

22 Nanotechnology — early lessons from early warnings

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Nanotechnology is the latest in a long series of technologies heralded as ushering in a new era of technology-driven prosperity. Current and future applications of nanotechnology are expected to lead to substantial societal and environmental benefits, increasing economic development and employment, generating better materials at lower environmental costs, and offering new ways to diagnose and treat medical conditions. Nevertheless, as new materials based on nanoscale engineering move from the lab to the marketplace, have we learnt the lessons of past 'wonder technologies' or are we destined to repeat past mistakes?

This chapter first introduces nanotechnology, clarifies the terminology of nanomaterials and describes current uses of these unique materials. Some of the early warning signs of possible adverse impacts of some nanomaterials are summarised, along with regulatory responses of some governments. Inspired by the EEA's first volume of *Late lessons from early warnings*, the chapter looks critically at what lessons can already be learned, notwithstanding nanotechnology's immaturity ⁽¹⁾.

Nanotechnology development has occurred in the absence of clear design rules for chemists and materials developers on how to integrate health, safety and environmental concerns into design. The emerging area of 'green nanotechnology' offers promise for the future with its focus on preventive design. To gain traction, however, it is important that research on the sustainability of materials is funded at levels significant enough to identify early warnings, and that regulatory systems provide incentives for safer and sustainable materials.

Political decision-makers have yet to address many of the shortcomings in legislation, research and development, and limitations in risk assessment, management and governance of nanotechnologies and other emerging technologies. As a result, there remains a developmental environment that hinders the adoption of precautionary yet socially and economically responsive strategies in the field of nanotechnology. If left unresolved, this could hamper society's ability to ensure responsible development of nanotechnologies.

⁽¹⁾ This chapter is based on and in parts identical to Hansen, S.F., Maynard, A., Baun, A., Tickner, J.A. 2008. 'Late lessons from early warnings for nanotechnology', *Nature Nanotechnology*, (3/8) 444–447.

22.1 What is nanotechnology and what are nanomaterials?

Nanotechnology is often described as having roots in a wide range of scientific and technical fields, including physics, chemistry, biology, material science and electronics. The field of nanotechnology is thus broad and covers a multitude of materials, techniques, scientific and commercial applications and products (RS and RAE, 2004). Originally the term nanotechnology, first used by Taniguchi in 1974, referred to the ability to engineer materials precisely at the nanometre (nm) level (Taniguchi, 1974). The term has since been framed and reframed by various actors over the decades and, despite the desire for a unifying all embracing definition of nanotechnology, many versions of the definition exist today. Here, we use the widely-accepted definition suggested by the United States National Nanotechnology Initiative (NNI):

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale (NNI, 2009).

Chemistry typically deals with large numbers of atoms and molecules acting together. The behaviour of individual atoms and molecules can best be understood within a quantum physics-based framework, while the motion of massive collections of atoms and molecules such as physical objects under the influence of force are best described through classical mechanics or Newtonian physics. Nanotechnology falls between these two domains and holds the possibility of revealing and exploiting unique novel phenomena as a result.

Although the wordings differ, a number of definitions require that two criteria must be fulfilled for materials to be considered as engineered nanomaterials ⁽²⁾:

- they must have some purposely engineered structure with at least one dimension in the approximate range 1–100 nm;
- this nanostructure must give the system properties that differ from those of the bulk forms of the same material.

Although the definition is broad, in most materials or systems it can be determined whether they involve nanomaterials or not (Hansen et al., 2007).

The range of nanomaterials that can be manufactured is extremely broad. However the techniques used to produce them can, roughly speaking, be divided into top-down and bottom-up approaches. Top-down techniques involve starting from a larger unit of material, and etching or milling it down to smaller units of desired shape, whereas bottom-up involves progressing from smaller sub-units (e.g. atoms or molecules) to make larger and functionally richer structures (RS and RAE, 2004; BSI, 2007b). Top-down techniques include processes such as high-energy ball milling, etching, sonication and laser ablation, whereas bottom-up techniques include sol-gel, chemical vapour deposition, plasma or flame spraying, supercritical fluid, spinning and self-assembly (Biswas and Wu, 2005). Both approaches pose specific challenges. Creating smaller and smaller structures with sufficient accuracy is a critical challenge for top-down manufacturing, whereas the challenge for bottom-up techniques is to make structures large enough and of sufficient quality (RS and RAE, 2004).

