hazard potential. Only in one process, PL1, was the remediation action implemented to primarily reduce environmental risk via the recycling of waste waters to recover zirconium ENMs.

The well-established cytotoxicity of silver based ENMs can be controlled by moderating their un-reacted ion content in order to render human exposure levels acceptable but not to the extent where they lose their sought after antibacterial effects. This compromise between human toxicity and antibacterial potential can be measured by defining a quality index for which values greater than one indicate the modified nonmaterial is antibacterial while presenting an acceptable risk to human health. The removal of ions can be achieved either through a filtration process or by immobilizing silver NPs in a TiO₂ matrix followed by a washing process that removes only the ions.

Low solubility high aspect ratio fibrous materials are difficult for the lungs to remove once inhaled, particularly if they enter into the alveolar regions owing to the inability of alveolar resident macrophages to engulf high aspect ratio NFs and then migrate to the higher lung regions for expulsion via the

mucociliary escalator²². The effective persistence of fibres in the lung can lead to recurring bouts of inflammation and subsequent healing resulting in a gradual thickening of lung tissue (fibrosis) causing a reduced lung capacity. It was found that the aspect ratio of TiO₂ NFs could be efficiently reduced by a ball milling procedure that breaks long fibres into shorter ones such that macrophages could efficiently engulf and remove them if inhaled. However, unbroken fibres still remained which on account of the very low occupational exposure limit (OEL) recommended for fibrous aerosols suggested that a residual exposure risk still remained, warranting further investigation. The risk of fibre inhalation could also be reduced by freeze and spray drying strategies to produce micron sized agglomerates but without negatively impacting their intended use. This technique was applied to carbon nanotubes in PL6.

Although low solubility and toxicity NPs such as those based on zirconium and titanium compounds may not present short term exposure risks, they may however pose chronic inflammation risks as a result of prolonged induction of oxidative stress, especially at concentrations based on OELs defined in terms of mass densities for larger particles. This follows from their bio persistence which tends to increase for decreasing NP diameter and to their intrinsic redox reactivity. It was also found that exposure concentrations measured in terms of number density could be reduced by 100 fold by promoting clustering of NPs and NFs into micron sized agglomerates via freeze drying and spray drying procedures and without compromising the nano scale reactivity and useful nano-metric properties to any significant degree.

In some instances it was found that simple organizational changes involving ventilation systems and fume hoods etc. could render exposure levels virtually undetectable. ENM modifications consisting of inorganic and organic coatings were implemented as toxicity inhibitors but it was found in

²² This is known as frustrated phagocytosis. Phagocytosis is the processes by which macrophages engulf and eliminate foreign objects, a process for which they are well adapted if the targeted pathogens have a low aspect ratio or are of a spherical nature.

almost all cases that such coatings had a negligible impact on ENM hazard measured in terms of cytotoxicity rates and ROS changes. In fact it was found in some instances that the modified materials were more potent than their pristine counterparts.

4.3.1 Outcome from exposure remediation techniques and partial implementation costs

4.3.1.1 PL1 -reactor washing and recovery of ZrO₂ production

This company's ZrO₂ ENM production reactor requires periodic washing. Ordinarily the waste water is treated by an external treatment facility from which the zirconium wastes may ultimately end up in the environment. This presents a potential environmental hazard which PL1 attempts to mitigate by removing and recycling the residual ZrO₂ ENM before discarding the waste water. The cleaning procedure comprises three steps: reactor washing; sedimentation of residual ZrO₂ in the resulting wastewater; and recovery of the ZrO₂ solids from the waste water sediment. Overall in terms of monetary benefits, the recovery of ZrO₂, as a result of implementing the risk mitigation steps is almost 100% efficient and translates to approximately a 7% savings in production costs. This saving should trickle down to consumers and users of ZrO₂ ENMs and be of an overall societal benefit in these terms alone. Importantly, there was no significant loss of functionalization with respect to thermal, mechanical and surface properties as a result of modifying the ZrO₂ ENMs. In terms of the intended effect of their application which was to increase dispersion during the reactor washing step, the silicate and citrate surface modifications did not result in any significant improvement. The bulk of the recovery efficiency is due to an improvement in the rate of sedimentation of the waste water solids from a rate that was too slow to measure within prescribed experimental parameters to less than one or two days after which the waste water solution had separated into a gel containing most of the ZrO₂ solid and a water solution almost entirely devoid of ZrO₂ ENM. This was achieved by changing the pH level of the wastewater ZrO₂ solution to a point that maximized the sedimentation rate as a result of the formation of micron

sized agglomerates. The final recycling step evaluated the combined contribution of all preceding steps with respect to recovery efficiency of ZrO_2 precursor; the gel that was formed as a result of accelerating the sedimentation process in step three was chemically treated to recover a ZrO_2 precursor which was approximately identical to that produced by the company's original manufacturing process. It was also noted that significant exposure levels of ZrO_2 ENMs followed the opening of the reactor door before washing. To reduce occupational exposure risk at this initial stage, ZrO_2 ENMs were first treated with a polymeric binder. This remediation step did not have the intended effect of reducing exposure. In fact, offline dustiness tests revealed it was dustier by a factor of three compared to the pristine material. The costs and benefits of the mitigation steps implemented by PL1 are summarized in Table 4.b in terms of environmental risk, toxicity levels, and efficiency enhancements and associated remediation costs

Table 4.b: ZrO₂_2_Sol denotes the waste water solution containing ZrO₂ NPs that are normally not recovered. ZrO₂_Sil_Sol and ZrO₂_Cit_Sol indicate ZrO₂ NPs in solution and coated with silicate and citrate respectively in an attempt to increase their dispersion to improve reactor washing efficiency. ZrO₂_gel indicates the gel that forms from the waste water containing most of the zro2 solid as a result of changing its ph. level to promote maximum sedimentation. ZrO₂_Pchem_Sol represents the gel from the sedimentation step chemically treated to recover the original ZrO₂ ENM precursor after which the waste water is discharged contaminant free

	No remediation	Washing		Sedimentation	recovery
	ZrO ₂ _2_sol	ZrO ₂ _Sil_Sol	ZrO ₂ _Cit_Sol	ZrO ₂ _gel	ZrO ₂ _Pchem_Sol
Time	2.7-4.4 hours per kg	Did not have a significant impact on washing efficiency in terms of ZrO ₂ dispersion in wastewater		48 hours for sedimentation to occur for 9.36 kg batch as compared to 1 week for pristine material. Also the waste water was left completely clear after sedimentation which is a positive environmental impact	1.2 hours per kg
Cost	ZrO ₂ _2 ENM powder: 674.14 Euros per Kg Colloid 600 g/L: 685.12 Eur per Kg	59.24 Euros per kg	67.34 Euros per kg	19.49 Euros per kg	9.64 Euros per Kg
Exposure	Human exposure low because the NPs are in a wet form. Environmental risk high since effluent may be discharged	Human exposure low because the NPs are in a wet form. Environmental exposure zero by definition		Human exposure low because the NPs are in a wet form. Environmental exposure zero by definition	Reduced environmental exposure since the waste water has been cleaned and ZrO ₂ recovered
Functional Change	None by definition	Did not significantly alter the functional properties of ZrO ₂ NPs		None	None
Human toxicity	Similar to reference material P25	<i>In conclusion, the tested RRS do not seem to influence the toxicological profile of pristine ZrO₂ NP. Rather, ZrO₂_10_Cit_Sol produced higher effects both in terms of oxidative stress and NO production.</i>			

4.3.1.2 PL2 - production of ZrO₂ by spray drying

The topology of this production line was such that the basic onsite measurement campaign revealed negligible emissions. Offline dustiness tests for the material ENM in question, ZrO₂ NPs, revealed that spray drying and freeze drying procedures promoted clustering of the NPs into micron sized aggregates which preserved the sought after nano-metric properties while reducing their emissivity potential by approximately a factor of 100. Since the remediation procedures didn't involve the use of additional compounds, as in ENM surface coatings, it was assumed their toxicity parameters were similar to those of the unmodified ZrO₂ NPs. It was found that for similar *in-vitro* dose levels, the toxicity of the ZrO₂ NPs in terms of oxidative stress and cytotoxicity were marginally lower than that of a reference material for which *in vivo* data was available. Based on emissivity factors, a particle number exposure estimate of 918 particles per cubic centimetre calculated from computer models was significantly below the recommended limit of 20000 particles per cubic centimetre. Estimated mass based exposure levels based on realistic particle diameters similarly came in at 0.00273 milligrams per cubic metre, well below the recommended OEL of 1 milligram per cubic metre. Overall, it was concluded that this manufacturing environment did not present a likely health risk to workers.

4.3.1.3 PL3 -production of polyamide nano fibres

Polyamide nano fibres are produced using an electro- spinning technique comprising an extrusion process of the bulk-material in the presence of a strong electric field. The overall effect is to produce a nano sized diameter fibre which is collected on a substrate above the extruder to form nano fibrous membranes. Offline abrasion and cutting tests on the resulting pristine membranes revealed no significant releases of fibres. Depositing layers of gelatine on the membranes, the proposed remediation technique intended to suppress fibrous releases during cutting, pleating and drilling operations had in any case a negative impact on their filtration efficiency. For these reasons it was concluded that a risk analysis wasn't feasible.

4.3.1.4 *PL4 -production of TiO₂ nano fibres*

TiO₂ nano fibres are produced by an electro-spinning process, as described above, for photo catalytic applications. The onsite and offline tests concluded that the set of activities involved in this production process presented likely health risks to workers. However, introducing ball milling as an extra risk remediation step in the manufacturing line that broke long fibres into shorter fibres was seen as an effective remediation strategy as small fibres are more easily cleared from the lungs if inhaled; the primary agents of insoluble particle clearance, the alveolar resident macrophages, are less compromised by short fibres than longer ones. Moreover, ballmilling had no significant impact on the sought after photo catalytic properties of the TiO₂ NFs.

4.3.1.5 *PL5 - TiO₂ and Ag NPs for spraying ceramics*

This production line exploits the photo catalytic properties of TiO₂ NPs to provide a self-cleaning mechanism for ceramic tiles. The tiles are sprayed with a dispersion of TiO₂ NPs before drying in an electric kiln in which the NPs are fixed to tile surfaces. Table 4.c contains hazard, exposure, risk and associated costing data in relation to the spraying operation which is considered a high risk exposure scenario. Exposure data for the pristine material, TiO₂_sol, was taken from the measurement campaign carried out by one of the Sanowork partners. Offline emission potentials were only investigated for the ENMs in powder form and their modified counterparts and not for solution dispersions, meaning there is no offline exposure data for the dispersions identified as TiO₂_NP_SD, TiO₂_NP_Sil_Sol and TiO₂_NP_Cit_Sol. It might be reasonable to conjecture that TiO₂_NP_SD is less emissive than the pristine form since this was found to be the case for zirconium NPs and CNTs that had been sprayed dried to produce micron sized agglomerates. PL5 also applies silver NP based coatings for their antibacterial effects, an operation that is again considered high risk for the workers involved. Hazard, exposure, risk and costing data in summarized in Table 4.c.

Table 4.c: Toxicity, exposure and risk data and remediation costs for the spraying of TiO₂ NPs operation in PL5, considered a high risk task for workers.

	TiO₂_Sol (unmodified TiO₂ NPs in solution for spraying)	TiO₂_NP_SD (spray dried TiO₂ to promote agglomeration into micron sized structures and then re- dispersed for tile spraying)	TiO₂_NP_Sil_Sol (TiO₂ NPs coated with silicate in solution)	TiO₂_NP_Cit_Sol (TiO₂ NPs coated in citrate in solution)
Exposure during spraying operation	8195 particles/cm ³ GMD: 0.018 (mg/m ³) φ 100 nano metre UL: 18 (mg/m ³) φ 1 μm (However, all only a tiny fraction are expected to be TiO ₂ particles)	?	?	?
Toxicity	Comparable to bench mark material P25	Oxidative stress comparable to pristine material. Stronger inflammogenic potential compared to pristine material	Oxidative stress comparable to pristine material. Stronger inflammogenic potential compared to pristine material	Oxidative stress comparable to pristine material. Stronger inflammogenic potential compared to pristine material
Risk	Health risk in worst case, i.e. assuming exposure levels are entirely attributable to TiO ₂ .	?	?	?
Functional Change	None by definition	Slightly less photo-catalytic than pristine material	Higher photo-catalytic than pristine material	Significantly less photo-catalytic than pristine material
Cost	13.5 Euros per Kg (procurement)	18 Euros per kg (production)	4 Euros per Kg (production)	15 Euros per Kg (production)
Production Time	Externally procured	2 hours per Kg	24 hours per kg	0.032 hours per Kg

The risk from the silver nano particles was hypothesized to come from the presence of un-reacted silver ions in the parent material. These were removed using either filtering procedure or were immobilized in a TiO₂ matrix. Toxicity data is not available for the immobilized state and in any case was found to be less cost effective than the filtration method

Table 4.d: Toxicity, exposure and risk data and remediation costs for the spraying of silver NPs operation in PL5, also considered a high risk task for workers.

	Ag_Sol (unmodified silver NPs in solution)	Ag_Sol_UF (silver NP solution that has been filtered to remove unreacted ions)	Ag_NP_IMMW (silver NPs that have been immobilized in titanium dioxide matrix and then washed to remove unreacted ions)
Exposure	<i>1.6 x10⁴ particles/cm³ GM: 0.089 (mg/m³) φ 100 nanometre UL: 89 (mg/m³)</i>	?	?
Toxicity	Very toxic	Much less toxic (but likely still antibacterial)	?
Risk	Likely unacceptable in worst case in which all the particles in the exposure measurement contain silver.	?	?
Functional Change	None by definition	None in terms of desired antibacterial effect	None in terms of desired antibacterial effect
Cost	60 Euros per Kg	90 Euros per Kg	65 Euros per Kg
Production Time	Externally procured	0.4 hours per Kg	0.6 hours per Kg

4.3.1.6 PL6 -Tio2 extrusion of plastic composite

This process produced a plastic composite via an extrusion process. The composite is embedded with CNTs to enhance its mechanical properties such as its breaking strength and flame retardant properties. The CNTs, identified as the main source of exposure risk during the extrusion process, were modified by promoting aggregation via freeze and spray drying

procedures to reduce the presence of isolated CNTs in the operators breathing vicinity. Onsite exposure measurements did not detect any discernible difference between levels of pristine and modified CNTs. The unexpected anomaly in exposure measurements was attributed to particles other than CNTs accounting for most of the measured exposure levels and insufficient information prevented the proportion of actual CNT levels to be estimated in each case. For this reason the exposure values in Table 4.e refer to offline measurements of pure CNT levels taken during dustiness tests.

Table 4.e: Toxicity, exposure and risk data and remediation costs for the extrusion of plastic composite embedded with CNTs.

	C_NT (unmodified carbon nano tubes)	C_Pol_NP_FG (carbon nano tubes that have been freeze dried to form micron sized agglomerates)	C_Pol_NP_SD (carbon nano tubes that have been spray dried to form micron sized agglomerates)
Exposure (From dustiness tests with capturing hood)	250 particles/cm ³ GMD: 0.00028 (mg/m ³) ϕ 100 nano metre UL: 4.42 (mg/m ³) ϕ 2.5 μ m	100 times less emissive than Pristine powder	No exposure
Toxicity	Induced higher ROS levels than the reference material	Expected to be less inflammatory <i>in vivo</i> than pristine material. Expected to produce slightly less ROS than pristine material	Expected to be less inflammatory <i>in vivo</i> than pristine material. Expected to produce slightly less ROS than pristine material
Risk	Health risk present	Substantially reduced	Substantially reduced
Functional Change	None by definition	No significant impact	No significant impact
Cost (measured as energy)	32 KWH per kg	60 KWG per kg	34.74 KWH per kg
Production time	Externally procured	2 hours per kg	11 hours per kg

4.4 Summary

This chapter detailed a hazard inference system based on the contribution certain ENM physicochemical attributes make to various modes of toxicity action. The suspected causative links between physicochemical properties and toxicological responses are supported by a series of observations that

have been documented from studies on nano materials, described in the past as ultrafine materials. The risk remediation strategies of the Sanowork project informed the system's underlying hypotheses regarding the contributing factors to ENM toxicity. As such the Sanowork output has been used as a case study to lend support to the feasibility of the system. It should be stressed however, that due to gaps in the gathered exposure data etc., the Sanowork output does not conclusively demonstrate the system's feasibility. It's important to note that the case study by itself also provides a close up view of activities and processes that are typical of the ENM industry at the present time. For this reason it may prove to be of some use for regulators or insurers in these terms alone.

For PL1, A remediation action eliminated an environmental exposure including human exposure. This was achieved by promoting agglomeration of ZrO₂ nano materials to accelerate a sedimentation process so they could be quickly recovered. This type of remediation is of the kind that reduces the probability of emission and therefore a toxicological response from being activated in the first instance. The risk remediation step deployed for PL2 was essentially of the same kind as that used for PL1. That is, emission probabilities of the material in question were reduced by promoting agglomeration. The remediation step proved successful as the dustiness factor for the material in question was reduced by approximately 100 fold. It was determined PL3 presented little to no health risk, hence no remediation actions were required. In the case of PL4, a health risk of the material in question was due to its fibrous nature (TiO₂ nano fibres) and its dry state, presenting a high emission potential. In accordance with the hypothesized hazard associated with fibrous materials, the remediation step was to reduce the lengths of the fibres using a ball milling procedure. Subsequent *in-vivo* testing revealed this action resulted in a significant reduction in toxicity. It was concluded however that some health risk remained as a minority of the fibres manage to evade the remediation action. Insufficient exposure data for PL5 prevented a full determination of the effectiveness of the remediation action to reduce exposure, which was spray and freeze drying to induce agglomeration. However, since the same remediation action

proved effective for reducing the emission potential of powdered ENMs, it might be fair to conclude it would have a similar effect on dispersions. In the case of TiO₂ NPs in dispersion, an attempt was made to reduce their reactivity using either silicate or citrate coatings. However these attempts had only a marginal effect on the observed levels of oxidative stress this material induced *in-vitro*. In the case of the silver NPs, the predominant source of toxicity was conjectured to stem from the unreacted silver ions present in the parent material, silver, coupled with a high surface area density per unit mass of the nano form that would foster an efficient release of the un-reacted ions into the host tissues. The proposed remediation strategy on the basis of this conjecture was to filter the ions from the silver NPs. This action proved effective in terms of reducing the toxicity of the silver NPs. In the case of PL6, emission potential was reduced by inducing CNTs to form micron sized aggregates via spray drying and freeze drying procedures. Oxidative stress and inflammatory levels were also marginally reduced as an after effect of a coating that had been applied to the CNTs to improve their dispersion before freeze drying and spray drying in order to produce more homogenous aggregates/agglomerates.