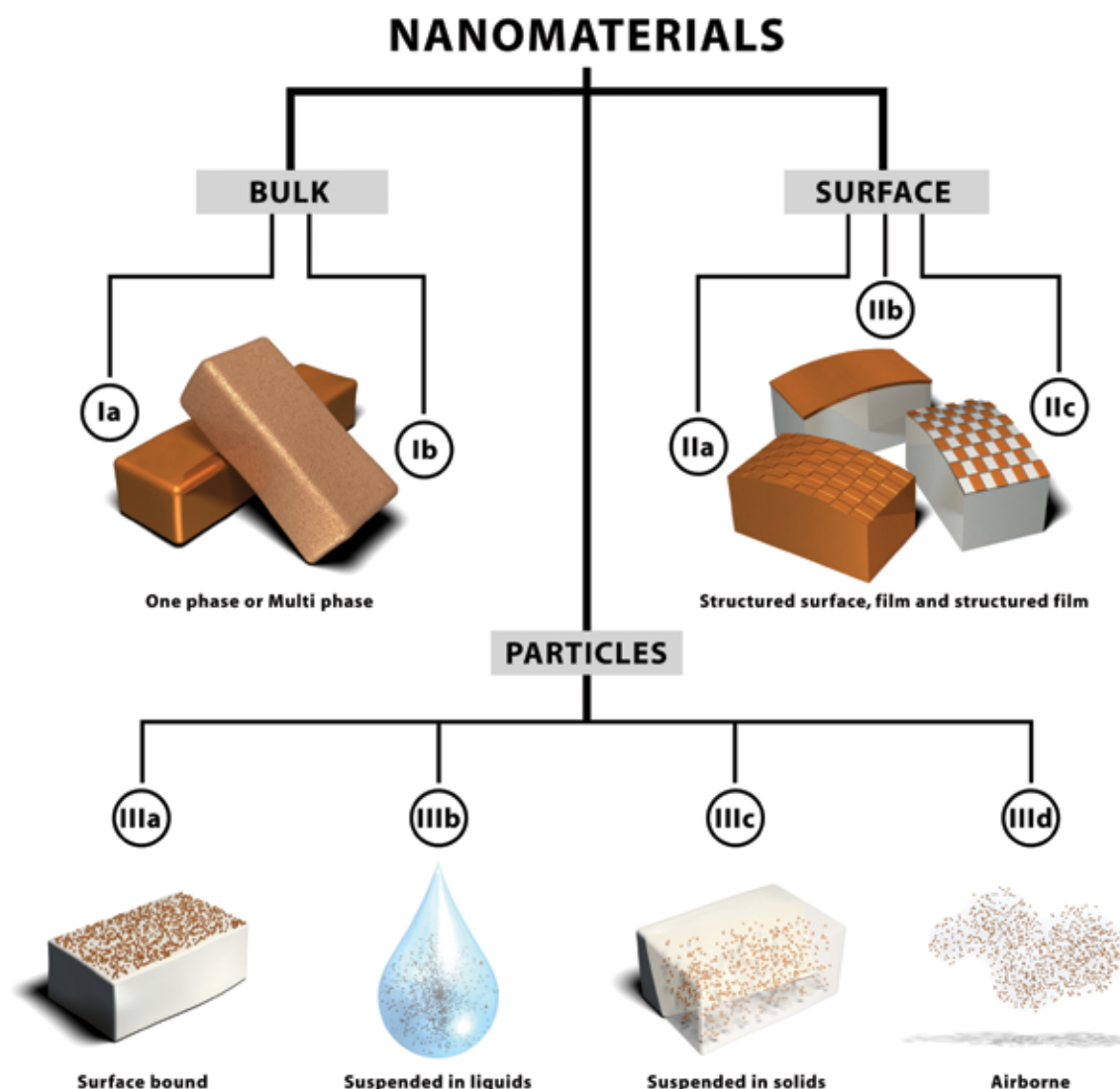
Starting with a palette of conventional materials, new nanomaterials may be formed by subtly altering the shape, size and form of these materials at the nanoscale. A further range of nanomaterials with new properties may be developed by combining two or more nanoscale materials. Familiar chemicals may also be used to construct new nanometre-scale molecules and structures, such as carbon-60 and carbon-70 molecules (C60 and C70), carbon nanotubes, nanoscale liposomes, self-assemble monolayers, dendrimers and aerogels. Various international standardisation institutes have expanded their focus of attention from trying to define nanotechnology to defining the nature of the many different kinds of nanomaterials such as carbon nanostructures, nanorods and nano-objects (BSI, 2007; ISO, 2008).

In order to facilitate hazard identification and focus risk assessment, a procedure for dividing nanomaterials into relevant subcategories has been developed by Hansen et al. (2007), as illustrated by Figure 22.1.

Hansen et al. (2007) suggest categorisation of nanomaterials depending on the location of the

⁽²⁾ Nanomaterials in this context specifically refer to materials that have been purposely engineered to have nanoscale structure.

Figure 22.1 The categorisation framework for nanomaterials. The nanomaterials are categorised according to the location of the nanostructure in the material



Source: Hansen et al., 2007, reprinted with permission.

nanoscale structure in the system. This leads to a division of nanomaterials into three main categories:

- materials that are nanostructured in the bulk;
- materials that have nanostructure on the surface;
- materials that contain nanostructured particles.

Nanoparticles have been defined by the ISO (2008) as particles having three external dimensions

between 1 and 100 nanometre ⁽³⁾. Category III above contains nanostructured nanoparticles that can have various forms and shapes and this category includes, for example, quantum dots, fullerenes, nanotubes and nanowires (Maynard and Aitken, 2007). There are four subcategories of systems with nanoparticles, depending on the environment around the nanoparticles:

- subcategory IIIa has nanoparticles bound to the surface of another solid structure;

⁽³⁾ It is important to note that this is not a universally accepted definition and that, as with the term nanotechnology, a number of different definitions as to what constitutes a nanomaterial exists. The articulation by the European Commission of their recommendation for a definition is discussed in detail in Section 22.5 of this chapter.

- subcategory IIIb consists of systems where nanoparticles are suspended in a liquid;
- subcategory IIIc is nanoparticles suspended in solids;
- subcategory IIId consists of airborne nanoparticles.

Most health and environmental impact concerns have been raised over nanoparticles that fall into subcategories IIIc and IIId (see, for example, SCENIHR, 2009; RCEP, 2008; Madl and Pinkerton, 2009). A major benefit of the proposed categorisation framework is that it provides a tool for dividing nanosystems into identifiable parts, thereby facilitating evaluations of, for example, relevant exposure routes or analysis of effect studies according to relevance to the material tested.

22.2 Development of nanotechnology and nanomaterials

The development of nanotechnology has been rapid when assessed by a number of metrics, including government funding and number of research publications and industrial patents (see, for example, Chen and Roco, 2009; Youtie et al., 2008; Sylvester and Bowman, 2011). Early nanotechnology development was driven by advances in materials science and scientific breakthroughs such as the discovery of fullerenes, quantum dots and carbon nanotubes (Iijima, 1991) along with innovations that allowed nanostructures to be visualised, such as the invention of the scanning tunnelling microscope and the atomic force microscope (Kroto et al., 1986; Iijima, 1991; Binning et al., 1982 and 1986).

One of the key turning points in science and technology policy in relation to nanotechnology was the establishment of the National Nanotechnology Initiative (NNI) by the United States of America (USA) Government in 2000, along with significant increases in research and development (R&D) funding for nanotechnology-related research (Igami and Okazaki, 2007). Since then, most developed and many emerging economies have launched national initiatives or prioritise research in nanotechnology (Roco, 2011). Although somewhat speculative in nature, Lux Research (2008) estimated that in 2008 alone global nanotechnology R&D investment was around USD 18.2 billion, representing USD 8.4 billion from governments, USD 8.6 billion from corporate sources and USD 1.2 billion from venture capital investors. Government funding of academic research has led to a significant increase in the number of

scientific research publications in nanotechnology (Linkov et al., 2009). Scientific activities sparked by government funding have had a crucial role in nanotechnology-related knowledge creation and technology transfer, although there is often some time lag before scientific knowledge is diffused into useful inventions and applications (Igami and Okazaki, 2007).

22.3 Current production and application of nanotechnology and nanomaterials

According to the Nanotechnology Company Database, there are now about 2 000 nanotechnology-focused companies around the world; the majority of these are based in the US (estimates suggest 1 100), and 670 have their headquarters within the European Union (Nanowerk, 2010). These companies range from multinationals to small and medium-size companies and university spin-offs. They span a wide range of sectors and applications including energy, analysis, textiles, anti-microbial wound dressings, paints and coatings, fuel catalysts and additives, lubricants, cosmetics and food packaging (Chaundry et al., 2006; Hodge et al., 2010).

Till now, the emerging nature of the technology has ensured that much of the public and private sector attention has been on R&D activities. However, one could argue that nanotechnology is entering in a new era in which both the number of products containing nanomaterials and the sophistication of these nanomaterials have increased spectacularly. Mundane products will soon, it would appear, be superseded by a range of innovative nanotechnology-based products.

In 2006, the Project for Emerging Nanotechnologies (PEN) at the Woodrow Wilson International Center for Scholars launched an online inventory of consumer products that are reported to include nanomaterials (the Consumer Products Inventory). At the time of its launch in March 2006, the global inventory contained 212 different products available for purchase. This number increased to 580 products in 2007, and in March 2011 the inventory contained 1 317 products from about 30 countries (PEN, 2011). These products fall into a number of different categories including health and fitness, home and garden, and electronics and computers. More than half (738) were considered to be health and fitness-related and included products as diverse as hair straighteners, sporting equipment and cosmetics. The primary material in many of the products was nanoscale silver (PEN, 2011). The

Woodrow Wilson Consumer Products Inventory contains information such as product name, company, manufacturer or supplier, country of origin, and a short product description. However, it does not contain information about how many units of a given product are produced and sold or the mass/volume of nanomaterial in each product. Such information is only available if the producers themselves make it available, which occurs rarely. It is therefore not surprising that the public, and even the relevant regulators themselves, have limited knowledge about the current production volumes of nanomaterials. Moreover, the veracity of the available information must be considered, given its scattered and incomplete nature.