The most effective mitigation strategy appears to be reducing emission via aggregate/agglomerate formation via spray drying and freeze drying procedures. In the case of PL4 reducing the length of TiO₂ nano fibres also proved effective. Surface coatings intended to reduce toxicity based on oxidative stress and inflammation mechanisms proved to be less effective. While addressing the toxicity of silver NPs, mitigation was achieved by changing a property of the parent material, which in this case was the removal of un-reacted silver ions

It's important to communicate these key results to key stakeholders given the growing prevalence of applications which use the materials and similar materials studied under the Sanowork project. Insurers and regulators would likely find the outcomes the Sanowork project and similar projects very informative, prompting them to possibly relax concerns they may be harbouring concerning workplace risks linked to ENMs. For the risks thus described, specific insurance provision would fulfil a self-regulatory role

that would be of optimum benefit to policy holders in terms of risk management costs and preserving the social or network capital formed by the labour force driving this industry. As a final point, it was important that a risk mitigation strategy did not impact upon the desired functional properties of the ENM in question. Such outcomes could undermine the profit margins, competitiveness and reputation among potential investors of the respective companies; a loss of revenue could curtail insurability options given that affordability is a key prerequisite of insurability.

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

5.1 Overview

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 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 nano particles that were supplied from a common batch. Each of the measurements in the set was carried out by one of several disparate institutions. It's in the authors 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.

5.2 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 and Xu 2009). This has led to many inconsistent

claims in the literature regarding the toxicity of certain classes of ENMs (Sophie et al. 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 and Lahti 2007).

With this in mind, the focus of this chapter is to describe a framework that incorporates marginal probability representations of a 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 and 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 and 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 et al. 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's 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 et al. 2013).

The next section briefly outlines some current approaches to 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 paper offers such a representation. Section 5.4 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 section 5.4, section 5.5 develops the paper'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 section 5.6 to the recovery of marginal probability density distributions of ENM

physical attribute and toxicity data for which the assumption of normality in section 5.5 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, section 5.7 finishes with a brief overview of the multi-parameter generalization of the one dimensional problems described in sections 5.5 and 5.6.

5.3 Current Approaches to Calculating Exposure Risk.

5.3.1 *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 responses²³. 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 et al. 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.

²³ 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.

A second cause for concern is that many *in vitro* studies to date involve pristine nano materials 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 et al. 2012). The effect of the corona is to essentially 'tame' the NPs by reducing their surface energies and thus their potential to illicit intra cellular damage. In fact it has been demonstrated that the intra cellular 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 and 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 et al. 2011).

5.3.2 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 reductionist²⁴ approach to the problem. For example, simulations of approximate models of entire viruses (Freddolino et al. 2006) have already been achieved, but opinions are mixed as to their 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 et al. 2009; Joyner and 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

²⁴ 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.

between themselves and the reality they are attempting to describe. This is known as the ‘*butterfly effect*’²⁵ 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 two weeks (Teixeira, Reynolds and 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 et al. 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 and Byrne 2013), similar to what currently happens in various fields of engineering.

²⁵Hypothetical 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.

5.3.3 Pharmacokinetics and its application to long term risk estimation

Pharmacokinetic approaches for estimating the distributions of bio-persistent 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 et al. 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 et al. 1996; Brook et al. 2004; Cass et al. 2000; Moulton and Yang 2012; Schwartz 2000; Schwartz and Neas 2000; Stone, V. , Johnston and Clift 2007; Tiitanen et al. 1999). An in depth investigation of this approach is carried out in chapter 5 in the context of developing a quantitative insurance model.

5.4 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.

5.4.1 Principle of maximum entropy

The principle of maximum entropy forms an important adjunct to Bayesian statistics, particularly in its application to estimating prior distributions (Guisu & Shenitzer, 1985). The natural world, as formed by the collective actions, influences and interplay of the geosphere, biosphere and Noosphere²⁶, is replete with distributions of an infinite variety. From the distributions of molecular speeds in gases²⁷ 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's 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

²⁶ Noosphere denotes the sphere of human intellect and its effects, through conscious intention, on the physical environment.

²⁷The 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.

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 article will be the need to uncover the entropy of certain marginal probability distributions that are consistent with experimental hazard and material characterization data (see section 5.6). Those distributions with the greatest entropy, that deem them most likely to occur in reality, are then selected as inputs to the model²⁸.

5.5 Probabilistic Relationship 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 potential²⁹ on ROS³⁰ levels for one particular cell line are

²⁸ Numerically, the entropy $H[P(x_1, x_2 \dots x_n)]$ of a general discrete multivariate distribution, $P(x_1, x_2 \dots x_n)$, is given by: $H[P] = \sum_X P(x_1, x_2 \dots x_n) \log(P(x_1, x_2 \dots x_n))$ in which the summation is taken over all allowable assignments of the vector $X = (x_1, x_2 \dots x_n)$. Informally, if P is 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.

²⁹ 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.

³⁰ 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 nano particle. There are many varieties with probably the most cited in the literature being reactive oxygen species (ROS), cytotoxicity, cell viability, cytokine numbers and geno toxic 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, e.g. metallic nano materials. 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). Geno toxicity effects measure changes in a cell’s DNA structure due to the presence of a pathogen.

measured for a set of n ENMs. A regression algorithm should extract from the data a parameterized 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 5.a. In Table 5.a, r_k represents a ROS measurement for the ENM labelled as I_k , for $k = 1, 2 \dots n$, 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 5.a 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 5.a 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 poly-disperse³¹ 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.

Allow $\rho(r_k, z_k | I_k) dr_k dz_k$ 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

³¹ A poly-disperse ENM is characterized as one having by a diverse range of values over a particular attribute or set of attributes.

analysis: using Bayes Theorem, this joint distribution is decomposed into posterior and prior marginal distributions given respectively by $\rho(r|z, I_k)$ and $\rho_1(z|I_k)$, or alternatively by $\rho(z|r, I_k)$ and $\rho_2(r|I_k)$, such that

$$\rho(r, z|I_k) = \rho(r|z, I_k)\rho_1(z|I_k) = \rho(z|r, I_k)\rho_2(r|I_k) \quad (5.1)$$

The posterior, $\rho(r|z, I_k)$, has the following interpretation: $\rho(r|z, I_k)dr$ 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's 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 section 5.7. The assumption that r is dependent on z only is reflected in $\rho(r|z, I_k)$ by dropping its dependence on I_k so that $\rho(r|z, I_k)$ is thus given simply by the universal quantity, $\rho(r|z)$, that is common to all ENMs (It's important to note that the Bayesian formulation of the least squares regression method being developed here hinges on the assumption that $\rho(r|z)$ is of a universal character).

Table 5.a: 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

The marginal quantities $\rho_1(r|I_k)$, $\rho_2(z|I_k)$ and $\rho(r|z)$ are related by first integrating over the joint distribution and then employing the Bayesian relation, Eq (5.1), such that

$$\begin{aligned}\rho_2(r|I_k) &= \int_0^\infty \rho(r, z|I_k) dz = \int_0^\infty \rho(r|z, I_k) \rho_1(z|I_k) dz \\ &= \int_0^\infty \rho(r|z) \rho_1(z|I_k) dz \quad (5.2)\end{aligned}$$

$\rho(r, z|I_k)$ provides a complete description of the relationship between ROS levels and zeta potentials for material I_k . Loosely speaking, it can be said that if $Max \rho(r, z|I_k) = \rho(r', z'|I_k)$ then a 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 $\bar{r}(z) = \int_0^\infty \rho(r|z) r dr$. 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, $\rho_2(r|I_k)$ and $\rho_1(z|I_k)$, that are reflected by the variance components Δr_k and Δz_k as shown in Table 5.a.

How to build $\rho(r, z|I_k)$ and $\rho(r|z)$ from the marginal quantities $\rho_1(r|I_k)$ and $\rho_2(z|I_k)$?

A first approximation is to assume that $\rho(r|z)$ and $\rho_1(z|I_k)$ are normally distributed about their average values so that $\rho_1(z|I_k) \approx N(\bar{z}_k, \Delta z_k^2)$. From the hypothetical data in Table 5.a we construct n such normal distributions for the zeta potential measurements of each material I_k . These distributions, as shown in Table 5.b, are then inserted into Eq (5.2) to yield n conditions that $\rho(r|z)$ must simultaneously satisfy, as shown in Table 5.c

Table 5.b: Representation of the error and mean values in Table 5.a as PDFs that describe the uncertainty in the ROS and ZP measurements. 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.

$\rho_2(z I_1)$	$\rho_1(z I_1) \approx N(\bar{z}_1, \Delta z_1^2)$	I_1
$\rho_2(z I_2)$	$\rho_1(z I_2) \approx N(\bar{z}_2, \Delta z_2^2)$	I_2
...
...
...
...
$\rho_2(z I_n)$	$\rho_1(z I_n) \approx N(\bar{z}_n, \Delta z_n^2)$	I_n

Table 5.c: The PDFs in Table 5.b must all satisfy Eq (5.2). This provides n conditions that $\rho(r|z)$ must simultaneously satisfy

$\rho_2(r I_1) = \int_0^{\infty} \rho(r z)\rho_1(z I_1) dz$
$\rho_2(r I_2) = \int_0^{\infty} \rho(r z)\rho_1(z I_2) dz$
...
...
...
...
$\rho_2(r I_n) = \int_0^{\infty} \rho(r z)\rho_1(z I_n) dz$

Since $\rho(r|z)$ is also assumed to be a normal distribution in which the mean and variance, given respectively by $\bar{r}(z)$ and $\sigma(z)$, are parameterized by z , such that

$$\rho(r|z) = N(\bar{r}(z), \sigma(z)^2) \quad (5.3)$$

means that the joint distribution for each material is given by;

$$\begin{aligned} \rho(r, z|I_k) &= \rho(r|z)\rho_2(z|I_k) \approx N(\bar{r}(z), \sigma(z)^2)N(\bar{z}_k, \Delta z_k^2) \\ &= \frac{1}{2\pi\sigma(z)\Delta z_k} e^{-\frac{(\bar{r}(z)-r)^2}{2\sigma(z)^2}} e^{-\frac{(\bar{z}_k-z)^2}{2\Delta z_k^2}} \\ &= \frac{1}{2\pi\sigma(z)\Delta z_k} e^{-\left(\frac{(\bar{z}_k-z)^2}{2\Delta z_k^2} + \frac{(\bar{r}(z)-r)^2}{2\sigma(z)^2}\right)} \end{aligned} \quad (5.4)$$

The expressions in Table 5.c 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 Eq (6.5), 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 5.a. The optimal choices of $\bar{r}(z)$ and $\sigma(z)$ are therefore those that minimize the sum of the squared terms in Eq (5.5)

SumProbabilitySquares

$$\begin{aligned}
&= \sum_{k=1}^n \left(\text{var}(\rho_2(r|I_k)) - \text{var}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \right)^2 \\
&\quad + \left(\text{mean}(\rho_2(r|I_k)) - \text{mean}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \right)^2 \\
&= \sum_{k=1}^n \left(\Delta r_k - \text{var}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \right)^2 \\
&\quad + \left(\bar{r}_k - \text{mean}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \right)^2 \quad (5.5)
\end{aligned}$$

In which

$$\begin{aligned}
\text{mean}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) &= \int_{r=0}^{\infty} r \left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) dr \\
\text{var}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \\
&= \sqrt{\text{mean}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) - \int_{r=0}^{\infty} r^2 \left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) dr}
\end{aligned}$$

It is further assumed that $\bar{r}(z)$ and $\sigma(z)$ are linear³² in z such that for constants a, b, c and d

$$\bar{r}(z) = a + b z \quad (5.6.1)$$

$$\sigma(z) = c + d z \quad (5.6.2)$$

Inserting Eq (5.1) and Eq (5.2) into Eq (5.5) 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 Eq (5.5) 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 ³³

$$\rho_1(z|I_k) \rightarrow \delta(\bar{z}_k - z)$$

$$\rho(r|z) \rightarrow \delta(\bar{r}(z) - r)$$

so that heuristically;

$$\begin{aligned} \text{mean}\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) &= \int_{r=0}^{\infty} r\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) dr \\ &= \int_{r=0}^{\infty} r\left(\int_{z=0}^{\infty} \delta(\bar{r}(z) - r)\delta(\bar{z}_k - z) dz\right) dr = \int_{r=0}^{\infty} r\delta(\bar{r}(\bar{z}_k) - r) dr \\ &= \bar{r}(\bar{z}_k) \quad (5.7) \end{aligned}$$

(See³⁴)

This implies that in the limit of negligible variances, Eq (5.5) reduces to

³² In general this assumption isn't 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.

³³ A normal distribution tends to a delta function for vanishing variance. That is $N(\bar{x}, \sigma^2) \rightarrow \delta(\bar{x} - x)$ as $\sigma \rightarrow 0$.

³⁴ 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 $f(z) = \delta(\bar{r}(z) - r)$

$$\begin{aligned}
SumProbabilitySquares &= \sum_{k=1}^{k=n} (\bar{r}_k - \bar{r}(\bar{z}_k))^2 \text{ in which } \bar{r}(\bar{z}_k) \\
&= a + b \bar{z}_k \quad (5.8)
\end{aligned}$$

In accordance with conventional least squares regression methodology, a and b are then chosen to minimize the sum of the squared terms in Eq (5.8) to provide a best fit to the data points (\bar{r}_k, \bar{z}_k) for $k = 1, n$.

5.5.1 Example case

The methodology is demonstrated by the following test case. For numerical expediency the variance term, $\sigma(z) = c + d z$, 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 Eq (5.5) is minimized. Loosely speaking, σ provides a measure of confidence regarding the accuracy of the mean fit as prescribed by $\bar{r}(z) = a + b z$, 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

Figure 5.a: Figure 5.a.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 Figure 5.a.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. Figure 5.a.b and Figure 5.a.c show the rather slow convergence to Figure 5.a.d by tending $\Delta z_2 = \Delta r_2 \rightarrow 0.1$ 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 $z_1 = 0, r_1 = 0.05, z_2 = 0.2, r_2 = 0.1, z_3 = 0.3, r_3 = 0.35$

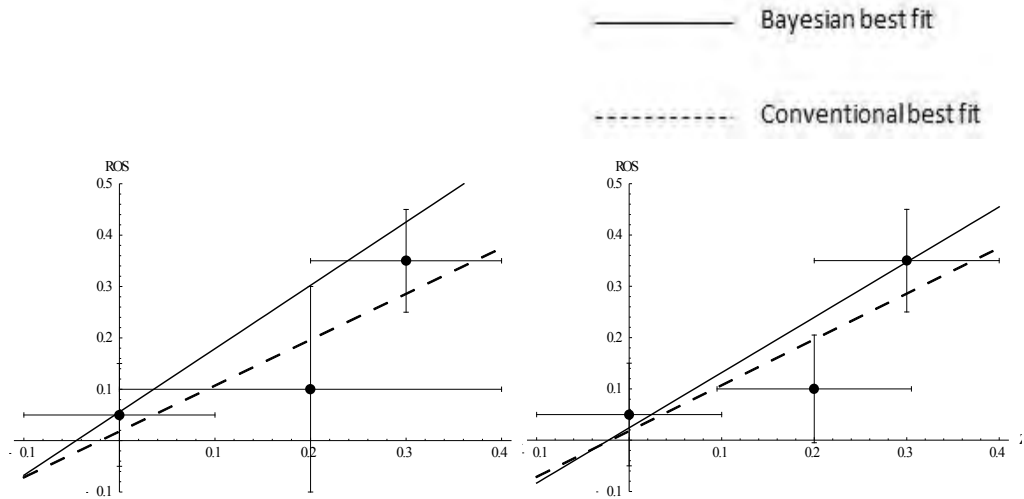


Figure 5.a.a $\sigma = 0.031, \Delta z_2 = \Delta r_2 = 0.2$ **Figure 5.a.b** $\sigma = 0.031, \Delta z_2 = \Delta r_2 = 0.105$

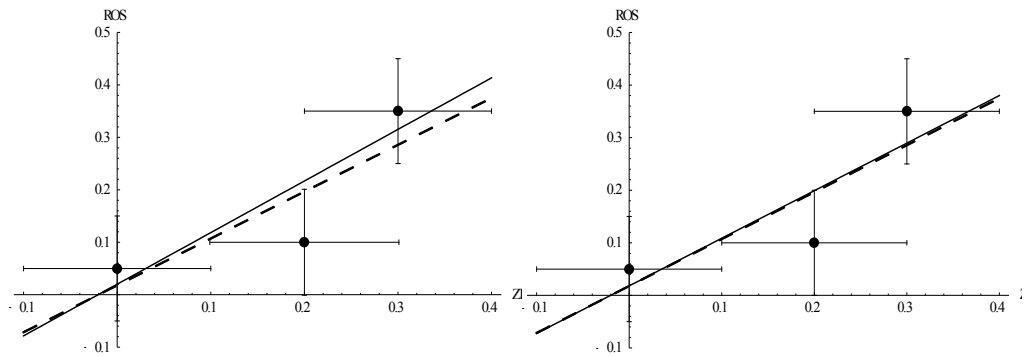


Figure 5.a.c $\sigma = 0.035, \Delta z_2 = \Delta r_2 = 0.101$ **Figure 5.a.d** $\sigma = 0.051, \Delta z_2 = \Delta r_2 = 0.1$

5.6 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 (see appendix 8.1). The usual practice is to summarize such data as a mean and variance as shown in Table 5.a. 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, $\rho(r|z)$, also has maximum entropy allows for a broader generalization of Eq (5.5) 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, $\rho'(r|I_k)$ and $\rho(z|I_k)$) :

SumProbabilitySquares

$$= \sum_{j=0}^l \sum_{k=1}^n \left(\text{moment}_j(\rho_2(r|I_k)) - \text{moment}_j\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I_k) dz\right) \right)^2 \quad \text{Eq(5.9)}$$

in which

$$\rho(r|z) \propto e^{m_0(z)+r m_1(z)+r^2 m_2(z)+\dots+r^n m_l(z)} \quad \text{Eq(5.10)}$$

It can be seen from Eq (5.10), 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 section 5.5, the functions $m_0(z), m_2(z) \dots m_l(z)$, are assumed to have a linear form given by $m_0(z) = a_0 z + b_0, m_1(z) = a_1 z +$

$b_1 \dots m_l(z) = a_l z + b_l$. The constants $a_0, b_0, a_1, b_1 \dots a_l, b_l$ are then chosen such that they minimize the probabilistic least squares expression given by Eq (5.9)

5.6.1 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*³⁵. Table 5d summarises the data consisting of a series of zeta potential measurements carried out by seven disparate institutions that comprised the study. Each of the ENM samples on which the measurements were carried out were supplied from a common ENM batch.

Table 5.d: zeta potential measurements made by seven institutions that formed the study.

Institution Id	1	2	3	4	5	6	7
Zeta Potential Measurement (Mv)	10	40	50	50	60	60	06

This group, comprising a number of institutions with ENM characterisation 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 nano particles) that were considered mono disperse with respect to both size and zeta potential.

³⁵ (<http://www.nanoehsalliance.org/>).

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 poly-disperse 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 poly-disperse across various metrics. Figure 5.b 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 Figure 5.c.

Figure 5.c depicts one particular set of results obtained by seven members of the group to measure the zeta potential of cerium oxide nano-particles 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's 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 figure 5.c to represent a realistic zeta potential distribution, more measurements would be required.

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 Figure 5.b.

Figure 5.b: 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.