Publicly available information on commercially produced engineered nanomaterials is at best patchy. For example, in 2001, the global production of carbon-based nanomaterials was estimated to be around several hundred tonnes per year; by 2003 global production of nanotubes alone was estimated to be about 900 tonnes (Kleiner and Hogan, 2003). Frontier Carbon Corp, a Japanese-based company, produces more than 40 tonnes of C60 per annum, mainly for use in a range of goods including sporting goods, batteries, lubricants and polymer additives (Fujitani et al., 2008). The consulting firm Cientifica (2006) has estimated that in 2006 the global annual production of nanotubes and fibres was 65 tonnes, giving it a commercial value of about EUR 144 million. Cientifica (2006) has suggested that the value of nanotubes and fibres will exceed EUR 3 billion by 2010, representing an annual growth rate of well over 60 %. The veracity of these claims is still to be tested. Even though information about the production of carbon-based nanomaterials is scarce, more is known, or at least guessed at, about such materials than about many other nanomaterials such as quantum dots, nano-metals and materials with nanostructured surfaces.

22.4 Signs of early warnings

Concerns have been raised about the potential risks of nanotechnology and nanomaterials almost since the emergence of nanotechnology (Drexler, 1986), and historical analogies have been made with both ambient ultrafine particles and asbestos (RS and RAE, 2004; Seaton et al., 2009; Mullins, 2010). Ambient ultrafine particles, which can come from multiple sources, are defined as airborne nanoscale particles, including particles incidentally produced such as those in diesel exhaust and incinerator stacks. Ultrafine particles are typically considered to be smaller than 0.1 micron (i.e. < 100 nm). Research

on ultrafine particles has found an increased morbidity and mortality from cardiovascular and pulmonary diseases inversely correlated with size i.e. the smaller the particles, the more dangerous (Oberdorster et al., 2005a; Pope and Dockery, 2006). Since nanomaterials are in the same size range as ultrafine particles, concerns have been raised on whether nanomaterials could have the same hazardous properties as ultrafine particles.

Much of the research performed on ultrafine particles in the 1990s now feeds into what we know about the potential risk of nanomaterials and lays the foundation for many of the current scientific research hypotheses in the field of nano(ecotoxicology) (Oberdorster et al., 2007). One of the most important hypotheses is that the hazard properties of nanoparticles might be related to inherent physico-chemical properties different from those traditionally used for industrial chemicals, e.g. particle size, shape, crystal structure, surface area, surface chemistry and surface charge. As early as 1990 Oberdorster et al. (1990) and Ferin et al (1990) reported that ultrafine titanium dioxide (TiO₂) and aluminium oxide (Al₂O₃) of 30 and 20 nm, respectively, induced a very striking inflammatory reaction in the lung of rats compared to larger particles of 250 and 500 nm. Two years later Oberdorster et al. (1992) reported that the crystallinity of TiO₂ nanoparticles influenced their toxicity and that surface area was a better descriptor than mass for the adverse effects observed in rats. Donaldson et al. (2002) have since observed a similar correlation for carbon black, when studying the ability of nano and micron particles to cause inflammatory effects in rats. Warheit et al. (2006) and Sayes et al. (2007), however, did not observe any correlation with surface area when evaluating biological response in rats after exposure to nano-sized TiO₂, SiO₂ and other particles.

One study has found a statistically significant increase in malignant lung tumours in rats following chronic inhalation of nano-sized TiO₂ (Heinrich et al., 1995) and, on the basis of this study, NIOSH (2011) has determined that ultrafine TiO₂ should be considered a potential occupational carcinogen. NIOSH further concluded that TiO₂ is not a direct-acting carcinogen, but acts through a secondary genotoxicity mechanism that is not specific to TiO₂ but primarily related to particle size and surface area and surface area was found to be the critical metric for occupational inhalation exposure to TiO₂.

Visual similarities between carbon nanotubes (CNTs) and asbestos fibres have led to others raising

concerns about them having the same hazardous properties (Huczko et al., 2001; Warheit, 2009). In 2004 Lam et al. (2004) published a study in which they exposed mice to a number of single-walled CNTs of different purity and found that all nanotubes induced dose-dependent granulomas and interstitial inflammation in the lungs. The results presented by Lam and co-workers were supported by observations by Warheit et al. (2004) who also observed pulmonary granulomas in rats after exposure to single-walled CNT soot. However, in contrast to Lam et al., the effects observed by Warheit et al. (2004) were not dose-dependent. Absence of pulmonary biomarkers suggests a potentially new mechanism of pulmonary toxicity and induced injury (Warheit et al., 2004). More recently, Poland et al. (2008) compared the toxicity of four kinds of multi-walled carbon nanotubes (MWCNTs) of various diameters, lengths, shape and chemical composition by exposing the mesothelial lining of the body cavity of three mice to 50 mg MWCNT for 24 hours or 7 days. This method was used as a surrogate for the mesothelial lining of the chest cavity. They found that long MWCNTs produced length dependent inflammation, foreign body giant cells and granulomas that were qualitatively and quantitatively similar to the foreign body inflammatory response caused by long asbestos. Only the long MWCNTs caused significant increase in polymorphonuclear leukocytes or protein exudation. The short MWCNTs failed to cause any significant inflammation at 1 day or giant cell formation at 7 days. The finding that the length of CNTs affects their biological activity is supported by findings by Takagi et al. (2008) and Muller et al. (2009). Poland et al. (2008) also found that water-soluble components of MWCNTs did not produce significant inflammatory effects 24 hours after injection, which rules out the concern that residue metals were the cause of the observed effects, an association that other researchers had previously hypothesised on the basis of *in vitro* studies (Shvedova et al., 2005; Kagan et al., 2006).

Most studies of CNTs have used intra-tracheal or intra-peritoneal administration. Intra-tracheal and intra-peritoneal instillation bypasses upper respiratory tract defences and does not deposit particles evenly in the lung in a manner similar to inhalation. This has historically led to the biological relevance of such studies being questioned (Oiser et al., 1997). Recently, however, a number of nose-only inhalation studies on CNTs have been published in peer-reviewed journals by industry (BASF, Nanocyl and Bayer) that support previous findings such as Ellinger-Ziegelbauer and Pauluhn (2009), Ma-Hock et al.

(2009) and Pauluhn (2010). For example, in a 90-day nose-only inhalation toxicity study of MWCNTs, Ma-Hock et al. (2009) found that the incidence and severity of granulomatous inflammation of the lung and the lung-draining lymph nodes were concentration-dependent, something which has previously been demonstrated for intra-tracheally instilled single-walled carbon nanotubes (SWCNTs) (Lam et al., 2004) and MWCNTs (Muller et al., 2005). Interestingly, exposure via inhalation revealed inflammation in the nasal cavity, larynx and trachea, where the particles are deposited during inhalation, as well as alveolar lipoproteinosis. This had not been observed using intra-tracheal or intra-peritoneal administration (Ma-Hock et al., 2009).

In addition to CNTs, substantial concerns have been raised over the use of nanometre-scale silver particles, or nanosilver, especially in regard to its widespread prevalence in everyday consumer products. Nanosilver is reportedly one of the most widely used nanomaterials in consumer products today (PEN, 2011), and the antibacterial properties of nanosilver have been exploited in a very diverse set of products and applications. These include dietary supplements, personal-care products, powdered colours, varnish, textile, paper, interior and exterior paints, printing colours, water and air purification, polymer-based products and foils for antibacterial protection such as washing machines, kitchenware and food storage (PEN, 2011). The scale of use is currently unknown as there are no labelling requirements for nanoproducts, and the concentrations used are also unknown for most of the products on the market (Boxall et al., 2008).

Many applications involving nanosilver involve direct exposure of the substance to humans. This has raised concern about the potential human health effect of the material. The potential health and environmental impacts of nanosilver have been subject to many reviews (Luoma, 2008; Aitken et al., 2009; Wijnhoven et al., 2009; Pronk et al., 2009; Stone et al., 2010; Christensen et al., 2010; Mikkelsen et al., 2011). The toxicity of silver metal is generally considered to be relatively low (Wijnhoven et al., 2009). At very high concentrations, repeated ingestion or inhalation of colloidal silver has been found to lead to deposition of silver metal/silver sulphide particles in the skin, eye and other organs, leading to blue or bluish-grey discolouration of the skin. Although cosmetically undesirable and irreversible, the condition — known as argyria — is not life threatening. It has been shown that silver from nanoparticles can enter the body via oral and inhalation routes and that silver is absorbed and distributed to target organs such as the liver, olfactory bulb, lungs, skin, brain, kidneys

and testes (Sung et al., 2008 and 2009; Kim et al., 2008). The form in which the silver is transmitted through and accumulated within the body is however unclear, i.e. whether it is present as particles, ions or complexes (Mikkelsen et al., 2011). Nanosilver has been associated with inflammation as well as slight liver damage in mice after oral exposure (Cha et al., 2008; Kim et al., 2008). Prolonged exposure to nanosilver particles via inhalation has been found to produce an inflammatory response in the lungs of rats, as well as inducing alterations in lung function (Sung et al., 2008).