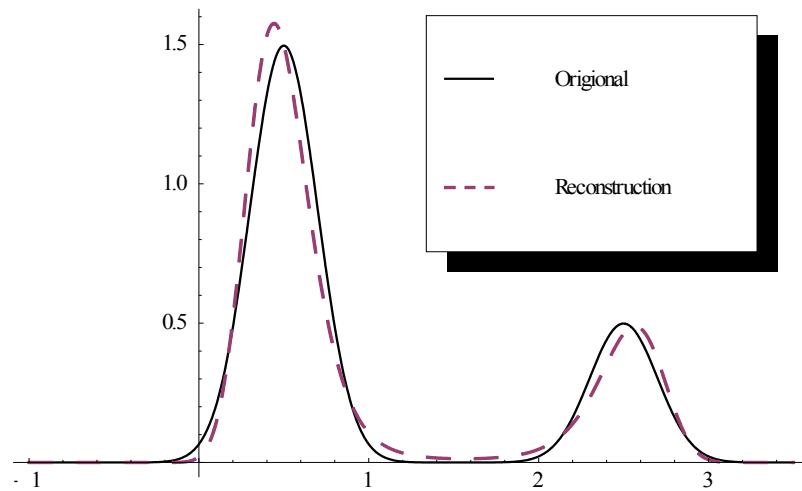
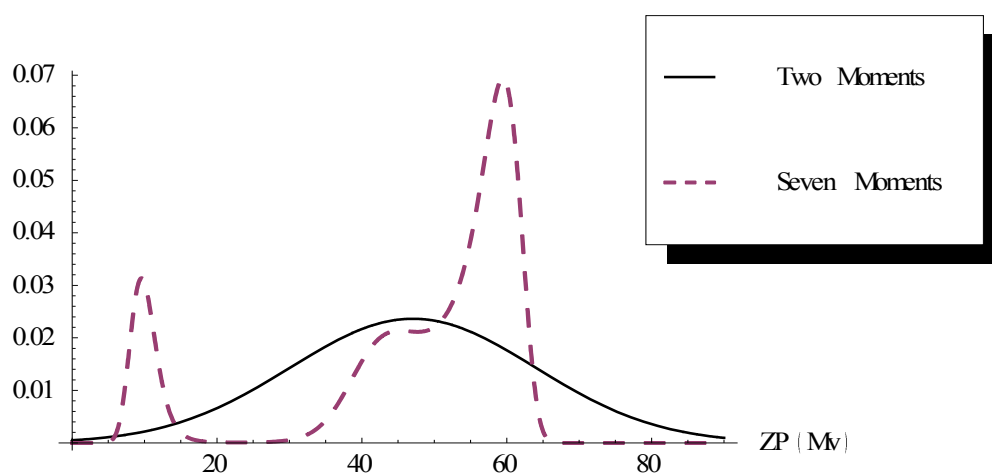


Figure 5.c: A discrete set of seven data points representing zeta potential measurements in millivolts of cerium oxide NPs taken from the same batch are used to build a PDF describing their distribution. The points are used to calculate the first seven moments that are then used to build the corresponding distribution from the Max entropy principle. The seven data measurements where; 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, 7.70714×10^6 , 4.37186×10^8 and 2.5045×10^{10} . While the first seven calculated from the PDF are; 1, 47.1345, 2499.45, 137537, 7.70539×10^6 , 4.37086×10^8 and 2.50397×10^{10}



It's important to note from Eq(5.9) 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, Eq(5.9) 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 Eq(5.9) 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 Eq(5.10),

SumProbabilitySquares

$$= \sum_{j=0}^{l \times n} \left(\text{moment}_j(\rho_2(r|I)) - \text{moment}_j\left(\int_{z=0}^{\infty} \rho(r|z)\rho_1(z|I) dz\right) \right)^2 \text{ Eq(5.10)}$$

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 Eq(5.9).

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 Eq (5.9) 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..

5.7 Multi-Dimensional Problem

The observed responses in terms of biomarkers to the presence of a pathogen such as a ENM depend not only on the pathogen but also 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 nano toxicology 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 multi-dimensional version of the example described in section 5.5 that will correlate multiple hazard values with multiple physical attribute data. This problem is formulated as identifying the multivariate joint distribution $\rho(h_1, h_2 \dots, z_1, z_2 \dots | I_k)$, in which h_1, h_2 denotes a list of hazard metrics taken from the hazard tensor³⁶ for material I_k and $z_1, z_2 \dots$ is a corresponding list of physical attribute metrics such as aspect ratio, size, zeta potential etc.

Tackling the multi-dimensional case should proceed analogously to the analysis of the two dimensional problems examined in section 5.5 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 multi-core/processor architectures.

5.8 Summary

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

³⁶ 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, \mathbf{H} , given by

$$\mathbf{H} = \begin{pmatrix} h_{1,1} & h_{1,2} & \dots & \dots \\ h_{2,1} & h_{2,2} & \dots & \dots \\ \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots \end{pmatrix}$$

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 met 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.

By extracting the optimum information content from potentially noisy data, 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 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 poly-disperse 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 Eq (5.9) 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 section 5.5. 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.

6 Insurance Model for ENM Exposure Risk

6.1 Overview

This chapter begins with a discussion about the role of risk communication in relation to quantitative risk modeling and underwriting which in the insurance world are considered two distinct functions. Underwriters tend to view actuarially determined outputs of quantitative risk models as suggestive rather than definitive; they will generally consider extraneous factors beyond quantitative risk estimates when setting premium rates and is the reason why communication of qualitative and meta aspects of risk is an essential input for underwriting functions. From these considerations, the author then distils the main requirements of an insurance model: not only must it provide quantitative risk modeling capabilities but equally essential, if not more so, is the ability to systematically represent and communicate qualitative and Meta aspects of risk to the underwriter. This follows with a description of how to formally define an insurance premium for the risk presented by a single manufacturing line in terms of premiums for elementary risk scenarios corresponding to basic manufacturing steps. The novelty here lies in the description of operations and sub operations as nested structures to describe a manufacturing process. This nesting structure then suggests a general architecture for a risk description and communication protocol that is described in section 6.3.7 in terms of a markup language. The latter has the advantage of being able to encapsulate Meta information together with quantitative modelling techniques within their appropriate contextual scopes for assessing the risk presented by an elementary manufacturing step. As an example, a hypothetical protocol is outlined and applied to one of the manufacturing lines described in chapter 4.

For the purpose of calculating premium rates for elementary risk scenarios, several quantitative models are also presented with increasing degrees of sophistication, culminating in a method for calculating premiums within a Bayesian framework. The latter incorporates a simple pharmacokinetic

model that describes ENM accumulation and depletion in an exposed worker. Within the Bayesian framework, account is taken of all possible exposure histories a worker might experience as well as the uncertainty in ENM hazards as expounded in chapter 4. The capability to deal with each possible exposure history addresses the difficulties associated with exposure estimation and measurement that was highlighted in chapter 4; for each possible exposure history, the problem of assessing risk becomes relatively simpler. Generally speaking, the value of applying Bayesian principles derives from their capacity to decompose a problem into relatively simpler and better defined problems that are easier to analyse.

6.2 The Necessity of Risk Communication for Insurance Underwriting

In addition to risk quantification as supplied by mathematical methods - insofar as they are available, underwriters also desire relevant contextual/qualitative information to develop a 'feel' for the risks in question, particularly for the purpose of recognizing potentially novel scenarios not accounted for in axiomatically driven quantitative models (Camerer and Weber 1992; Kunreuther 1989; Kunreuther et al. 1995). Since it is underwriters who bear ultimate responsibility for deciding to insure given risks at given costs, determining fair premium rates is crucial since such decisions bear directly on the solvency and profit margin of the insurers they work for; a pattern of mispricing insurance premiums would have implications for job security and future career prospects. Depending on extraneous background information and circumstances, an underwriter may judge actuarial estimates that are axiomatically and therefore blindly generated by computer models, to either understate or overstate the risk in question. Such judgement calls require an in-depth understanding of the circumstances and environments in which a particular risk could arise and the range of applicability of computational models.

Underwriting competency is sharpened by specializing in a specific risk category; by accumulating knowledge and understanding of the relevant risk contexts and technical backgrounds, underwriting specialists develop and

come to rely on acute intuitive mental risk models that predominate over the insurability decision making and costing process and that are sensitive to subtle contextual anomalies. Quantitative based computer tools are relegated to more secondary guiding roles in which ‘what if’ and ‘worst case’ scenarios can be simulated. That said, the importance of quantitative tools should not be downplayed; their capability to model ‘what if’ scenarios constitutes an invaluable learning tool that helps underwriters develop mental risk models for correctly pricing premium rates. Moreover, underwriters can adjust a model’s underlying parameter weightings in order to generate premiums in line with their expectations for risk scenarios for which they may have accumulated substantial experience and knowledge. Such empirically determined weightings can then infer premiums for less familiar scenarios.

The learning curve associated with the ever expanding body of research on nano material properties and toxicology could prove overly steep for even the most adept specialist underwriter to make competent judgement calls, even if equipped with state of the art ‘black box’ quantitative risk modelling tools. In such circumstances, underwriters tend to overestimate the risks in question to compensate for their uncertainty, potentially rendering these risks uninsurable. The verbosity of technical detail typically associated with descriptions of nanomaterials and their toxicology is comparatively greater than that required to profile the corresponding parent materials, potentially obfuscating the underlying risks to the non-expert. Moreover, the current level of expertise required for parsing, interpreting and disseminating such information increases accordingly. In order to provide a ‘sense’ of the risks for the non-specialist, it is insufficient to merely quantify them. The more immediate need, especially for insurers and regulators, is to economically and unambiguously describe their qualitative and contextual aspects in a non-technical language but without loss of essential information.

6.3 Insurance Modelling

6.3.1 Macroscopic premium modelling

The exposure risk presented by a manufacturing process such as what was described in chapter 4 can be codified in terms of a sequence of scenarios that each refer to the exposure risk presented by individual operations that comprise the process. This concept can be extended indefinitely with each scenario decomposed into sequences of more elemental scenarios corresponding to the most basic manufacturing steps. This reductive process eventually terminates when ‘atomic’ scenarios are encountered that are considered too elementary to be further reduced. Specifically, an atomic scenario should describe one worker executing a logically irreducible task involving a single ENM. Formally, the risk scenario S_0 presented by a manufacturing process is described recurrently as a nested sequence of scenarios:

$$S_0 = \{ S_{0,1}, S_{0,2}, S_{0,3} \dots \dots \dots \} \quad Eq (6.0)$$

Each scenario in the list in Eq (6.0) is recurrently expressible in terms of more elementary scenarios such that,

$$\begin{aligned} S_{0,1} &= \{ S_{0,1,1}, S_{0,1,2} \dots \dots \dots \} \\ S_{0,2} &= \{ S_{0,2,1}, S_{0,2,2} \dots \dots \dots \} \end{aligned} \quad Eq (6.1)$$

....., and so on

The premium rate required to insure S_0 is then determined additively.

$$\begin{aligned} Prem(S_0) &= Prem(S_{0,1}) + Prem(S_{0,2}) + Prem(S_{0,3}) + \dots \\ Prem(S_{0,1}) &= Prem(S_{0,1,1}) + Prem(S_{0,1,2}) + Prem(S_{0,1,3}) + \dots \\ Prem(S_{0,2}) &= Prem(S_{0,2,1}) + Prem(S_{0,2,2}) + Prem(S_{0,2,3}) \\ &+ \dots \quad Eq (6.2) \end{aligned}$$

....., and so on

At the level where atomic risk scenarios are encountered in a manufacturing description and the recurrence process terminates, the problem of determining a premium rate for atomic risk scenarios still remains. The expected elementary and well defined nature of atomic steps suggests their

associated exposure risks should be easier to model than a composite risk scenario comprised of sequences of steps. Sections 6.3.3 – 6.3.6 present a series of methodologies of increasing sophistication for calculating premium rates for atomic risk scenarios.

6.3.2 Insurance model Anatomy

In light of the importance of risk communication and scenario simulation for underwriters, it is proposed that an insurance model must comprise at least two distinct elements. Firstly, it should contain a standardized machine and human readable³⁷ protocol for aggregating, storing and communicating data pertaining to risk scenarios presented by manufacturing operations. Its standardization would foster a universal language for manufacturers to convey risk information to insurers and regulators. The protocol should be as economic in its expression as possible with minimum redundancy and verbosity to add clarity and consistency to the information it codifies. In section 6.3.7 such a protocol is proposed in terms of a mark-up language based on XML for describing a manufacturing process. By virtue of the inherent ability of mark-up languages to model recurrent data structures, such a protocol would efficiently describe the expected nesting structure depicted in Eq (6.0) and Eq (6.1). Moreover, mark-up languages, on account of being well defined, are easily compiled and subsequently parsed using simple and efficient automated methods. The latter may have far reaching implications in terms of risk assessment. Provided that potential insureds agree to codify descriptions of their manufacturing processes in terms of the same mark-up language that insurers agree to accept them in, then the composition and communication to insurers of risk data by insureds, and its subsequent analysis by insurers can be automated. Specifically, such a protocol would allow insureds to specify their own software tools and scripts to aggregate and encode risk data in the protocol independently from

³⁷ For example the context free grammars that define most high level computer languages are both machine and human readable. Another example are mark-up languages, such as HTML and Latex with their embedded machine readable formatting directives for displaying human readable text.

the way the data would be decompiled and used by underwriters. Contextual anomalies could be thus quickly flagged by underwriters using automated parsing tools to interrogate the supplied risk data, indicating the reliability of premium estimates supplied by quantitative methods. The second requirement is a bidirectional pricing capability³⁸. In addition to calculating premiums for novel risk scenarios, this feature would allow an underwriter to also calibrate unknown parameter weightings in pricing models using subjectively determined reference premiums for risk scenarios the underwriter may be more familiar with. Parameter calibration of financial pricing models using liquid market data is a well-established practice in the financial world among quantitative analysts. The technique allows for arbitrage free price discovery of much less liquid products (See subsection 6.3.6.2.3)

6.3.3 Rudimentary premium pricing model for atomic risk scenarios

A simple ‘rule of thumb’ method is outlined in this section that extrapolates a premium rate for a given atomic risk scenario using a relative risk value and a prior assigned reference premium for a qualitatively similar scenario. Suppose S represents an atomic risk scenario and S_{ref} represents a scenario for which a premium amount $Prem(S_{ref})$ has been pre-assigned. In the absence of more sophisticated techniques, the following extrapolates a risk premium for S from $Prem(S_{ref})$. To wit

$$Prem(S) = RelativeRisk(S, S_{ref}) * Prem(S_{ref}) \quad Eq(6.5.1)$$

in which

$$RelativeRisk(S, S_{ref}) = \frac{Risk(S)}{Risk(S_{ref})} \quad Eq(6.5.2)$$

such that

$$Risk(S) = \text{expected exposure of novel material} \\ \times \text{expected hazard of novel material} \quad Eq(6.5.3)$$

³⁸ A feature that allows an existing price data set to calibrate a quantitative model’s unknown parameter weightings so that the model can infer prices outside the calibration set.

$$Risk(S_{ref}) = \text{expected exposure of reference material} \\ \times \text{expected hazard of reference material} \quad Eq(6.5.4)$$

Of course, an underwriter would be free to override this value on examination of the contextual aspects of S if he or she felt that anomalies associated with S rendered this calculation suspect.

At this point two conditions are stated that S and S_{ref} must henceforth meet if $Prem(S)$ is to be inferred from $Prem(S_{ref})$ by any method of calculation: S and S_{ref} must both be considered atomic; S and S_{ref} must share similar contexts, that is they must be qualitatively similar and be disguisable only by degree. For example, the respective exposure risks presented by the Sanowork sample materials described in chapter 4 and their modified counterparts are arguably qualitatively the same, since in all likelihood they share similar modes of toxicity action. That is, the risks presented by each material and its modified counterpart are of the same 'kind', only differing by degree or intensity for similar exposure levels.

6.3.4 Heuristic premium pricing for atomic risk scenarios based on interpolating hazard and exposure levels.

Figure 6.a depicts a framework for interpolating a risk premium for an atomic risk scenario from two neighbouring scenarios (in the sense of being qualitatively similar) for which premiums have already been assigned. The first premium is attributed to a material that is considered high risk for a given exposure, while the other corresponds to a material that is assumed benign at a particular exposure and is hence stipulated to be zero. The interpolating variable is the product of the known hazard and expected exposure levels for the material in question. This method is equivalent to the scheme described in section 6.3.3 when the product of the exposure and hazard levels for the benign material is zero. As such it is therefore somewhat of a generalization of the method described in section 6.3.3.

Figure 6.b represents a simple Multi Criteria Decision Analysis (MCDA) scheme that resembles the control banding description in (Mullins et al.

2013). The categories for the premium rates are inferred from the graph in Figure 6.a. Essentially, the entire scheme hinges on the choice of the reference premium which the underwriter must first assign to the high risk scenario. All other rates for different exposures and hazards are then determined in relation to it. The advantage of using reference points is that it helps facilitate consistent premium pricing for different ENM exposures

Figure 6.a: A reference premium of P_{max} is assigned to a worker who experiences an expected daily exposure of E_1 from a material with a hazard of H_1 . A daily exposure of E_0 to a material of hazard H_0 is considered safe and does not require insurance. Premium rates for a given exposure to arbitrary materials with a known hazard can then be linearly interpolated

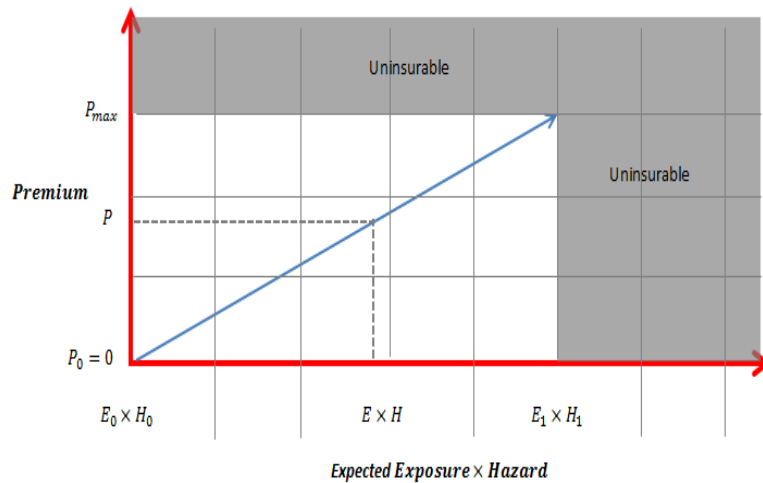
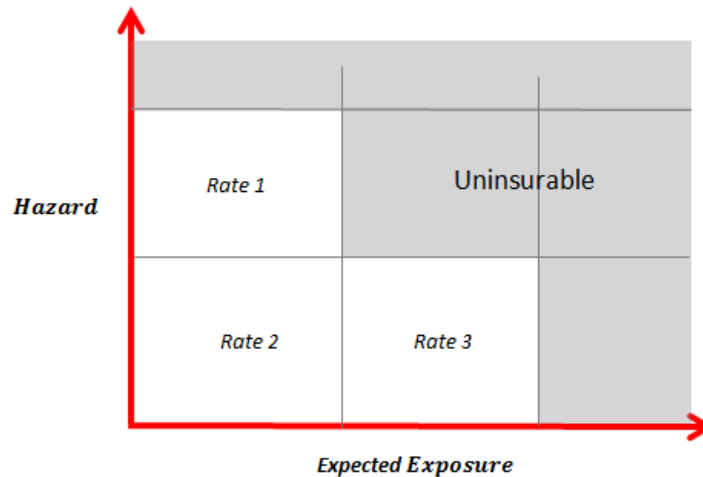


Figure 6.b: Underwriting decision space. The graph in Figure 6.a can then be used to consistently assign premium rate categories for given daily average exposures to materials with known hazards as well as define those categories in the decision space that cannot be insured



6.3.4.1 Determining a reference premium

In order to gauge a reference premium, an insurer might first assume a maximum loss per worker it was willing to bear from a material that it considered high risk at a given exposure. A leading candidate would be asbestos given that insurers already have access to its extensive claims history and its toxicological effects are already well established and understood.