A number of *in vitro* studies have found that the toxicity of nanosilver is mediated by an increase in the production of reactive oxygen species, stimulating inflammation and subsequent cell death. The relevance of this is unclear and subject to scientific investigation (Stone et al., 2010; Christensen et al., 2010; Mikkelsen et al., 2011). In an extensive review of risk assessments of nanosilver, Wijnhoven et al. (2009) concluded that the number of well-controlled studies on the potential toxicities of nanosilver as well as current knowledge of the kinetics of nanosilver is too limited to provide a proper foundation for human risk assessment.

With regard to environmental organisms, concerns have been raised by the expected increased emissions and toxicity of nanoscale materials compared to bulk forms of the same material. In this respect, silver nanoparticles may serve as an example since the substance is being used in an increasing number of consumer products because of its antibacterial properties. Silver is known to be ecotoxic. However the toxicity is highly dependent on the form and speciation of the metal. In the registration of silver under REACH (Registration, Evaluation and Authorisation of Chemicals) (Regulation (EC) No 1907/2006), predicted no-effect concentrations (PNECs) are reported as 0.04 µg/L (micrograms per litre) (freshwater), 0.86 mg/L (marine water) and 0.025 mg/L (sewage treatment plants) (ECHA, 2011). Toxicity tests using silver nanoparticles also reveal very-low-effect concentrations. For freshwater algae EC50-values as low as 4 µg/L have been found, and values far below 1 mg/L have been reported for crustaceans (Navarro et al., 2008; Griffitt et al., 2008). EC50 is the maximum concentration that induces a response halfway. Inhibition of nitrifying bacteria can occur at concentrations below 1 mg/L (Hu, 2010) and the function of wastewater treatment plants may therefore be affected by the presence of silver nanoparticles. For ionic silver it is known that the speciation in aqueous media determines bioavailability and toxicity. This is likely also to

be the case for elemental silver nanoparticles, but the influence of speciation on uptake, depuration and toxicity has yet to be studied in depth. The environmental concentrations resulting from the use of nanosilver in consumer products are at present uncertain, although a number of different estimates have been made (e.g. Mueller and Nowack, 2008; Gottschalk et al., 2010). Where silver nanoparticles are incorporated in textiles, they can be released during washing (Benn et al., 2010). Resulting environmental concentrations in the low ng/L range have been proposed by Gottschalk et al. (2010). It remains uncertain whether silver nanoparticles are more toxic than their bulk counterpart or ionic silver, since the effects can in many cases be ascribed to the ionic form of silver (Ag⁺). Some studies have documented a more pronounced effect associated with nanosilver (e.g. Navarro et al., 2008), but the data so far are not conclusive.

After reviewing the current level of scientific knowledge of nanosilver, Aitken et al. (2009) stated that there is:

...indicative evidence of the harm of silver nanoparticles at low concentrations on aquatic invertebrates, which suggests that the environmental release of silver nanoparticles will be detrimental for the environment and that any industry/institute using silver nanoparticles should consider taking the necessary steps to reduce or eliminate the potential exposure of the environment to these nanoparticles.

The authors further stated that there is insufficient evidence to make a risk assessment feasible for nanosilver. They did however go on to state ... there is sufficient evidence to suggest that silver nanoparticles may be harmful to the environment and therefore the use of the precautionary principle should be considered in this case (Aitken et al., 2009).

Although preliminary, these studies on the nanoforms of TiO₂ and silver as well as carbon nanotubes are indicative of wider concerns that materials intentionally designed and engineered at the nanoscale to exhibit novel properties may also pose emergent risks. They therefore arguably trigger indicators of early warnings regarding the potential impacts of engineered nanomaterials, and as a consequence have led to increased attention and funding on various aspects of nanotechnological health and environmental risks (Hankin et al., 2011; Aitken et al., 2011; National Academy of Sciences, 2012).

22.5 Current (lack of nano-specific) regulation for nanomaterials

Whereas there has been some government funding of environmental, health and safety research into the potential adverse effect of nanotechnology and nanomaterials, there has been limited action from regulatory decision-makers towards changing existing technology-neutral regulation to take the unique properties of these materials into account. This is not surprising given the current state of scientific understanding of nanomaterial hazards and risks. Nor is this lag in regulatory response unique to nanotechnologies. As observed by Ludlow et al. (2009), the emergence of a new technology is, for example, likely to be perceived as a period of under-regulation in which the development of a specific regulatory response will occur subsequent to an initial period of research and development (R&D) and commercialisation. It must also be remembered that the regulatory frameworks under which nanomaterials currently fall are in any case not perfect, with many current regimes outdated and needing to be overhauled. Such recasts were needed prior to the commercialisation of nanotechnology and in many respects nanomaterials highlight many of the deficiencies that have existed for some time.

In an effort to elicit information regarding the types of nanomaterials being produced and imported into their jurisdictions, some governments, for example in the United Kingdom, USA and Australia, have implemented voluntary reporting schemes for nanomaterials (see, for example, DEFRA, 2006a and 2006b; US EPA, 2007; Weiss, 2005; NICNAS, 2008). Voluntary in nature, and somewhat onerous in operation, the schemes can be described as at best underwhelming. In the United Kingdom, for example, the Department for Environment, Food and Rural Affairs (DEFRA) received a total of 13 submissions over the life of the programme (2 years). The US scheme, which ended in 2009, fared a little better with the Environmental Protection Agency (EPA) receiving submissions from a total of 31 organisations (DEFRA, 2008; Hansen, 2009; Maynard and Rejeski, 2009). Given the lack of buy-in from stakeholders, it is not surprising that other jurisdictions, including France and California, have focused their efforts on mandatory nanomaterial reporting schemes.

Nanomaterials which are defined as chemical substances are regulated by the EPA under the Toxic Substances Control Act (TSCA) (US EPA, 2009a; Breggin et al., 2009). Pursuant to the TSCA, chemical substances are typically regulated on the basis of their Chemical Abstract Service (CAS) number;

this system differentiates chemicals on the basis of their novel molecular structure and not their size. Silver, for example, is an existing chemical under the TSCA with its own unique CAS number. The TSCA Inventory is not able to differentiate nanosilver from bulk silver under the current framework, as the nanoscale and bulk versions of the substances both have the same CAS number. This approach ignores evidence that size and shape often lead to nanomaterials behaving in substantially different ways from their bulk counterparts. In the case of nano-silver, this failure to trigger regulatory oversight for the nanoscale substance has already raised considerable debate among various stakeholders, including those within the scientific community, due to its increasingly widespread use in consumer products (see, for example, Chen and Schluesener, 2008; Wijnhoven et al., 2009).

It is important, however, to note that the approach adopted under the TSCA is not unique, with chemical substances traditionally regulated on the basis of being existing or new based on their CAS number in most jurisdictions. At this stage, the majority of nanoscale substances are considered to be existing chemical substances under these frameworks.

One approach that the EPA has implemented in order to gather additional data on existing chemicals manufactured at the nanoscale is through the use of its significant new use rule (SNUR). As explained by Widmer and Maili (2010), Section 5(a)(2) of the TSCA provides the EPA with the regulatory authority to request additional information on existing chemicals for the purpose of regulatory review where the proposed use of the chemical has significantly changed since it was initially reviewed. This regulatory tool has so far been employed for several types of nanomaterials, including single-walled and multi-walled CNTs. The EPA has proposed a more encompassing SNUR that would require companies that intend to manufacture, import or process new nanoscale materials based on chemical substances listed on the TSCA Inventory to submit a significant new use notice (SNUN) to the EPA at least 90 days in advance (Matus et al., 2011).

Even if a nanomaterial has a novel molecular structure, the US EPA must show that it may pose an unreasonable risk of significant exposure before manufacturers are required to undertake environmental, health and safety testing. These are just the data the agency needs to determine whether the substance poses an unreasonable risk — a classic regulatory paradox. Nonetheless, the EPA has proposed a data collection rule that would require the submission of certain existing data

on nanomaterials, including production volume, methods of manufacture and processing, exposure and release information, and available health and safety data. Despite these limitations and some recent moves towards reform of the TSCA, actual amendments have yet to be implemented (Davies, 2006 and 2009; US EPA, 2009b; Breggin et al., 2009). A December 2011, EPA Office of the Inspector General report (EPA OIG, 2011) found several limitations in the EPAs evaluation and management of engineered nanomaterials, including:

- Program offices do not have a formal process to coordinate the dissemination and utilisation of the potentially mandated information;
- EPA is not communicating an overall message to external stakeholders regarding policy changes and the risks of nanomaterials;
- EPA proposes to regulate nanomaterials as chemicals and its success in managing nanomaterials will be linked to the existing limitations of those applicable statutes;
- EPAs management of nanomaterials is limited by lack of risk information and reliance on industry-submitted data.

The Office of the Inspector General concluded that:

'these issues present significant barriers to effective nanomaterial management when combined with existing resource challenges. If EPA does not improve its internal processes and develop a clear and consistent stakeholder communication process, the Agency will not be able to assure that it is effectively managing nanomaterial risks.'

The EUs approach towards ensuring adequate protection of human health and the environment also relies heavily on chemical legislation, in particular the REACH Regulation, which was adopted by the Council and Parliament in 2006 and has been implemented progressively within the EU since 2007 (EP and CEU, 2006). As articulated in Article 1 of REACH, the purpose of the scheme is to ensure a high level of protection of human health and the environment. To fulfil this overarching objective, the regulation has expressly incorporated the precautionary principle into its text and sets out a no data, no market requirement under Article 5. Pursuant to this Article, REACH prohibits the manufacture or sale of any substance in the EU that has not been registered with the European Chemical Agency in accordance with the regulation. In this

respect, REACH applies uniformly to existing and new chemicals, thus overcoming some of the difficulties associated with systems analogous to the TSCA.