Among other possibilities are the many inorganic bio persistent nano materials that are present in air pollution, particularly those that have metal oxide components that are believed to be especially harmful to exposed populations. As mentioned in chapter 2, there is increasing epidemiological evidence to suggest they are linked to chronic conditions such as heart disease and various forms of dementia. This evidence could help measure the losses attributable to these exposures and thus indirectly infer equivalent premium costs for hypothetical scenarios in which such losses were insured against.

As mentioned previously, these approaches are only valid when the interpolation is done with respect to risk scenarios that are atomic and qualitatively similar. Specifically, the modes of toxicity action of the respective ENMs defining the reference scenarios should be the same, or very similar, to those materials for which premiums are sought. So that in the case of the asbestos example, asbestos would only be suitable if the ENM to be insured against was similar to asbestos in terms of its assumed mode of toxic action.

Large producers of a particular ENM that sell through the INSCX exchange³⁹ may self-insure the occupational risks attributable to it. The cost of the material's production has to include the cost of this risk and the cost of mitigating it through safety measures etc. By subtracting out known costs of production and mitigation, insurers might obtain a rough estimate for the cost of this risk and from it infer an equivalent premium that would reflect the same insurance costs. Through such a mechanism, large ENM producers might unwittingly communicate a fair risk cost to smaller companies and thereby help them remain competitive.

The interpolating scheme thus described is by no means ideal but it at least provides a starting point for the design of more advanced techniques. For example, it would be more insightful from a health risk perspective to consider dose levels rather than expected exposure. This is an important distinction. The expected accumulations of a particular ENM in a workers body as a function of a given exposure history would provide a better risk indicator than the exposure alone. Such an approach is explored in section 6.3.6. As a further refinement, knowing the way in which a given dose is distributed among internal organs would provide increasingly refined risk estimates, especially when compared to the expected distributions of

³⁹ *INSCX™ exchange is a self-regulating organisation [SRO] providing an electronic trade platform specific to the listing of accredited, inspected and validated engineered nanomaterials, nano-enabled commodities and categories of more traditional commodities for physical delivery*

naturally occurring ENMs and their associated epidemiological data sets and *in vitro* measured toxicity.

6.3.5 Extrapolating from parent material exposure limits for atomic risk scenarios

Along with its surface reactivity potential, this line of attack is premised on the idea that a particle's surface area is a dominant determinant of its biological hazards. The latter is assumed to be valid across all particle sizes provided the particles are non-soluble in the target mediums, which for example in the case of inhalation exposure would be the lungs. Parent material exposure limits, normally quoted in terms of mass densities, are equally expressible in terms of surface area densities given the average particle diameter. Given that exposure limits quoted in terms of surface area densities should be valid for all particle sizes, implies that exposure limits in terms of mass densities for the nano form of the material can then be estimated given its average nano scale dimensions. Since insurance models already exist for estimating the cost of exposure risk to parent materials, then it should be relatively straightforward to adapt them under this paradigm for insuring against exposure to materials' nano forms.

Caution must be exercised however when applying this method since the dynamics of particles *in-vivo* are generally very much size dependent. For instance, where particles deposit in the lung is largely determined by their aerodynamic diameters; their translocation potential from the lung to the circulatory system and across the blood brain barrier requires them to be below a certain threshold diameter; and the clearance efficiency of macrophages is very much dependent on size and shape. This issue is dealt with to an extent in the following section.

6.3.6 Premium pricing using Bayesian methods for atomic risk scenarios

In the context of section '*Employer liability insurance*' in chapter 3, the author describes a Bayesian based framework for estimating insurance premiums for valuing the cost of occupational risk per worker from exposure to ENMs. The framework is based on the hypothesis that the

enhanced occupational risk of incurring a loss at some future time is a form of injury in itself. As was described in chapter two, this hypothesis is supported by at least two court rulings concerning asbestos in which awards have been made on the basis of enhanced risk as a form of injury as distinct from actual injury, and arguments from several sources that enhanced risk should be recognized as a form of injury in and of itself.

The time of injury, and therefore the trigger event for a policy pay-out, is defined as the time of detection of a predefined bio-marker, or collection of markers, at predefined levels. It is supposed this set of markers correlates with existing epidemiological data to give a measure of the likelihood of an exposed individual incurring a loss, for example through some form of impairment at some future time after the detection event. This risk must be over and above that presented to unexposed individuals. In accordance with the normal provisos of employer liability policies, the terms of such a policy also stipulate that a compensated worker cannot bring suit against the company whose insurance carrier facilitated said compensation.

Suppose that in the event of detection of a particular biomarker, or collection of biomarkers, in an exposed worker the prevailing opinion among expert witnesses is that the worker has a risk R_1 (probability) of developing a condition at some future time which would render him or her unemployable or be the cause of reduced income or a temporary loss of income estimated to be L . Suppose also that the risk among similar but unexposed individuals is given by R_0 (probability). It's important to stress that it's irrelevant whether R_1 or R_0 ultimately prove to be accurate. The size of the awards made to potential plaintiffs in the courts will largely be based on the current scientific consensus, or group opinion, as expressed by expert witnesses providing testimony on behalf of plaintiffs, even if such consensus is subject to change in the future. To put it another way, risk levels for the purpose of determining compensation for claimants will ultimately be defined by legal procedures, albeit guided by generally accepted scientific theory that could however ultimately be shown to be

incorrect. Suppose the average court award made to claimants from similar cases is given by A , as determined by some legally defined formula involving R_1, R_0 and L so that A can be thought of as some function of R_1, R_0 and L , i.e. $A(R_1, R_0, L)$. Note, that $A(R_1, R_0, L)$ should be zero when either $R_1 = R_0$ or $L = 0$. It should also be a fraction of L since it is an award based on the *risk* of loss, L , that may never crystalize. The following argument leads to a feasible form for A in terms of R_1, R_0 and L , an argument that one might envisage playing out in some court room: heuristically, the expected loss for an unexposed individual is estimated as $L \times R_0$, arguably a loss for which no blame can be assigned to any individual or party. Similarly, the expected loss for an exposed individual is approximated as $L \times R_1$. It is fair to argue that the additional expected loss of $L \times (R_1 - R_0)$ incurred by an exposed individual should be redeemed by the entity responsible for the exposure, which in this context would be the ENM producer or user via its employer liability carrier. Thus, the expected non contested pay-out for a insurance claimant should be commensurate with what could be obtained via the litigation route if the claimant decided to exercise that option. Therefore, the author submits that in order to dissuade a potential claimant from pursuing litigation in favour of exercising a claim via his/her employer's liability carrier, the maximum pay-out or policy limit for such a claim should be stipulated as

$$policylimit = A(R_1, R_0, L) = L \times (R_1 - R_0) \quad Eq (6.3).$$

An insurance carrier that provides employer liability coverage for the kind of risk described in the previous paragraph, armed with the knowledge of relevant legal case histories and knowledge of $A(R_1, R_0, L)$, could proactively design policies so as to pre-empt and avoid possible court challenges with uncertain outcomes.

6.3.6.1 Premium calculation

In order to determine a fair market premium in terms of a policy limit value, it will be also necessary to stipulate the probability of the trigger event, the

term of the policy, the time value of money as stated in terms of a discounting factor and the insurer's commission rate. Let $Q(t)$ represent the probability, as seen at time zero, of the pay-out event (caused by detection event) being triggered before time t . The life of the policy is given by T , denoted in years, and $Prem$ denotes the annualized premium per insured worker given conditions of market equilibrium. CR is a measure of the commission, expressed as a percentage of the base premium or minimum premium that has to be charged to cover the expected costs of all claims throughout the term of the policy. The insurer's commission represents the value of the service provided by the insurer. It includes operating costs such as salaries etc. and a small margin representing the insurers' profit if the insurer is privately held non-mutual company. $B(t)$ is the discounting factor representing the time value of money and is defined as the value of a risk free bond that after t years is redeemable for one unit of currency. Assuming conditions of market equilibrium, it is straightforward to show that

$$Prem \cong \frac{policylimit \times \int_0^T B(t) \frac{\partial Q(t)}{\partial t} dt}{\int_0^T B(t)(1 - Q(t)) dt} \left(1 + \frac{CR}{100}\right) \quad Eq (6.4)$$

(See appendix 8.8 for further details). The primary difficulty in evaluating Eq (6.4) lies with the determination of $Q(t)$. The aim here will not be to calculate explicit values for $Q(t)$ since this would be impossible given the present lack of available data, but to try and ascertain the minimum parameter set needed to generate a feasible family of curves of which $Q(t)$ is likely a member. This will allow for optimum regression fits when and if epidemiological data becomes available. Generally, this is an important consideration for regression fitting as the parametric forms of functions that are to be fitted to empirical data are oftentimes chosen arbitrarily (with linear curves being a common choice) with little consideration given to how well they represent the underlying processes that have generated the data being analysed.

If $Q(t)$ is to be ultimately determined by correlating biomarker(s) detection events with known exposure histories and ENM hazard potentials then an immediate problem arises: $Q(t)$ is only a function of time and includes no references to exposure or hazard parameters. Moreover, possible exposure histories cannot be known ahead of time and hazard values will contain a degree of uncertainty. The solution lies in applying Bayesian decomposition to $Q(t)$ to express it in terms of conditional or posterior probabilities which in principle could be empirically determined using regression techniques. Thus, $Q(t)$ is decomposed into a sum of posterior probabilities, $Q(t|\mathbf{E}, h)$, weighted by the respective prior probabilities, $Q(\mathbf{E})$ and $Q(h)$, in accordance with the Bayesian probability decomposition principle. That is

$$Q(t) = \int Q(t|\mathbf{E}, h)Q(\mathbf{E})Q(h)D\mathbf{E} dh \quad Eq (6.5)$$

\mathbf{E} represents a possible future exposure history unfolding for an exposed worker. Specifically, $\mathbf{E} := E(t)$ in which $E(t)$ indicates the Level of the ENM in question at time $t < T$. As seen at time zero, $Q(t|\mathbf{E}, h)$ is the probability of a detection event before time t given that the worker has experienced a known exposure history, as denoted by \mathbf{E} , to a ENM that is characterized by the *in vitro* measured hazard parameter(s) h . In principle $Q(t|\mathbf{E}, h)$ can be empirically determined by applying regression methods to relevant epidemiological data, i.e. the frequency distribution of biomarker(s) detection events, and causative exposure histories and *in vitro* measured hazards. In the sense that the object \mathbf{E} is a function, $Q(t|\mathbf{E}, h)$ is therefore a partial function of a function (functional) and a function of h and t .

The interpretation of $E(t)$ is left open. For example it could be the atmospheric level of the ENM in a worker's vicinity at time t as measured in mass density, number density or surface area density. It could also represent each of these quantities in direct contact with the workers skin. In each case the formulation of the problem is the same. The integral is

summed over all possible histories and in this respect is a path integral⁴⁰. $Q(\mathbf{E})D\mathbf{E}$ is the prior probability of the exposure history \mathbf{E} , confined within a band of possible histories prescribed by the functional measure $D\mathbf{E}$, unfolding before time T . The parameter h is an *in-vitro* defined measure of hazard for the ENM. In general, h will not be a single number but a collection of quantities that refer to the *in-vitro* measured departure of various biomarkers from normal levels in different cell lines that have been dosed with a fixed amount of the ENM being investigated. By increasing the size of the group, this collection of biomarkers should become increasingly specific to the ENM in question, forming a unique hazard profile or signature⁴¹ and in such instances would justify the use of h as a toxicological label for the ENM under study; from a toxicological perspective, this suggest that two materials distinguishable on a physicochemical basis can be treated as the same material if they happen to share the same toxicological profile. For ease of explanation however, h is henceforth treated as a single magnitude. As emphasised in chapter 4, there is presently a lack replication of hazard levels for the same ENMs in the experimental community. This means that at best, h can only be expressed

⁴⁰ Informally, a path integral is an integral in which the integrand is a function of some function (path) which constitutes the integrating parameter, i.e. it represents a sum over paths and contrasts with a sum over real numbers as expressed by the familiar Riemann integral in which the integrand is a well behaved real function and the integrating parameter is a real number.

⁴¹ 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, \mathbf{H} , given by

$$\mathbf{H} = \begin{pmatrix} h_{1,1} & h_{1,2} & \dots & \dots \\ h_{2,1} & h_{2,2} & \dots & \dots \\ \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots \end{pmatrix}$$

as a marginal probability distribution. However, progress towards standardization of hazard testing procedures should lead to $Q(h)$ expressing increasingly narrower distributions.

6.3.6.2 Computing the posterior probabilities

The simplest estimation for $Q(t|\mathbf{E}, h)$ is to assume that $\mathbf{E} := E_0$ is constant, that is levels remain steady throughout a worker's exposure history, This can be stated as $Q(t|\mathbf{E}, h) = Q(t|E_0, h)$. After imposing the boundary condition, $Q(t|0, h) = Q(t|E_0, 0) = Q(0|E_0, h) = 0$ ⁴² and performing a first order Taylor expansion about $Q(0|0,0)$ yields

$$Q(t|E_0, h) \propto E_0 \times h \times t + \text{higher order terms} \quad \text{Eq (6.6)}$$

This expression conforms to the intuitive definition of risk which is

$$\text{Risk} = \text{ExposureLevel} \times \text{Hazard} \times \text{ExposureTime} \quad \text{Eq (6.7)}$$

For arbitrary large values of t it can be generalized somewhat to read

$$Q(t|E_0, h) = 1 - e^{-W \times (E_0 \times h \times t) + \text{higher order terms}} \quad \text{Eq (6.8)}$$

in which W is a universal positive weight. In the more realistic case in which h is replaced by the hazard tensor, $\mathbf{H} := h_{i,j}$, and where the exposure history is non-constant, Eq (6.8) would further generalize to,

$$Q(T|\mathbf{E}, \mathbf{H}) = 1 - e^{-\int_0^T E(t) dt \times \sum (W_{i,j} \times h_{i,j}) + \text{higher order terms}} \quad \text{Eq (6.9)}$$

in which $W_{i,j}$ are a set of universal weights that measure the significance of each of the entries in the hazard matrix. The summation is taken over all entries in the set (see appendix 8.2). However, the assumptions required to obtain this approximation betray its limitations for calculating risk.

⁴² This follows from the assumption that zero exposure or hazard presents no risk.

Crucially, it takes no account of dose, which is the accumulation in a worker's body as a result of prolonged exposure to the ENM in question. Presently, a better method has been obtained for calculating $Q(t|\mathbf{E}, h)$ that depends on being able to relate exposure levels to accumulation levels of non-soluble and therefore bio persistent ENMs. This approach is therefore better suited to model longer term or chronic risk as opposed to near term acute risk. It's important to note that many ENMs have both soluble and non-soluble components, as described in chapter 4. Since the soluble components would arguably have the same metabolic and excretion characteristics as their constituent compounds, suggests their exposure levels may be monitored using existing risk management and regulatory frameworks that are based on time averaged occupational exposure limits (OEL) for these compounds, as stated in terms of mass densities. For this reason, the author considers only exposure to the non-soluble components of ENMs that following exposure would be prone to accumulation before the body is able to eventually expel them. The author also acknowledges that this may be somewhat of an oversimplification since the metabolic and solubility characteristics of a bio-persistence pathogen can change over time. In the first iteration of the model, \mathbf{E} is modelled as a flat background level superimposed with spikes of random magnitude, modelled as delta functions⁴³, and temporally sequenced according to a Poisson distribution that together model incidental exposure and an average ambient exposure. This description of \mathbf{E} is analytically tractable and allows for the calculation of the prior $Q(\mathbf{E})$ and the expected dose (see appendix 8.5). The prior quantity $Q(h)$ can be estimated from existing hazard data, however inaccurate and inconsistent, using the principle of maximum entropy as described in chapter 4. This principle will efficiently select the most unbiased distribution that describes the available data. Exposure and hazard data for ENMs is presently scant and inconsistent. However, this does not

⁴³ 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 $f(z) = \delta(\bar{r}(z) - r)$

make it useless; the framework outlined here will extract the most unbiased risk estimates based on the available data, regardless of quality. Moreover, these risk estimates will be automatically refined as new data become available but without having to modify the framework.

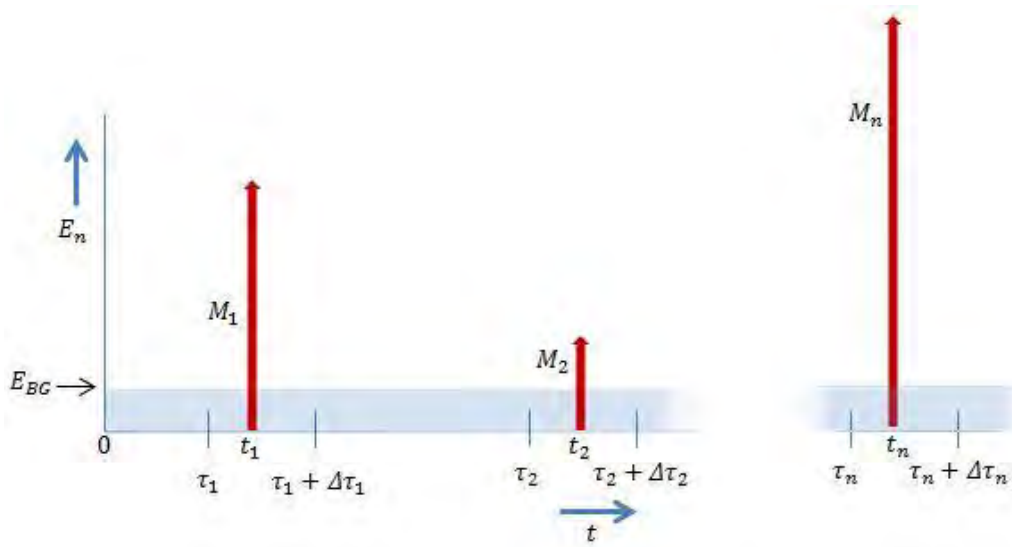
6.3.6.2.1 Simple pharmacokinetic model for determining dose accumulation from exposure history

This section describes a rudimentary analytically tractable pharmacokinetic model for relating an individual's exposure history via the respiratory system to his or her total accumulation of non-soluble ENMs. The model assumes a constant half-life decay parameter, γ , that characterises the excretion or depletion behaviour of the ENM in question as an exponential fall of, and a parameter, λ , that model's the individual's absorption rate (see appendix 8.3). In support of these assumptions, one study has revealed that Tio2 levels in the lungs of rats follow an approximate exponential decay following a period of known exposure (Oberdörster, Ferin and Lehnert 1994). In general, λ and γ will not be constant but will be functions of exposure levels and dose levels respectively, although a plausible argument based on Taylor series expansions shows that the assumption of constancy holds when exposure and accumulation/dose levels are small (again see appendix 8.3). In light of these constraints, this model should be viewed as an approximate phenomenological description of the relationship between dose and exposure dynamics.

As illustrated in Figure 6.c, the exposure history $E_n(t)$ is defined as an average ambient level, E_{BG0} , superimposed on n incidental exposures, each of intensity $M_1, M_2 \dots M_n$, occurring respectively at times $\tau_1, \tau_2 \dots \tau_n$

$$E_n(t) = \sum_{i=0}^n M_i \delta(t - \tau_i) + E_{BG0} \quad Eq (6.10)$$

Figure 6.c: A possible exposure history is represented as a steady ambient background level E_{BG} that reflects time averaged exposure levels. Incidental random emissions of random intensity occurring over small time intervals would tend to evade periodic exposure measurements that are used to calculate the time averaged value E_{BG} . For this reason, incidental exposures are modelled separately as delta functions which are then superimposed on the ambient level forming a complete exposure history. Note, E_{BG} would not be known ahead of time but would need to be characterized as a marginal distribution. The random character of the incidental emission times and intensities together with the distribution of possible values of E_{BG} would all be encapsulated by $Q(\mathbf{E})$.



In reality, incidental exposures will occur over finite time intervals and not instantaneously as the model would seem to indicate. However, the instantaneous exposure assumption is reasonably valid provided such intervals are small compared to the typical time periods between exposure incidents.

The dose level, $C_n(t)$, is the total accumulation of the ENM as a result of the individual having an exposure history given by $E_n(t)$. Following from the assumption that the absorption rate is given by $\lambda E_n(t)$ and that accumulated levels would decrease exponentially in the absence of exposure, it can be shown that

$$C_n(\mathbf{E}, t, \lambda, \gamma) = \lambda \gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma} t} \right) \text{ for } t < \tau_1$$

$$C_n(\mathbf{E}, t, \lambda, \gamma) = \lambda \left(\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma} t} \right) + \sum_{i=1}^m M_i e^{-\frac{1}{\gamma} (t - \tau_i)} \right) \text{ for } \tau_m \leq t < \tau_{m+1} \text{ when } 1 \leq m < n$$

$$C_n(\mathbf{E}, t, \lambda, \gamma) = \lambda \left(\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}t} \right) + \sum_{i=1}^n M_i e^{-\frac{1}{\gamma}(t-\tau_i)} \right) \text{ for } \tau_n$$

$$\leq t \text{ Eq (6.11)}$$

(see appendix 8.4). In many ways, Eq (6.10) together with Eq (6.11) may be considered the simplest non-trivial pharmacokinetic model in the sense that it fulfils a minimum requirement of simultaneously accounting for absorption and depletion in the exposed individual. Subsequent iterations would seek to describe ENM distributions within an exposed individual prior to excretion and toxicological changes such as those associated with nano particle corona modification etc. Even at this most basic level, the model however reveals factors that go beyond *in-vitro* measured toxicity that must be considered in order to address the question of exposure risk to ENMs at the organism level. In this instance, it can be argued that a more general notion of hazard must be prescribed in term of three quantities, namely the *in-vitro* define hazard, h , and the absorption and depletion parameters, λ and γ , forming what the author terms, a *general hazard space*. It follows that those models with increasingly larger parameter sets would correspond to higher dimensional general hazard spaces. In the same way in which h encodes both properties of the ENM and the cell lines that are used to define it, λ and γ encode properties of the ENM and the exposed individual at the *in-vivo* level. In the case of absorption via respiration for instance, λ will depend on the aerodynamic characteristics of the ENM in question as well as the lung capacity and breathing rate of the exposed individual. γ will similarly depend on the morphology of the ENM in combination with factors such as body weight, metabolism, age and state of health etc of the exposed worker. For example, studies have shown that the bio persistence/retention time of ENMs depends on both size and shape (Longmire, Choyke and Kobayashi 2008).

6.3.6.2.2 Modeling reversible chronic risk

Given this expanded notion of hazard, Eq (6.5) must be modified to take account of the absorption and depletion factors and λ and γ . That is

$$Q(T) = \int Q(T|\mathbf{E}, h, \gamma, \lambda) Q(\mathbf{E}) Q(h, \gamma, \lambda) D\mathbf{E} dh d\gamma d\lambda \quad Eq(6.12)$$

In the context of Eq (6.12), it can be shown to lowest order that the accumulated reversible risk from a given exposure history \mathbf{E} may be modelled as

$$Q(T|\mathbf{E}, h, \gamma, \lambda) \approx 1 - e^{-W \times \int_0^T C(\mathbf{E}, t, \lambda, \gamma) dt} \times h + \text{higher order terms} \quad Eq (6.13)$$

where W is a universal weight constant which is the same for all ENMs (see appendix 8.6). Specifically, $Q(t|\mathbf{E}, h, \gamma, \lambda)$ as defined by Eq (6.13) depends on the dose level at time t that has been accumulated rather than the most recent exposure level which takes no account of accumulation through absorption and a delayed depletion and is thereby unable to model accumulated risks. In contrast, Eq (6.13) can be said to describe both chronic and acute risk since it takes account of previous exposures by virtue of the dose, $C(\mathbf{E}, t, \lambda, \gamma)$, that has been accumulated from prior exposures as codified by the exposure history \mathbf{E} . It's important to observe however that this risk is reversible since if the accumulated dose is zero at time t , following from Eq (6.13), implies the risk must also be zero as seen at time t (see appendix 8.6 for further clarity on this remark).

6.3.6.2.3 Modeling irreversible chronic risk

As a first approximation, and for reasons that are expounded in appendix 8.7, it can be shown under reasonable assumptions that the irreversible enhanced risk of an exposed worker incurring a loss at some future time as a result of prolonged exposure to an ENM may be phenomenology modelled as $\int_0^t C(\tau, \gamma, \lambda) d\tau \times h$. Including this term in the model leads to the following lowest order non-zero correction to Eq (6.13)

$$\begin{aligned} & Q(T|\mathbf{E}, h, \gamma, \lambda) \\ & \approx 1 \\ & - e^{-\left(W_1 \times \int_0^T C(\mathbf{E}, t, \lambda, \gamma) dt + W_2 \times \int_0^T \left(\int_0^t C(\mathbf{E}, \tau, \lambda, \gamma) d\tau \right) dt\right)} \times h + \text{higher order terms} \quad Eq (6.14) \end{aligned}$$

W_1 and W_2 are universal weights that apply to all ENMs. For example, permanent damage might entail arterial plaque formation as a result of the enhanced ROS generation resulting from the presence of the ENM or cell death in organs that do not replace dead cells such as the heart or brain. In this instance, $\int_0^t C(\tau, \gamma, \lambda) d\tau \times h$ is taken as the aggregate measure of all possible sources of permanent damage that might be incurred.

Thus, at a phenomenological level, the minimum set of parameter types that must be considered when attempting to model acute and chronic risk from exposure to a non-soluble ENM pathogen, both reversible and irreversible, has to include a measure of local toxicity, h , as defined by *in-vitro* assays and a measure of the absorption and depletion factors given by λ and γ respectively.

Eq (7.14) should be viewed as the general form for parametric curves that best describe the relationship between ENM epidemiological data, as represented by $Q(t|\mathbf{E}, h, \gamma, \lambda)$, and experimentally determined values for h, λ and γ . Optimum fits for the universal weights W_1 and W_2 can then be determined using standard regression methodologies. Once determined, risk scenarios for novel materials outside those used to supply the regression data can then be estimated from Eq (6.12). As mentioned previously, anthropogenic nano materials, such as those identified in air pollution for which associated epidemiological data has been obtained, could effectively act as reference materials, provided their modes of toxicity action are similar to those of the engineered materials for which $Q(t|\mathbf{E}, h, \gamma, \lambda)$ is sought.

It can be seen from Eq (6.12) and Eq (6.14) that $Q(t)$ ultimately depends on the unknown universal weights W_1 and W_2 since the parameters h, γ, λ are integrated out. This suggests that as an alternative to using epidemiological data to estimate these weight parameters, which may not be available for some time, market premium rates for select risk scenarios and policy terms

might permit Eq (6.4) to be used in reverse in order to infer or ‘back-out’ W_1 and W_2 . This would allow for consistent premium pricing across a spectrum of insurance policies with varying terms and conditions for which market rates weren’t available. As previously alluded to, a similar approach is used in vanilla option markets in which market rates for vanilla call and put options are used to imply volatility weights for the underlying securities from vanilla option pricing formulae. These implied volatilities can then be used to estimate fair market prices for much less liquid ‘exotic’ option types which typically entail an array of complicated contractual contingences not present in the simpler vanilla types.

6.3.7 An XML based mark-up machine readable protocol for describing and communicating risk scenarios to regulators and insurers

The wealth of current and accumulating toxicity and physical characterisation data for ENMs is for the most part contained in the scientific literature. The latter represents an unstructured format and as such presents a formidable barrier for automated parsing and data extraction algorithms. Such information in most instances is not included in safety data sheets and may be especially difficult for insurers or regulators to apply it within the context of a manufacturing process encompassing a complex sequence of operations for which the toxicity data available in the literature may be only partially relevant. Thus, an arduous and time consuming effort is required for the specialist and non-specialist alike to sift through and extract useful information. Alternatively, relational databases can efficiently and cost effectively store and retrieve such information. However, the fixed relational database format is generally unsuitable for representing and communicating the unstructured information that would be typical of the heterogeneous risk scenarios presented by the increasing number of manufacturing processes that either produce or involve nanomaterials and the variety of ways in which such materials can affect workers through occupational exposure. Superficially, it would seem the traditional journal article represents the only pragmatic possibility for the storage and

communication of this kind of information. Mark-up languages on the other hand, such as those based on XML, offer the possibility of storing semi structured information that is both human and machine readable, allowing relevant aspects to be readily extracted using efficient and well defined parsing rules, saving much time and effort and enhancing the fluidity of risk communication. In this sense, a mark-up language application represents a middle ground between the efficient yet inflexible traditional database and the comparatively unstructured format of the typical journal article. All that is required is an agreed upon set of tags and rules for best encoding the relevant information, forming a universal language for describing manufacturing occupational risk in both qualitative and quantitative terms. Automated comparisons to arbitrary degrees of granularity between novel manufacturing processes and existing processes for which risk information is more available then become possible. It may also be possible to infer the likely exposure levels for the different stages of a manufacturing process by merely considering their topology in comparison to those for which exposure risks may be better known. Such a risk communication protocol could encapsulate both qualitative and quantitative information as it would contain all contextual and Meta risk information beyond what is quantifiable, and could be extended to encode context sensitive rules for invoking or suggesting appropriate quantitative models for calculating default premium rates and relative risk etc.

6.3.7.1 Summary points and further remarks

- Advantages: encapsulates both qualitative and quantitative aspects of a complete risk scenario for a manufacturing process in a single standardized format. Moreover, such a scheme is scalable in that it can be extended indefinitely to describe more information as it becomes available and can include context sensitive rules for when to apply appropriate quantitative models. Note, the value of a quantitative model is largely dependent on recognizing the circumstances in which it should be applied.

- This is an important requirement for underwriters as they need to consider all aspects of an insurable risk. That is, its quantification and perhaps more crucially, it's qualitative and meta aspects which are not amenable to quantification.
- A standardized communication protocol based on a well-defined grammar allows for the design of efficient parsing methods for transforming risk scenario descriptions into new formats that can be targeted at different demographic groups. For example, the level of detail intended for consumption by the general public, public interest groups and popular media outlets may be considerably less than that required by insurers or regulators. Thus depending on the target consumer groups, risk scenario descriptions can be 'pruned and repackaged' as desired.
- It also becomes possible to automate the comparison between risk scenarios for different manufacturing operations and to decide if the differences are in kind (qualitative) or in degree (quantitative). Manufacturing operations can be automatically grouped on the basis they generate risk scenarios that differ only by degree. For example, two manufacturing processes that each produce CNTs but of different lengths are likely to share strong qualitative similarities, rendering their respective risk scenarios suitable for quantitative comparison. While the production process for TiO₂ ENMs would be expected to be qualitatively distinguishable from the production of CNTs, since both processes would be expected to be different at all levels.
- Topologically based groupings would be a useful tool for underwriters to assign occupational risk levels and corresponding insurance premiums which can then be used for quantitative model calibration for pricing insurance costs for more novel situations.

6.3.7.2 XML background

XML is a mark-up language. Mark-up languages were originally designed for the purpose of annotating a document in a way that was syntactically

distinguishable from the document text. The concept and terminology originates from the *marking up* of paper manuscripts by editors, traditionally written with a blue pencil on the author's manuscript. For digitized texts, the *blue pencil* directives are replaced by machine readable tags that allow a digitized document to be automatically formatted for printing and displaying on computer monitors.

The same characteristics that allow a mark-up language to describe a machine interpretable presentation format for documents also provide a mechanism for standardizing the communication of information between data vendors and consumers, especially semi structured data. With XML, data vendors can define tags and instructions forming data communication protocols. In addition to data, these protocols can be embedded with meta and semantic directives for describing how the conveyed data should be interpreted by consumers. Moreover, the received data can be programmatically parsed and manipulated with software that is independent of that which is used by the vendor to compile it; all that is required is a description of the protocol in terms of the collection of tags and meta tags and their relationships to one another. This avoids interoperability issues that have plagued proprietary messaging/communication platforms, such as that used by SWIFT for interbank currency transfers⁴⁴.

XML has addressed many different communication problems across a wide spectrum of organizations, too numerous to be listed here. A few examples are mentioned from finance, risk management and governance and from research and development: The financial services industry is heavily reliant on the use of XML applications to standardize the efficient transfer of financial data and instructions. For example, there is the XML based Financial Information Exchange protocol (**FIX**). FIX is an industry specific protocol that communicates securities information such as quotes, market data, and trade orders. Another example from finance is **FpML** (Financial

⁴⁴ SWIFT is the Society for Worldwide Interbank Financial Telecommunication, a member-owned cooperative through which financial institutions conduct their business.

products Mark-up Language) which defines a protocol for streamlining the trading of financial securities. **GRC-XML** is an XML based standard to facilitate institutional transparency for the sharing of governance, risk management and compliance (GRC) information within and between disparate organizations such as corporations and industry auditors. An example from the life sciences is the Systems Biology mark-up Language (**SBML**) for storing and communicating computational models of biological systems to facilitate interoperability between heterogeneous simulation software platforms⁴⁵.

6.3.7.3 A simple XML based ENM exposure risk communication protocol

An XML schema is outlined and used to describe a single manufacturing processing line that formed part of the case study in chapter 4. As mentioned previously, the essence of XML and mark-up languages in general is their efficacy for representing not only data but also data contexts or meta data and semantic directives ect. In XML, a context or scope is opened with the scope name within angled brackets while it is closed using the same name, also inside angled brackets, preceded by a forward slash. That is

$$\textit{scope} ::= < \textit{scopename} > \textit{scope definition} < / \textit{scopename} >$$

The scope definition can be structured in terms of single items of text, numbers or sequences of other scopes. The formal XML specification includes many more grammar rules beyond what has been stated here. In what follows the author does not strictly adhere to the formal specification. In the interest of economy, the schemas depicted below are written in a much less verbose pseudo version of xml that however still manages to convey its viability as a risk communication platform.

6.3.7.3.1 Manufacturing process description schema

⁴⁵ See The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models (Hucka et al. 2003)

A manufacturing process consists of a sequence of operations and sub operations. This hierarchy structure is reflected by the schema in Figure 6.d in which a series of <operation> scopes are nested within a <process> scope denoting the parent manufacturing process.

Figure 6.d: Processing line scope definition

```

<Process>
  <Description>string</Description>
  <NumberOfOperations>number</NumberOfOperations>
    <Operation> operation definition </Operation>
    <Operation> operation definition </Operation>
    .....
    .....
    .....
    <Operation> operation definition</Operation>
</Process>

```

The *operation definition* is either defined recursively in terms of <process> scopes representing sequences of sub operations or it terminates with a description of an atomic operation.

That is

operation definition :=

< Process > *process defintion* </Process > or

operation definition :=< AtomicOperation

> *atomic operation definition* </AtomicOperation >

in which the < AtomicOperation > scope is defined in Figure 6.e.

Figure 6.e: Atomic operation scope definition

```
<AtomicOperation>
    <Description>string</Description>
    <Environment> environment definition</Environment>
    <Material>material definition</Material>
    <MaterialAmount>number</MaterialAmount>
    <Duration> number</Duration>
    <Worker> worker definition</Worker>
</AtomicOperation>
```

An atomic operation scope describes an operation involving only one material and one worker. Its <Description> scope encapsulates a text description of the operation in the context of the larger process of which it is part. The <Environment> scope describes the environment in which the operation takes place. This includes such details as specifications of forced ventilation systems, temperature and humidity levels, locations of doors and windows, fire mitigation systems and if clean room conditions exist. Such details could be described in terms of their respective sub scopes to arbitrary levels of detail. The <Material> scope member is defined in Figure 6.f. The <Duration> and <Frequency> scopes are the approximate time to complete the operation and how often the operation is performed respectively. The <MaterialAmount> scope simply indicates the amount of material being used in the operation. The <Worker> scope contains details of the worker performing the operation such as age, gender, ethnicity, medical history, his or her use of personnel protective equipment (which is further detailed in terms of sub scopes) and levels of training, experience and overall professional competency. The <AtomicOperation> scope would be the primary object of interest for regulators or insurers. Instances of this scope could be analysed and interrogated independently of all other activities pertaining to the parent processing line. Moreover, <AtomicOperation> objects that bore certain similarities in terms of the risks they presented could be efficiently identified by automated parsing methods and assigned

to individual underwriters in order to foster competency attainment for particular categories of risk assessment.

Figure 6.f: ENM scope definition

```
<Material>
  <Name> string </Name>
  <Aspect Ratio> number </AspectRatio>
  <ZetaPotential> number </ZetaPotential>
  <CoreComposition>core composition definition</CoreComposition>
  <CoronaComposition>corona composition definition </CoronaComposition>
  <Toxicity>
    <HazardMatrix> hazard matrix definition </HazardMatrix>
    <ModeOfToxicity> mode of toxicity definition</ModeOfToxicity>
    <QuantRiskModel> quantitative risk model definition</QuantRiskModel>
  </Toxicity>
  <MacroscopicState>
    <AggregateState>aggregate state definition</AggregateState>
    <Dustiness>dustiness definition</Dustiness>
  </MacroscopicState >
</Material>
```

The <AggregateState> member of the <MacroscopicState> scope describes the degree of agglomeration of the ENM. The <Dustiness> member indicates the emission potential of the ENM depending on whether the material is in dispersion or powder form. Physicochemical properties such as pH levels, intrinsic reactivity and the fraction of soluble components can be inferred from the <CoreComposition> and <CoronaComposition> scopes. The <HazardMatrix>,<ModeOfToxicity> and <QuantRiskModel> scopes are grouped in a common context denoted by the <Toxicity> scope. The reason for this is that a risk model specification has to reflect the hypothesised mode of toxicity. For instance, models describing the risk of fibre inhalation would by necessity have to reflect the behaviour of macrophages in terms of how they remove fibres from the lung. Likewise a risk model describing how surface charge, inferable from a materials zeta

potential, can compromise the integrity of cell membranes leading to cell lysis, would be premised on entirely different principles, as would a model describing the risk of oxidative stress induction.

6.3.7.3.2 Application to ZrO₂ waste recovery as described in chapter 4

The following presents an example application of the previously described risk communication protocol to an actual processing line. The processing line chosen was the first to be described in chapter 4. The latter involved the recovery of zirconium dioxide waste materials from the reactor in which zirconium based ENMs were synthesized. This recovery operation mitigates environmental exposure by removing possible ZrO₂ contaminants from waste water before being released to the environment. Three steps are involved: reactor washing after which the waste material from the reactor becomes dispersed in the cleaning medium which in this case was water. The second step involved sedimentation in which the waste water solids were allowed to settle before being finally recovered in the third step. For further details see chapter 4. The entire process is denoted by *zirconium recovery process* such that

zirconium recovery process :=

<Process>

<Description>

ZrO₂ nano material precursor recovery from waste water after reactor washing

</Description>

<NumberOfOperations>3</NumberOfOperations>

<Operation> *operation washing* </Operation>

<Operation> *operation sedimentation*

</Operation>

<Operation> *operation recovery*</Operation>

</Process>

in which the operation, *operation washing*, is considered logically irreducible and is defined as

operation washing :=

```
<AtomicOperation>
    <Description>
        reactor washing to obtain ZrO2 wastes
    </Description>
    <Environment> not specified </Environment>
    <Material> waste water </Material>
    <MaterialAmount>not specified</
MaterialAmount >
    <Duration> not specified </Duration>
    <Worker> not specified </Worker>
</AtomicOperation>
```

Insufficient information was available for the specification of the sub scopes of *operation washing* apart from the <Description> and <Material> scopes. The <Material> scope profiled the modified material *ZrO₂_Sil_Sol* in which the silicate coating of *ZrO₂* nano particles was intended to improve their dispersion characteristics in water in order to enhance the efficiency of the washing step. A citrate coating was also tested for the same purpose and is describable using a similar scope to that which was used to profile the silicate coated particles.

< *Material* > waste water </*Material* >:=

```
<Material>
    <Name> Silicate coated ZrO2 nano particles in solution (ZrO2_Sil_Sol) </Name>
    <Aspect Ratio> spherical definition </AspectRatio>
    <Diameter> not specified </Diameter>
    <ZetaPotential> not specified </ZetaPotential>
    <CoreComposition> zirconium core definition </ CoreComposition >
    <CoronaComposition> silicate corona definition </CoronaComposition>
```

```

<Toxicity>
  <HazardMatrix> hazard matrix for ZrO2_Sil_Sol </HazardMatrix>
  <ModeOfToxicity> oxidative stress definition</ModeOfToxicity>
  <QuantRiskModel> oxidative stress risk model definition</QuantRiskModel>
</Toxicity>
<MacroscopicState>
  <AggregateState> dispersed particles definition</AggregateState >
  <Dustiness>wet state definition</Dustiness>
</MacroscopicState >
</Material>

```

The <ModeOfToxicity> member of the <Toxicity> sub scope is defined in terms of a description of oxidative stress since this is the expected way in which ZrO_2 nano particles are expected to harm exposed individuals. Therefore the <QuantRiskModel> would need to describe a risk model based on this assumed mode of action. The <AspectRatio> scope basically describes the morphology of the ENM which in this instance would be a description of ZrO_2 nano particles as characteristically spherical objects.

The second operation, *operation sedimentation*, is similarly defined as

operation sedimentation :=

```

<AtomicOperation>
  <Description>
    Sedimentation of ZrO2 wastes in settling tank to form semi solid gel
  </Description>
  <Environment> not specified</Environment>
  <Material> zirconium dioxide gel</Material>
  <MaterialAmount>not specified</MaterialAmount >
  <Duration> not specified </Duration>
  <Worker> not specified </Worker>
</AtomicOperation>

```

as can the operation, *operation recovery*, so that

operation recovery :=

<AtomicOperation>

<Description>

Recovery of ZrO₂ nano particles precursors from settling tank gel using chemical synthesis methods

</Description>

<Environment> *not specified*</Environment>

<Material> *chemically altered zirconium dioxide gel*</Material>

<MaterialAmount>*not specified*</MaterialAmount >

<Duration> *not specified* </Duration>

<Worker> *not specified* </Worker>

</AtomicOperation>

The <Material> scope definition of *zirconium dioxide gel* is basically the same as the definition of *waste water*, as is the definition for *chemically altered zirconium dioxide gel* except for their respective <Material> scopes which reflect the various states of the ZrO₂ wastes, and associated toxicology, on the path to being recovered. Specifically, in the second stage, the zeta potential of the ZrO₂ nanoparticles are altered from the first step in order to accelerate the sedimentation process to form a gel like substance which forms at the bottom of the sedimentation tank. The zeta potential change is induced by changing the pH. level of the wastewater dispersion in the first step. In the third stage the ZrO₂ products from step two are recovered via a chemical synthesis method leaving the waste water free of contaminants.

6.4 Summary

A series of quantitative techniques were developed but relegated to describing the exposure risks presented by elementary steps in a manufacturing process. These began with proposals for ad hoc rules of thumb for calculating insurance premiums based on notions of relative risk and implied known risks for analogous risk scenarios for which premium rates had been subjectively assigned. This approach was then somewhat generalized by a linear interpolation scheme using the product of hazard and exposure variables as the interpolating variable. Extrapolating exposure limits for bulk materials to their nano form and utilizing existing pricing methods for parent material exposure risks was briefly discussed while emphasizing limitations of this approach. Lastly, a rigorous framework using Bayesian methods was presented for insuring a single worker against exposure risk to ENMs under assumptions of market equilibrium. The latter was formulated within the context of a legal definition of injury that recognizes enhanced risk of future losses as a form of injury in and of itself. Bayesian techniques applied to a simple pharmacokinetic model were utilized to express a claims probability function in terms of posterior probabilities that depended on known exposure histories and hazard levels. Although it wasn't possible to explicitly compute a claims probability function due to unavailable epidemiological data, its general phenomenological form in terms of a minimum set of three parameter types was ascertained. The author argues that the value of knowing the general form of this probability function lies in the optimum fits it should achieve if used to match epidemiological data whenever it becomes available. Alternatively, it was suggested that hypothetical market rates for a discrete set of policies could be used to calibrate the model's unknown parameter weightings for consistent pricing across a continuum of policies.

Recognizing the significance of risk communication for underwriting, the insurance model described in this chapter also included a mechanism for systematically communicating all aspects of risk. This included those

qualities of risk that can't be described quantitatively. Although the primary target of this communication mechanism was insurers, it could be applied to regulatory problems or be adapted to convey risk information to other interested parties. This mechanism took the form of a communication protocol based on the mark-up language XML. The author then gave an overview of how it could be used to describe and encapsulate all aspects of risk presented by a processing line involving possible ENM exposure.

7 Conclusions

7.1 Overview

The fate of many nanotechnologies and associated industrial processes depends on affordable access to key groups of ENMs, such as those materials that were the focus of the Sanowork project and which have found a diverse range of industrial applications. The cost of producing ENMs or the costs associated with using them include the cost of risk (insurance) to human and environmental health and the cost of controlling this risk through regulation. Therefore, to remain cost effective, the costs of insurance and regulation have to be optimally balanced such that their combined cost is minimized. For regulators and insurers to come up with the cheapest solutions they have to understand the risks. Unfortunately, in the case of ENMs they have few precedents to guide them as ENMs are essentially new materials with behaviours and properties distinct from the bulk forms of their constituent compounds or elements. In the absence of risk quantification insurers will however continue to provide insurance, although likely at a higher premium to compensate for uncertainty. For example, in the early days of commercial aviation, aircraft and airport insurance was very high, only becoming lower as the industry matured and the real risks to people and property became apparent. Regulators will also continue to regulate, but such regulation in an environment of uncertainty will adhere to the precautionary principle and tend to overcompensate, with the implied additional costs being born by ENM users and producers to maintain their market share.

At the social level, there is a need to diffuse anxieties among public interest groups about the dangers of nano materials to human health and to offer regulators an effective framework to define safety standards for the production and use of nano materials. Simply extending current regulatory frameworks to include engineered nano materials could expose nano

technology companies to additional risk in the form of unnecessarily high compliance cost (at the expense of innovation) and exploitive litigation. An effective risk communication and management framework, developed as a collaborative exercise involving all stakeholders, would help insurers to set affordable premiums, be cost effective for companies to implement and allow standards bodies to draft a vocabulary of clear and unambiguous industry definitions and conventions. Such a vocabulary will lend precision to the wording of future regulatory statutes and provide a much needed policy language for insurers.

In the context of the case study described in Chapter 4, the Sanowork project and similar initiatives may ultimately inspire insurers and regulators to adopt generally favourable perspectives on ENMs regarding their risks. Specifically, the outcome of the Sanowork project and similar projects should help quell concerns that might arise among regulators, insurers and public interest groups about the human and environmental health risks they may perceive coming from the increasing use of ENMs. That is, the real benefit lies in mitigating the risk of lost opportunity through public reassurance and persuasion that the risks are manageable and outweighed by the growing contributions ENMs are making to society.

7.2 Specific Findings and Key Contributions

ENMs are identified as a possible bridge between future needs and current methods of production and supply, either as new sources of capital or as agents that extend the lifetimes and reduce maintenance costs of existing supplies of capital stock. Since many of the ENM producers and users are small and medium enterprises with limited self-insurance options, insurance has been identified as the primary means of sustaining this industry and securing its economic promise. To help secure the insurance needs of the ENM community, this thesis presents several key initiatives and findings. These are:

- Not only does insurance facilitate risk transfer and thereby help preserve social capital by allowing companies to stay solvent and intact, but it also provides a self-regulatory function that in the interim is affordable and could be a template for future command and control frameworks. The role of insurance in this regard is critical; it may afford the ENM industry some “breathing space” at this critical juncture in its development until such time as command and control regulation becomes less uncertain, in term of its potential long term impacts, and more suited to the particular needs of the ENM sector.
- A strong argument is made that insurers may need to prepare for enhanced risk of occupational disease becoming a de facto form of injury and proactively design insurance contracts within this emerging legal environment. This is an important realization. In the past insurers had little to be concerned about regarding the prospect of claims for occupational disease. Indeed, without the prospects of enhanced risk obtaining legal standing there would have be little need to develop a model in the first instance to assess these types of claims.
- A key contribution is the development of a Bayesian regression framework that can accommodate ill-behaved probability distributions for ENM physicochemical and toxicity data. Moreover, the regression algorithm, at least for the data it was tested on, appears to automatically assign more significance to those more precise data points without the need for subjective inputs that can be a source of bias.
- A key contribution is a method for dealing with difficult to measure exposure levels, and their relationship to accumulated doses, for the purpose of calculating insurance costs. This is accomplished by a rigorous application of Bayesian techniques to accommodate uncertain exposure and hazard levels.
- Subjective risk assessments by underwriters can be used to calibrate insurance pricing models. Calibrated models can then be deployed to

suggest insurance costs for less familiar risk scenarios. This concept was borrowed from the practice of using market data to calibrate derivative pricing models in the financial world.

- A key contribution is a specification for a risk communication protocol that can accommodate complex risk information for arbitrary manufacturing processes. Since the protocol is machine readable, simple parsing methods can be deployed to interrogate complex risk data as a risk assessment aid for non-specialists.

7.3 Chapter Summary

7.3.1 Chapter 2

The contributions ENMs are making to key areas of production primarily as efficiency enhancers and as substitute materials were reviewed. ENMs were identified as a possible bridge between future needs and current methods of production and supply, either as new sources of capital or as agents that extend the lifetimes and reduce maintenance costs of existing supplies of capital stock. The primary economic sectors where ENMs are expected to have the biggest impact are in energy, agriculture, water supplies, manufacturing and raw material extraction.

7.3.2 Chapter 3

In this chapter it was argued that insurance was the primary vehicle for securing and nurturing the long term viability of ENM development in an environment of regulatory uncertainty and unpredictable public sentiment towards ENMs. Not only does insurance facilitate risk transfer and thereby help preserve social capital by allowing companies to stay solvent and intact, but it also provides a self-regulatory function that in the interim is affordable and could be a template for future command and control frameworks. Within the insurance paradigm, the latent character of ENM exposure risks and uncertainty pertaining to evolving definitions of injury was identified as the primary obstacle to insurers carrying out this all important function. Traditionally, toxic tort cases were hard to win and

presented little threat to a defendant's (insurer's) financial bottom lines. However, this state of affairs is not expected to continue. As such, it was argued that insurers need to prepare for enhanced risk becoming a de facto form of injury and proactively design insurance contracts within this emerging legal environment. The chapter ended with a key contribution pertaining to some strategies an insurer could adopt to manage short term, and more critically, the long term risks to worker's health from prolonged exposure to ENMs.

7.3.3 Chapter 4

A case study of several actual production processes involving ENMs revealed the issues from a practical perspective surrounding the regulation and insurability of ENM production and use. As a first step towards making this problem manageable, a qualitative risk assessment framework based on ENM physicochemical attributes was described. This circumvented the intractable nature of an ENM risk assessment on a case by case basis given the vast and growing number of ENMs currently available. The dominant attributes to be alert to included morphology characteristics, especially the aspect ratio and effective aerodynamic diameter. The next consideration was the material's reactive and soluble impurities. One also needed to consider the intrinsic reactivity of the ENM's parent form and its acidity level. This categorization framework was constructed on the basis of assumed modes of toxic action which in some respects is a limitation in that only risks characterised by *known unknowns* can be addressed. Ambiguous risks characterised by *unknown unknowns*, specifically those which originate from unforeseen mechanisms of toxic action remain an outstanding issue for ENM risk assessment.

7.3.4 Chapter 5

Within the framework described in chapter 4, an ENM can only be toxicologically profiled in terms of yes/no type answers respecting a list of questions pertaining to its physical characteristics. For it to work,

quantitative characterizations did not need to be overly precise. A more refined tool would include the need for quantitative data, particularly if it was to form an input for a higher risk model at the *in-vivo* level that included exposure data. However, ENM characterisation, both physicochemical and toxicological, is limited by heterogeneous measurement protocols; measurements for the same ENM sample can be expected to vary widely depending on the institution carrying out the measurements and the method used. This problem is true for both toxicity measurements and physicochemical measurements. The degree of toxicity as a function of a particular set of physicochemical attributes, given the nature of available data and the way it is generated, can only be stated in probabilistic terms. The key contribution from this chapter was the development of a Bayesian regression framework that could account for these probability spreads by optimally correlating seemingly ambiguous toxicity and physiochemical data points. Moreover, the regression algorithm, at least for the data it was tested on, appeared to automatically assign more significance to those more precise data points without the need for subjective inputs that could be a source of bias.

7.3.5 Chapter 6

Along with a mechanism for communicating meta and qualitative aspects of risk to insurers and regulators based on a specification written in XML, a key contribution from this chapter was a method for dealing with difficult to measure exposure levels in a manufacturing environment. This was accomplished by a rigorous extension of the Bayesian framework developed in chapter 4 to encompass the problem of exposure uncertainty. Within this framework was located a simple pharmacokinetic model to relate exposure and dose dynamics. Notwithstanding its simplicity, this model revealed a macroscopic aspect to ENM hazards. It could be seen that a holistic notion of ENM hazard has to include a material's absorption and persistence characteristic at the organism level in addition to its toxicity at the cellular level in order to offer more complete risk assessments.

A second significant output from this chapter involved the idea of risk model calibration. Regardless of the tools underwriters may have available

to them, they eventually have to assign premium rates to given risk scenarios. Such assignments have value. They represent subjective judgements based on mental risk models that underwriters develop through experience, intuition and trial and error. A key finding was the realization that quantitative risk models could in principle be calibrated using subjectively ascertained premiums. This would allow for the consistent pricing of a continuum of policies for qualitatively similar circumstances and would be a useful tool for portfolio management. In support of this idea, such practices are commonplace in the financial modelling community, particularly of note for derivative model calibration. In this manner, model calibration would allow an underwriter to leverage the value of his or her knowledge of risk in specific situations to infer risk levels in less familiar settings.

7.4 Future Research Directions

This thesis is quite interdisciplinary in nature. As such, some of the topics it covered warrant further in-depth research as more data becomes available. In particular, the Bayesian framework developed in chapter 6 was able to accommodate unpredictable exposure scenarios. However, due to time constraints and its vast scope, the problem of determining prior exposure distributions was not examined. The principle of maximum entropy could provide initial estimates for these distributions, best exploiting future data sources. With a view to garnering more accurate data, the lack of an efficient methodology for estimating ENM exposure levels for manufacturing environments still represents a formidable problem given that exposure measurement technology, particularly for measuring surface area densities and differentiating materials in real time, is still in early development. Computer simulations of exposure distributions and evolution based on ENM emission potential characteristics and environmental factors offers an alternative approach. Early incarnations of this strategy were in fact deployed in Sanowork to provide exposure estimates based on the emission potentials of powdered ENMs, measured in terms of dustiness factors. The challenge here is not as much methodological, since the models

are based on well established principles of aerosolized particles being convected in air flows, as it is computational. Essentially, the path of each nano particle in a sample is separately analysed as a random walk from the point and time of its emission. The probability of a particle's emission and the probability of where it will be after a particular time can then be used to determine an exposure distribution comprised of many particles and its evolution in time. Random walk type problems are usually addressed with Monte-Carlo techniques that are generally computationally demanding. The computational size of this task however becomes magnified if not intractable from the presence of hidden or indeterminate variables that essentially swells the sample space of exposure distribution possibilities. This presents a well defined research challenge to identify computational shortcuts to execute such simulations in reasonable time frames.

8 Appendices

8.1 Determination of Marginal Distributions from Scaling and Translation Invariance Arguments and Maximum Entropy Considerations

A distribution that characterizes a random quantity should be independent of the units in which that quantity is expressed. Equivalently, the probability of an event occurring should be independent of the method by which it is observed. This principle reveals certain general features that all probability density functions must have and is useful for estimating their forms when a minimum of information is available. For a one dimensional density distribution, this principle is formally stated as:

$$P(x|1)\Delta x = P(\alpha x|\alpha)\alpha\Delta x \quad \forall x, \forall \alpha > 0 \quad Eq(8.1.0)$$

In which αx is a random variable expressed in units represented by the scaling factor α . For example, if x is measured in metres with the metre represented by a scaling factor of 1, then the scaling factor, $\alpha = 1000$, indicates that αx is now measured in millimetres. In order to satisfy this scaling invariance, it can be shown that $P(x|\alpha)$ must be of the form given by;

$$P(x|\alpha) = \frac{g\left(\frac{x}{\alpha}\right)}{x} \quad \forall x, \forall \alpha > 0$$

In which g is an arbitrary function except for the requirement that $g(0) = 0$ to prevent the distribution from becoming singular at $x = 0$

Proof: Since $P(x|1)\Delta x = P(\alpha x|\alpha)\alpha\Delta x \quad \forall x, \forall \alpha > 0$ then

$$P(x|1) = P(\alpha x|\alpha)\alpha \quad \forall \alpha > 0 \quad Eq(8.1.1)$$

Letting $z = \alpha x$ and differentiating both sides of Eq (8.1.1) with respect to α gives,

$$\begin{aligned} 0 &= \left(\frac{\partial P(z|\alpha)}{\partial \alpha} + \frac{\partial P(z|\alpha)}{\partial z} \frac{\partial z}{\partial \alpha} \right) \alpha + P(z|\alpha) \\ &= \frac{\partial P(z|\alpha)}{\partial \alpha} \alpha + \frac{\partial P(z|\alpha)}{\partial z} z + P(z|\alpha) \quad Eq(8.1.2) \end{aligned}$$

Treating Eq (8.1.2) as a partial differential equation with respect to the independent variables z and α , leads to a general solution for $P(z|\alpha)$ given by,

$$P(z|\alpha) = \int_{-\infty}^{\infty} \frac{A(y)}{\alpha^y z^{1-y}} dy = \frac{g(\frac{z}{\alpha})}{z} \quad Eq(8.1.3)$$

with

$$g(x) = \int_{-\infty}^{\infty} A(y)x^y dy \quad Eq(8.1.4)$$

in which $A(y)$ is arbitrary. This completes the proof.

To identify the most unbiased⁴⁶ form of $P(x|\alpha)$ given a complete absence of any information pertaining to g requires that g should have no preferences for any particular argument values. Thus $g(x)$ must be assigned equal weight for all arguments, or equivalently, $g(x) = Constant$. However, such a distribution fails to satisfy the condition that the sum of all probabilities is equal to unity, since (assuming only positive argument values)

$$\int_0^{\infty} \frac{1}{x} dx \rightarrow \infty. \quad Eq(8.1.5)$$

This condition can only be met by imposing the minimum requirement that x be confined by lower and upper bounds. That is

⁴⁶The term 'unbiased' is rigorously defined by the following thought experiment. If a number of independent observers are presented with the same information, I , regarding the likelihood, $P(X|I)$, of an observation, X , then the probability function, $P(X|I)$, is unbiased if all observers independently deduce its form.

$$\int_{x_{min}}^{x_{max}} P(x | 1) dx = 1 \quad Eq (8.1.6)$$

and

$$P(x | 1) = 0 \quad \forall x < x_{min} \text{ and } \forall x > x_{max} \quad Eq(8.1.7)$$

so that

$$\begin{aligned} 1 &= \int_{x_{min}}^{x_{max}} P(x | \alpha) dx = Constant \times (\ln(x_{max}) - \ln(x_{min})) \\ &= Constant \times \ln \frac{x_{max}}{x_{min}} \end{aligned}$$

which is the same as

$$P(x | 1) = \frac{1}{\ln \frac{x_{max}}{x_{min}}} \quad Eq(8.1.8)$$

Beyond the observation of scale invariance that all density distributions must have, the next most elementary piece of information to aid in the determination of a density function is to know that it is unbiased with respect to its argument values. That is, if it is known that $P(x | 1)$ is independent of, or has no special preference for any value of x , then it must be the case the most unbiased density has to be constant. That is $P(x | 1) = constant$ so that $g(x) \propto x$ for $x_{min} \leq x \leq x_{max}$. In this case

$$P(x | 1) = \frac{1}{x_{max} - x_{min}} \quad Eq(8.1.9)$$

The next level in the hierarchy for determining a distribution function is reached when prior knowledge of its moments is supplied. When data on the moments of $P(x | 1)$ is available, the most unbiased form of $P(x | 1)$, and hence $g(x)$, can be selected using the *principle of maximum entropy*. Essentially, this principle selects the single most unbiased distribution from an infinite number of distributions that are consistent with the distribution's known moments. Mathematically, it translates to the following algorithm for obtaining this unique distribution, $P(x | 1)$

Given that the first n moments, M_k , are known, that is

$$\int_0^{\infty} P(x | 1) x^k dx = M_k \text{ for } 1 \leq k \leq n \text{ Eq(8.1.10)}$$

then

$$P(x | 1) = \frac{1}{Z(\lambda_1 \dots \lambda_n)} e^{\lambda_1 x + \lambda_2 x^2 + \dots + \lambda_n x^n} \text{ Eq(8.1.11)}$$

In which the 'partition function' Z is defined as

$$Z(\lambda_1 \dots \lambda_n) = \int_0^{\infty} P_0(x | 1) e^{\lambda_1 x + \lambda_2 x^2 + \dots + \lambda_n x^n} dx \text{ Eq(8.1.12)}$$

The λ_k parameters are determined by solving simultaneously the following equations;

$$M_k = \frac{\partial}{\partial \lambda_k} \log Z(\lambda_1 \dots \lambda_n) \text{ for } 1 \leq k \leq n \text{ Eq(8.1.13)}$$

The distribution $P_0(x | 1)$ is the most unbiased distribution that could be obtained given no prior knowledge of the moments. Therefore $P_0(x | 1)$ has to be obtained using the invariance arguments described in the previous paragraphs.

8.2 Modelling Acute Risk

Without loss of generality, the probability, $Q(T|\mathbf{E}, h)$, as seen at time zero, of a predefined biological endpoint being realized for the first time before time T , given a known exposure history, $\mathbf{E} := E(t)$, in which $E(t)$ denotes the level of exposure at time t , can be expressed in terms of a hazard function, $H(t|\mathbf{E}, h)$, as;

$$Q(T|\mathbf{E}, h) = 1 - e^{-\int_0^T H(t|\mathbf{E}, h) dt} \text{ Eq(8.2.0)}$$

in which $H(t|\mathbf{E}, h) dt$ is the probability of the same event occurring within the time interval $(t, t + dt)$ but as seen at time t . The advantage of

expressing $Q(T|\mathbf{E}, h)$ in the form given by Eq (8.20) is that $H(t|\mathbf{E}, h)$ is typically easier to measure or model than $Q(T|\mathbf{E}, h)$. $Q(T|\mathbf{E}, h)$ and $H(t|\mathbf{E}, h)$ are *functions* of time and the hazard parameter h but functionals⁴⁷ of the entire exposure history, \mathbf{E} .

An intuitive notion of acute hazard derives from the expectation that a biological response, if elicited, depends on the most recent exposure level and only to a much lesser extent on a worker's entire history of exposure. This concept allows for a working definition of an acute hazard function, H_a , such that

$$H(t|\mathbf{E}, h) = H_a(E(t), h) \quad Eq(8.2.1)$$

That is, the hazard function dependence on the exposure history \mathbf{E} at time t can now be stated as a dependence only on its most recent value, $E(t)$, as seen at time t .

Applying a first order Taylor series expansion to $H_a(E(t), h)$ about $E(t) = 0$ and $h = 0$ while observing the boundary condition, $H_a(0, h) = H_a(E(t), 0) = 0$, gives

$$\begin{aligned} H_a(E(t), h) &= W \times E(t) \times h \\ &= \text{acute risk (probability of event occurring within unit time as seen at time } t) \end{aligned} \quad (8.2.3)$$

in which the universal weight constant W is given by

$$W = \frac{\partial^2 H_a}{\partial E(t) \partial h} \Big|_{E(t)=h=0} \quad Eq(8.2.4)$$

Note that the weight W would have to be empirically determined.

This approach reflects the notion of acute risk in that it derives from the most recent exposure event. As such it cannot be used to model chronic or aggregate risk which generally will depend on the accumulated effects from experiencing a given exposure history.

⁴⁷ A functional is a function of a function

A more general analysis would involve a *functional Taylor expansion* such that;

$$H(t|\mathbf{E}, h) = h \times \int_0^t E(t')w(t-t')dt' + \text{higher order terms} \quad Eq(8.2.5)$$

In which the hazard potential is now characterized by a weight function, $w(t-t')$. In principle, such a function would contain both chronic and acute risk data.

The acute description given by Eq (8.2.3) can be recovered by substituting $w(t-t') = W \times \delta(t-t')$ in Eq (8.2.5). In appendices 8.6 and 8.7 it is shown how to determine $w(t-t')$ from a simple pharmacokinetic model developed in appendix 8.3 that accounts for the non-soluble ENM that has been accumulated in a worker's body following a known exposure history.

If instead of using a single magnitude h to represent the intrinsic toxicity of the NM under study, all the entries in the hazard matrix, $\mathbf{H} := h_{i,j}$, are used, then $H_a(E(t), h)$ generalizes to

$$H_a(E(t), h_{1,1}, h_{1,2} \dots h_{2,1}, h_{2,2} \dots \dots) \quad (8.2.6)$$

$$\begin{aligned} & \text{for which } H_a(0, h_{1,1}, h_{1,2} \dots h_{2,1}, h_{2,2} \dots \dots) \\ & = 0 \text{ and } H_a(E(t), 0, 0 \dots 0, 0 \dots \dots) = 0 \quad Eq(8.2.10) \end{aligned}$$

The first non-zero lowest order terms in a Taylor series expansion of Eq (8.2.6) about $E(t) = 0$ and $h_{i,j} = 0 \forall i \text{ and } j$ which is consistent with the boundary conditions prescribed by Eq (8.2.10), is given by

$$\begin{aligned} & H_a(E(t), h_{1,1}, h_{1,2} \dots h_{2,1}, h_{2,2} \dots \dots) \\ & = E(t) \times \sum_{\forall i \text{ and } j} W_{i,j} \times h_{i,j} \\ & + \text{higher order terms} \quad Eq(8.2.11) \end{aligned}$$

in which

$$W_{i,j} = \frac{\partial^2 H_a}{\partial E(t) \partial h_{i,j}} \Big|_{E(t)=h_{i,j}=0} \quad Eq(8.2.12)$$

Using the expression for the hazed function given by Eq (8.2.11) in Eq (8.2.0) yields

$$Q(T|\mathbf{E}, \mathbf{H}) = 1 - e^{-\int_0^T E(t) dt \times \Sigma(W_{i,j} \times h_{i,j}) + higher\ order\ terms} \quad Eq(8.2.13)$$

and reduces to

$$Q(T|\mathbf{E}, h) = 1 - e^{-\int_0^T E(t) dt \times W \times h \times T + higher\ order\ terms} \quad Eq(8.2.14)$$

when the intrinsic toxicity is treated as a single magnitude which in this case is denoted by h .

If it is further assumed that exposure levels remain approximately steady throughout a worker's exposure history such that $\mathbf{E} := E(t) = E_0$, in which E_0 is constant, then Eq (8.2.13) becomes

$$Q(T|E_0, \mathbf{H}) = 1 - e^{-E_0 \times T \times \Sigma W_{i,j} \times h_{i,j} + higher\ order\ terms} \quad Eq(8.2.15)$$

and reduces to

$$Q(T|E_0, h) = 1 - e^{-E_0 \times W \times h \times T + higher\ order\ terms} \quad Eq(8.2.16)$$

for a single hazard parameter.

8.3 Simple Pharmacokinetic Model for Relating Exposure Histories to Dose Accumulations

Let $C(\mathbf{E}, t, p_1, p_2 \dots p_n)$ indicate the dose level, or amount of non-soluble ENM accumulated by an exposed worker following the exposure history, $\mathbf{E} := E(t)$. In general, $E(t)$ and $C(\mathbf{E}, t, p_1, p_2 \dots p_n)$ are stochastic processes and will take account of the random movements of the worker together with spatial and temporal variations in exposure levels of the ENM in question. The parameters, p_k encode various physical characteristics of the exposed worker, the worker's environment and ENM taken together as a single physical system. To illustrate the concept, a rather simplified model is presented to relate dose levels and exposure. Within a predefined time interval, τ , it is assumed that

change in dose level =

amount of material that enters worker

– amount of material that leaves worker(depletion)

That is

$$\Delta C = \Delta S^+(E, \tau) - \Delta S^-(C, \tau) \quad Eq(8.3.1)$$

$\Delta S^+(E, \tau)$ is defined as the amount of ENM absorbed by the worker during the time interval τ due to an exposure level of E in the worker's vicinity and which is assumed to remain constant over the interval. This assumption is valid provided τ is small. $\Delta S^+(E, \tau)$ can be expanded about $E = \tau = 0$ to lowest non-zero order as a Taylor series to yield

$$\Delta S^+(E, \tau) \cong \lambda \times E \times \tau \quad Eq(8.3.2)$$

in which the constant λ is given by

$$\lambda = \frac{\partial^2 \Delta S^+}{\partial E \partial \tau} \Big|_{E=\tau=0} \quad Eq(8.3.3)$$

$\Delta S^-(C, \tau)$ indicates the amount of ENM depleted from the same worker after the interval τ given an initial dose of C . Similarly, $\Delta S^-(C, \tau)$ is expanded as a Taylor expansion around $C = \tau = 0$ to yield

$$\Delta S^-(C, \tau) = \frac{1}{\gamma} \times C \times \tau \quad Eq(8.3.4)$$

whereupon the constant γ is defined as

$$\frac{1}{\gamma} = \frac{\partial^2 \Delta S^-}{\partial C \partial \tau} \Big|_{E=\tau=0} \quad Eq(8.3.5)$$

In this example, the parameter space, p_k , consists of absorption and depletion constants λ and γ respectively.

Substituting ΔS^+ and ΔS^- in Eq (8.3.1) for the expressions given by Eq (8.3.2) and Eq (8.3.4) and taking the limit $\tau \rightarrow dt \rightarrow 0$ yields

$$\frac{dC(\mathbf{E}, t, \lambda, \gamma)}{dt} = \lambda E(t) - \frac{1}{\gamma} C(\mathbf{E}, t, \lambda, \gamma) \quad Eq (8.3.6)$$

Eq (8.3.6) can then be integrated to finally yield

$$C(\mathbf{E}, t, \lambda, \gamma) = \lambda \left(\int_0^t E(t') e^{-\frac{1}{\gamma}(t-t')} dt' \right) \text{ Eq(8.3.7)}$$

If the exposure level becomes zero and remains zero thereafter, then according to Eq (8.3.6), the accumulated dose C should decay exponentially. The time for half the accumulated dose to be eliminated from the worker is given by $\gamma \ln 2$.

8.4 Modelling Exposure History

Each possible exposure history is modelled as a sum of a continuous stochastic background, E_{BG} , and a series of random spikes of magnitudes, M_i , whose occurrence times, τ_i , follow a Poisson distribution. That is

$$E_n(t) = \sum_{i=0}^n M_i \delta(t - \tau_i) + E_{BG}(t) \text{ Eq(8.4.1)}$$

in which

$$\tau_1 < \tau_2 < \dots < \tau_n$$

Such spikes can represent sudden releases of material that are for example typical of industrial accidents and which would likely evade periodic exposure measurements. When the inverse of the bio-persistence half-life, $\gamma \ln 2$, of the ENM in question is small compared to the frequencies of expected cyclic variations in the background level due to the regulatory of working shifts and periodic manufacturing, maintenance and cleaning operations etc., it can be shown that the background level can effectively be treated as constant and equal to its time averaged value. To see this, express the background level in terms of its Fourier components;

$$E_{BG}(t) = A_0 + \sum_{n=-\infty}^{n=\infty} A_n e^{i\omega_n t} = E_{BG0} + \sum_{n=-\infty}^{n=\infty} A_n e^{i\omega_n t} \text{ Eq(8.4.2)}$$

This would tend to be the case for ENMs that have metallic components which studies have shown are sequestered by the body for some time before being expelled.

Now consider the contributions from each of the Fourier terms in Eq (8.4.2) to the integral term in Eq (8.3.7), to wit

$$\begin{aligned}
& \int_0^t E_{BG}(t') e^{-\frac{1}{\gamma}(t-t')} dt' \\
&= E_{BG_0} \int_0^t e^{-\frac{1}{\gamma}(t-t')} dt' + \sum_{n=-\infty}^{n=\infty} A_n \int_0^t e^{i w_n t'} e^{-\frac{1}{\gamma}(t-t')} dt' \\
&= E_{BG_0} \int_0^t e^{-\frac{1}{\gamma}(t-t')} dt' \\
&+ e^{-\frac{1}{\gamma}t} \sum_{n=-\infty}^{n=\infty} A_n \int_0^t e^{t'(i w_n + \frac{1}{\gamma})} dt' \quad Eq(8.4.3)
\end{aligned}$$

Provided the w_n for the dominant Fourier components are large compared to $\frac{1}{\gamma}$, that is those components which contribute the most to $E_{BG}(t)$, then the last term in Eq (8.4.3) should be small since

$$\begin{aligned}
& e^{-\frac{1}{\gamma}t} \int_0^t e^{t'(i w_n + \frac{1}{\gamma})} dt' = \frac{e^{-\frac{1}{\gamma}t}}{(i w_n + \frac{1}{\gamma})} \left(e^{t(i w_n + \frac{1}{\gamma})} - 1 \right) \\
&= e^{-\frac{1}{\gamma}t} \int_0^t e^{t'(i w_n + \frac{1}{\gamma})} dt' = \frac{1}{(i w_n + \frac{1}{\gamma})} \left(e^{i w_n t} - e^{-\frac{1}{\gamma}t} \right) \rightarrow 0 \text{ as } w_n \\
&\rightarrow \infty \quad Eq(8.4.4)
\end{aligned}$$

Thus under these assumptions and in the context of Eq (8.4.1) and Eq (8.3.7), $E_{BG}(t)$ can effectively be replaced by the constant term, E_{BG_0} so that

$$E_n(t) = \sum_{i=0}^n M_i \delta(t - \tau_i) + E_{BG_0} \quad Eq(8.4.5)$$

Substituting $E(t')$ in Eq (8.3.7) for Eq (8.4.5) gives;

$$\begin{aligned}
C_n(\mathbf{E}, t, \lambda, \gamma) &= \lambda \gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}t}\right) \text{ for } t < \tau_1 \\
C_n(\mathbf{E}, t, \lambda, \gamma) &= \lambda \left(\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}t}\right) + \sum_{i=1}^m M_i e^{-\frac{1}{\gamma}(t-\tau_i)} \right) \text{ for } \tau_m \leq t \\
&< \tau_{m+1} \text{ when } 1 \leq m < n \\
C_n(\mathbf{E}, t, \lambda, \gamma) &= \lambda \left(\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}t}\right) + \sum_{i=1}^n M_i e^{-\frac{1}{\gamma}(t-\tau_i)} \right) \text{ for } \tau_n \\
&\leq t \quad Eq(8.4.6)
\end{aligned}$$

It's important to note the contribution of the bio-persistence half-life parameter γ to the $\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}t}\right)$ term in Eq (8.4.6). It indicates that ENMs that have a large bio-persistence even for relatively low background exposure levels may result in much larger doses that tend to persist, potentially contributing in chronic complications for exposed workers.

8.5 Definition of DE and Calculation of $\int Q(E)DE$ and Expected Dose

8.5.1 $\int Q(E)DE$

For this calculation it is assumed that exposure histories are in accordance with Eq (8.4.5). As mentioned previously, it has been assumed that emission occurrences are independent and follow a Poisson distribution so that,

$$\begin{aligned}
Prob_SingleEmission(M, M + \Delta M, t, t + \Delta t) \\
= \rho(M)\Delta M \times e^{-I\Delta t} I\Delta t \quad Eq(8.5.1)
\end{aligned}$$

$$Prob_NoEmission(t, t + \Delta t) = e^{-I\Delta t} \quad Eq(8.5.2)$$

in which I is the average number of emissions per unit time and $Prob_SingleEmission(M, M + \Delta M, t, t + \Delta t)$ is the probability of an emission with a magnitude in the range M to $M + \Delta M$ occurring in the time interval t to $t + \Delta t$. If an emission does occur, $\rho(M)\Delta M$ is the probability it will have a magnitude in the range M to $M + \Delta M$.

The probability of the history E_n unfolding within the limits defined by the functional measure DE_n , is then given by;

$$\begin{aligned}
Q(E_n)DE_n &= Prob_NoEmission(0, \tau_1) \times Prob_NoEmission(\tau_n \\
&\quad + \Delta\tau_n, T) \times \prod_{i=1}^{n-1} Prob_NoEmission(\tau_i + \Delta\tau_i, \tau_{i+1}) \\
&\quad \times \prod_{i=1}^n Prob_SingleEmission(M_i, M_i + \Delta M_i, \tau_i, \tau_i + \Delta\tau_i) \\
&= e^{-IT} I^n \prod_{i=1}^n \rho(M_i) \Delta M_i \Delta\tau_i \quad Eq(9.5.3)
\end{aligned}$$

Eq (9.5.3) follows from applying the following two identities

$$\begin{aligned}
e^{-I\tau_1} e^{-I(T-\tau_n-\Delta\tau_n)} \prod_{i=1}^{n-1} e^{-I(\tau_{i+1}-\tau_i-\Delta\tau_i)} \prod_{i=1}^n e^{-I\Delta\tau_i} \\
= e^{-I(\tau_1+T-\tau_n-\Delta\tau_n+\sum_{i=1}^{n-1}(\tau_{i+1}-\tau_i-\Delta\tau_i)+\sum_{i=1}^n \Delta\tau_i)} \\
\equiv e^{-IT} \quad Eq(8.5.4)
\end{aligned}$$

and

$$\sum_{i=1}^{n-1} (\tau_{i+1} - \tau_i) \equiv \tau_n - \tau_1 \quad Eq(8.5.5)$$

It follows that the functional measures DE_n and DE can be identified as $DE_n \equiv \prod_{i=1}^n \Delta M_i \Delta\tau_i$ and $Q(E)DE \equiv \sum_{n=1}^{\infty} Q(E_n)DE_n$ in which $Q(E_n) = e^{-IT} I^n \prod_{i=1}^n \rho(M_i)$.

To check the consistency of these identities it is straightforward to demonstrate the expected result that

$$\int Q(E)DE = \sum_{n=1}^{\infty} \int Q(E_n)DE_n = 1 \quad Eq(8.5.6)$$

Proof:

$$\begin{aligned}
& \int Q(E_n)DE_n \\
&= \int_{\tau_1=0}^T \dots \int_{\tau_{n-1}=\tau_{n-2}}^T \int_{\tau_n=\tau_{n-1}}^T \int_{M_1=0}^{\infty} \dots \int_{M_{n-1}=0}^{\infty} \int_{M_n=0}^{\infty} e^{-IT} I^n \prod_{i=1}^n \rho(M_i) dM_i d\tau_i \\
&= e^{-IT} I^n \int_{\tau_1=0}^T \dots \int_{\tau_{n-1}=\tau_{n-2}}^T \int_{\tau_n=\tau_{n-1}}^T \prod_{i=1}^n d\tau_i = e^{-IT} I^n \frac{T^n}{n!} \\
&= e^{-IT} \frac{(IT)^n}{n!} \quad Eq(8.5.7)
\end{aligned}$$

Eq(8.5.7) simplifies by noting that

$$\int_{D_1=0}^{\infty} \dots \int_{D_{n-1}=0}^{\infty} \int_{D_n=0}^{\infty} \prod_{i=1}^n \rho(M_i) dM_i = 1$$

It therefore follows that

$$\begin{aligned}
\int Q(E)DE &= \sum_{n=1}^{\infty} \int Q(E_n)DE_n = e^{-IT} \sum_{n=1}^{\infty} \frac{(IT)^n}{n!} = e^{-IT} e^{IT} \\
&= 1 \quad Eq(8.5.8)
\end{aligned}$$

This completes the proof.

8.5.2 Expected dose

For this calculation it is also assumed that exposure histories are in accordance with Eq (8.4.5) and dose accumulations in accordance with Eq (8.4.6). The expected dose to be accumulated before time T as seen at time zero is given as

$$\begin{aligned}
Ex(C(\mathbf{E}, T, \lambda, \gamma)) &= \int C(\mathbf{E}, t, \lambda, \gamma) Q(E) DE Q(\lambda, \gamma) d\lambda d\gamma \\
&= \sum_{n=1}^{\infty} \int C_n(\mathbf{E}, t, \lambda, \gamma) Q(E_n) DE_n Q(\lambda, \gamma) d\lambda d\gamma
\end{aligned}$$

$$= \int \left(\gamma E_{BG_0} \left(1 - e^{-\frac{1}{\gamma}T} \right) + \langle M \rangle e^{-IT} \sum_{n=1}^{\infty} \sum_{i=1}^n L_{i,n}(T) \right) Q(\lambda, \gamma) d\lambda d\gamma \quad Eq(8.5.9)$$

where

$$L_{i,n}(T) = I^n \left(\frac{T^{i-1}}{(i-1)!} \frac{(-1)^{n-i}}{\gamma'^{n-i+1}} (n-i)! - \frac{\partial^{n-i}}{\partial \gamma'^{n-i}} \left(\frac{e^{-\gamma'T}}{\gamma'} \frac{(-1)^i}{\gamma'^{i-1}} (S(e^{-\gamma'T}, i-1, 0) e^{\gamma'T} - 1) \right) \right) \quad Eq(8.5.10)$$

$S(f, n, x)$

= first n terms in Taylor series expansion of f about x Eq(8.5.11)

$$\gamma' = 1/\gamma \quad Eq(9.5.12)$$

$\langle M \rangle$

$$= \int_{M_i=0}^{\infty} \rho(M_i) M_i dM_i \quad (\text{the average emission, the same for all } i) \quad Eq(8.5.13)$$

Eq (8.5.9) and Eq (8.5.10) were arrived at with the help of *mathematica* since a hand calculation proved to be too involved.

8.6 Modelling Reversible Chronic Risk

In appendix 8.2, Eq (8.20) modelled acute risk by limiting the hazard function in Eq (8.2.1) to depend explicitly on the most recent value of the given exposure history. In order to model chronic reversible risk or risk that is accumulated from prolonged exposure but is still reversible, the hazard function will instead be based on the current accumulation of the ENM in question using the pharmacokinetic model expressed by Eq (8.3.7) rather than just the last exposure level. That is

$$H(t|\mathbf{E}, h) = H_{rc}(C(\mathbf{E}, t, \lambda, \gamma), h) \quad Eq(8.6.1)$$

Eq (8.6.1) reflects reversible risk in the sense that if $C(\mathbf{E}, t, \lambda, \gamma)$ is zero at time t then so will H_{rc} or that is to say the present probability as seen at time t of registering an enhanced risk of experiencing a loss at some future time. For instance a critical accumulation of ENM in the lungs could directly induce oxidative stress leading to a high risk of associated complications for the exposed worker. Allowing the worker to recover by allowing the accumulated dose to dissipate would then eliminate the risk of developing future complications.

Taylor expanding H_{RC} to first order around $C(\mathbf{E}, t, \lambda, \gamma) = h = 0$ while observing the conditions $H_{RC}(0, h) = H_{RC}(C(\mathbf{E}, t, \lambda, \gamma), 0) = 0$, yields

$$H_{rc}(C(\mathbf{E}, t, \lambda, \gamma), h) = W \times C(\mathbf{E}, t, \lambda, \gamma) \times h \quad Eq(8.6.2)$$

in which the universal weight constant W is defined as

$$W = \frac{\partial^2 H_{rc}}{\partial C \partial h} \Big|_{C=h=0} \quad Eq (8.6.3)$$

Using Eq (8.6.2) in Eq (8.2.0) then gives

$$Q(T|\mathbf{E}, h) = 1 - e^{-W \times h \times \int_0^T C(\mathbf{E}, t, \lambda, \gamma) dt} \quad Eq(8.6.4)$$

8.7 Modelling Irreversible Chronic Risk

Let p represent a measure of irreversible damage to a workers health incurred as a result of the presence of an ENM accumulated from a given exposure history. Specifically $\Delta p(C, h, \tau)$ measure the advance of irreparable damage over the time interval τ as a result of the accumulated dose, C . Taylor expanding $\Delta p(C, h, \tau)$ about $C = h = \tau = 0$ subject to the assumption that $\Delta p(C, h, 0) = \Delta p(C, 0, \tau) = \Delta p(0, h, \tau) = 0$ yields

$$\Delta p(C, h, \tau) = P \times C \times h \times \tau \quad Eq(8.7.1)$$

where the constant P is defined as

$$P = \frac{\partial^3 \Delta p}{\partial C \partial h \partial \tau} \Big|_{C=h=\tau=0} \quad Eq(8.7.2)$$

Examples of what p could represent include the fraction of heart cells permanently damaged from ROS production induced by an ENM accumulation in the pulmonary system, a measure of arterial plaque accumulations from free radical production stimulated by the redox potential of the ENM in question, or the amount of reduced lung capacity caused by fibrosis following prolonged retention of nano fibres in the lungs.

Eq (9.7.1) can be integrated with respect to time to give

$$p(\mathbf{E}, t, \lambda, \gamma, h) = P \times h \times \int_0^t C(\mathbf{E}, t', \lambda, \gamma) dt' \quad Eq(8.7.3)$$

In order to model irreversible risk in addition to the direct reversible risk component from current accumulations, $H(t|\mathbf{E}, h)$ is chosen to explicitly depend on $p(\mathbf{E}, t, \lambda, \gamma, h)$ as well as $C(\mathbf{E}, t, \lambda, \gamma)$ such that

$$H(t|\mathbf{E}, h) = H_{irc}(C(\mathbf{E}, t, \lambda, \gamma), p(\mathbf{E}, t, \lambda, \gamma, h), h) \quad Eq(8.7.4)$$

Taylor expanding Eq (8.7.4) to the lowest non zero order such that all parameters are included in the expansion while observing the constraint, $H_{irc}(C(\mathbf{E}, t, \lambda, \gamma), P(\mathbf{E}, t, \lambda, \gamma, h), 0) = H_{irc}(0, 0, h) = 0$, yields

$$\begin{aligned} H_{irc}(C(\mathbf{E}, t, \lambda, \gamma), P(\mathbf{E}, t, \lambda, \gamma, h), h) \\ &= W_1 \times C(\mathbf{E}, t, \lambda, \gamma) \times h + W_2 \times p(\mathbf{E}, t, \lambda, \gamma, h) \\ &= W_1 \times C(\mathbf{E}, t, \lambda, \gamma) \times h + W_2' \times P \times h \\ &\times \int_0^t C(\mathbf{E}, t', \lambda, \gamma) dt' \quad Eq(8.7.5) \end{aligned}$$

where the universal weight constants are given by

$$W_1 = \frac{\partial^2 H_{irc}}{\partial C \partial h} \Big|_{C=h=p=0} \quad \text{and} \quad W_2' = \frac{\partial H_{irc}}{\partial p} \Big|_{C=h=p=0}$$

It can be argued that the constant P has also a universal quality since it is derived from the universal function given by Eq (8.7.2). For this reason the

$W_2' \times P$ product in Eq (8.7.5) can be absorbed into a single universal weight constant, W_2 , such that

$$\begin{aligned}
 H_{irc}(C(\mathbf{E}, t, \lambda, \gamma), P(\mathbf{E}, t, \lambda, \gamma, h), h) \\
 &= W_1 \times C(\mathbf{E}, t, \lambda, \gamma) \times h + W_2 \times p(\mathbf{E}, t, \lambda, \gamma, h) \\
 &= W_1 \times C(\mathbf{E}, t, \lambda, \gamma) \times h + W_2 \times h \\
 &\times \int_0^t C(\mathbf{E}, t', \lambda, \gamma) dt' \quad Eq(8.7.6)
 \end{aligned}$$

The risk from a given exposure is modelled as irreversible in the sense that even if the current accumulation of the ENM is zero at time t , the present probability as seen at time t of an exposed worker registering an enhanced risk of experiencing a loss at some future time will generally not be zero due to the contribution of the $\int_0^t C(\mathbf{E}, t', \lambda, \gamma) dt'$ term in Eq (8.7.6).

Using Eq (8.7.6) in Eq (8.2.0) then gives

$$\begin{aligned}
 Q(T|\mathbf{E}, h) = 1 \\
 - e^{-W_1 \times h \times \int_0^T C(\mathbf{E}, t, \lambda, \gamma) dt + W_2 \times h \times \int_0^T (\int_0^t C(\mathbf{E}, t', \lambda, \gamma) dt')} dt \quad Eq(8.7.7)
 \end{aligned}$$

8.8 Premium Calculation Based on Market Equilibrium

Assume that premiums are paid yearly and designate all times to be measured in years. Let N_0 represent the number of identical policies in the same risk pool, RP , each with a policy limit Pl , a yearly premium payment of Pr and a life of T years. Let $B(t)$ represent the present value (at time zero) of a risk free bond redeemable for one unit of currency after time t years. Let $N(t)$ be the number of claims that RP has paid out by time t . It is assumed that after a claim has paid out, the policy holder is removed from RP and assigned to a different risk pool. Let $Q(t)$ be the probability of a detection event before time t that would trigger a filing and subsequent pay-out from RP . It must be the case then that $Q(t) = N(t)/N_0$ provided N_0 is sufficiently large. When the number of policies in the pool is large it can be assumed without loss of accuracy that the premium payments are paid into RP on a continuous basis rather than as discrete payments every year.

The present value (at time zero) of payments to *RP* between times t and $t + \Delta t$ is $B(t)(N_0 - N(t)) Pr \Delta t$. Thus the present value of all payments to *RP* between times zero and T must be $Pr \times N_0 \times \int_0^T B(t)(1 - Q(t)) dt$

The present value (at time zero) of payments made from *RP* to claimants between times t and $t + \Delta t$ (assuming the full policy limit is paid out in each case) is $B(t) \frac{\partial N(t)}{\partial t} \Delta t Pl$. Thus the present value of all payments from *RP* to claimants between times zero and T is $Pl \times N_0 \times \int_0^T B(t) \frac{\partial Q(t)}{\partial t} dt$.

Notwithstanding insurers commission, market competition between providers would force payments made from risk pools to come into line with payments made to them; payments in excess of pay-outs would be a source of risk free profit for the provider in question and would provoke competitors to offer cheaper rates for customers exposed to similar kinds of risks, forcing the original provider to lower its rates or risk losing business. Likewise, pay-outs in excess of payments into a risk pool would force providers to raise their premiums to stem the obvious losses. It must therefore be the case that

$$\begin{aligned} Pl \times N_0 \times \int_0^T B(t) \frac{\partial Q(t)}{\partial t} dt \\ \cong Pr \times N_0 \times \int_0^T B(t)(1 - Q(t)) dt \quad Eq (8.8.0) \end{aligned}$$

or equivalently,

$$Pr \cong \frac{Pl \times \int_0^T B(t) \frac{\partial Q(t)}{\partial t} dt}{\int_0^T B(t)(1 - Q(t)) dt} \quad Eq (8.8.1)$$

Since Eq (8.8.1) does not allow for a source of profit for the provider, it is necessary to amend it to account for the provider's commission necessary for covering operating costs and lodging a profit if it is a non-mutual insurer etc. Assuming the commission rate, CR , is based on a percentage of the

base premium required to cover the cost of pay-outs, Eq (8.8.1) is thus modified to read

$$Pr \cong \frac{Pl \times \int_0^T B(t) \frac{\partial Q(t)}{\partial t} dt}{\int_0^T B(t)(1 - Q(t)) dt} \left(1 + \frac{CR}{100}\right) \text{ Eq (8.8.2)}$$

8.9 The Diminishing Returns on Loss Mitigation Investment

Let $\Delta C(C, \Delta p)$ be the reduction in losses as a result of the additional investment Δp in loss mitigating strategies. If C is already zero to begin with then ΔC should likewise be zero since there is no loss to reduce regardless of how much of an additional investment Δp is made. Similarly, if no investment is made to reduce losses then ΔC should likewise be zero. These observations represent boundary values that constrain the form $\Delta C(C, \Delta p)$ since $\Delta C(0, \Delta p) = \Delta C(C, 0) = 0$. Taylor expanding $\Delta C(C, \Delta p)$ about $C = \Delta p = 0$ subject to these boundary conditions leads to

$$\begin{aligned} \Delta C & \\ &= -aC\Delta p \\ &+ (\text{higher order products of powers of } C \text{ and } \Delta p) \text{ Eq(8.9.1)} \end{aligned}$$

in which the constant a given by

$$a = - \frac{\partial^2 \Delta C}{\partial C \partial \Delta p} \Big|_{C=\Delta p=0}$$

If it is further assumed that the fractional reduction in losses should be only dependent on the level of loss mitigation investment and not on the initial loss levels, then further simplifications can be made to Eq (8.9.1) such that

$$\frac{\Delta C}{C} = -a\Delta p + (\text{higher order powers of } \Delta p \text{ only}) \text{ Eq(8.9.2)}$$

Although exceptions exist, there are still many examples where it can be argued this assumption is approximately true. For instance, an investment in a smoke alarm should reduce the probability of home loss from fire by an

amount independent of the home's value; insuring the oil level in a car's engine is maintained would tend to extend its life by a particular margin independent of its initial value; arguably, fixed investments in flood barriers at the mouths of rivers are independent, within limits, of the value of the upstream infrastructure and associated population densities and sizes.

Dividing Eq (8.9.2) through by Δp and taking the limit $\Delta p \rightarrow dp \rightarrow 0$ leads to

$$\frac{1}{C} \frac{dC}{dp} = -a \quad Eq(8.9.3)$$

This has the solution

$$C(p) = C_0 e^{-ap} \quad Eq(8.9.4)$$

The economic gains $G_r(p)$ from loss mitigation investment expressed as a percentage of the original losses C_0 caused by an absence of mitigation efforts is then prescribed by

$$G_r(p) = \left(\frac{C_0 - C(p) - p}{C_0} \right) \times 100 = \left(1 - e^{-ap} - \frac{p}{C_0} \right) \times 100 \quad Eq(8.9.5)$$

Defining the finite risk control measure R_c as

$$R_c = \left(1 - e^{-\frac{p}{C_0}} \right) \times 100 \quad Eq(8.9.6)$$

such that $0 \leq R_c < 100$

and expressing G_r in Eq (8.9.5) in terms of R_c yields

$$G_r(R_c) = \left(1 - \left(1 - \frac{R_c}{100} \right)^{aC_0} + \ln \left(1 - \frac{R_c}{100} \right) \right) \times 100 \quad Eq(8.9.6)$$

The graph of $G_r(R_c)$ in the range $0 \leq R_c < 100$ has the general form depicted in Figure 3.c

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