As with the US system, however, REACH relies on the CAS identification system for the registration of chemical substances. One of the limitations of REACH yet to be addressed is related to whether a nano-equivalent of a substance with different physico-chemical and (eco)toxicological properties from the bulk substance would be considered as the same or different from the bulk substance under REACH. The regulation requires that a registration dossier be submitted to the European Chemical Agency containing information about manufacture and uses, classification and labelling, and guidance for safe use. If a nanomaterial is considered to be different from its bulk equivalent, hazard information has to be generated for this registration dossier if more than 1 tonne/year is produced. On the other hand, if the nanomaterial is considered to be the same as a registered bulk material, the appropriateness of the hazard information data submitted in the registration dossier is open to discussion (Chaundry et al., 2006; Breggin et al., 2009; Milieu and RPA, 2009). To date, the only amendment has been to annul the exemption status of carbon and graphite under REACH (CEC, 2008a; Breggin et al., 2009; Milieu and RPA, 2009).

It has recently been reported that companies have set up two different data-gathering groups on carbon nanotubes — one group of companies considers them as new substances while the other, including global chemical producing companies such as Arkema and Bayer, consider them as bulk graphite (Milmo, 2009). This example shows that whether nanomaterials are to be considered new or not is not just a theoretical question, but a source of confusion among regulated parties. Clearer guidance is expected on the issue from the European Commission as a result of the review of REACH in 2012.

If nanomaterials are considered to be different from their bulk counterpart, and if they are produced or imported in quantities of more than 10 tonnes, companies have to complete a chemical safety assessment. Companies are urged to use existing guidelines, however both the Commission of the European Communities (CEC, 2008a) and SCENIHR (2007) and others have pointed out that current test guidelines that support REACH are based on conventional methodologies for assessing chemical risks and may not be appropriate for assessing risks associated with nanomaterials. This means that,

although manufacturers and importers might be required to provide a chemical safety assessment, they cannot rely on the toxicological profile of the equivalent bulk material and cannot use existing test and risk assessment guidelines since these might not provide any meaningful results or be practically applicable, because of the limitations of conventional methods (Hansen, 2009; Milmo, 2009).

Pursuant to the text of the regulation, REACH is to be reviewed in 2012. It is generally expected that the revisions will include provisions related to nanomaterials. This is not surprising given the last-minute attempts to specifically include nanomaterials in the text of REACH during the second reading speech in 2006 (Bowman and van Calster, 2007). However, how REACH can be modified to expressly regulate nanomaterials — and the extent thereof — is still up for debate among politicians, regulators and stakeholders in the EU.

Expressly differentiating nanomaterials from their bulk equivalents in legislation is not new to the European Parliament and Council, as highlighted by the recent recast of the regulatory regime for cosmetics. While this recast was not initiated in response to the increasing use of nanomaterials in cosmetic products — but rather to increase transparency and streamline human safety requirements — considerable debate centred on the issue of nanomaterials (Bowman et al., 2010).

The Cosmetic Regulation, adopted in 2009, requires that all cosmetics that contain nanomaterials — which are defined as an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm (Article 2(k)) — be labelled. This will be done by placing the word nano in brackets after the nanoscale ingredient (Article 19(1)(g)) and will come into effect in 2012. As observed by Bowman et al. (2010), the regulation does not set a minimum threshold for this labelling requirement, which suggests that the mere presence of any nanoparticles in the cosmetic will be enough to trigger this requirement.

In addition to the labelling requirements, producers will have to provide a safety assessment of the nanomaterial used (European Parliament, 2009). The regulation also requires the European Commission to create a publicly available catalogue of all nanomaterials used in cosmetic products placed on the market ... and the reasonably foreseeable exposure conditions (Article 16(10)(a)). Titanium dioxide, zinc oxide and lipid-based nanocapsules are examples of materials used in cosmetics such

as sunscreens and moisturisers, while it has been reported that fullerenes have been used in a small number of facial creams (PEN, 2011).

Although the recast of the Cosmetic Regulation could be interpreted as a successful political effort to address the potential risk and transparency concerns relating to the use of nanomaterials in such consumer products, recent controversies surrounding the recast of the EU Novel Foods Regulation is evidence of the challenges that lie ahead for implementing future nano-specific revisions to existing legislation such as REACH. In regard to the EU Novel Foods Regulation, the European Parliament and the Council of the European Union recently failed to reach an agreement about changes to the instrument that would have ensured that the regulation includes foods modified by new production processes such as nanotechnology.

In its current form, the EU Novel Foods Regulation requires pre-market approval of all new food ingredients and products as well as safety assessments by European Food Safety Authorities on the composition, nutritional value, metabolism, intended use and level of microbiological and chemical contaminants. Studies on the toxicology, allergenicity and details of the manufacturing process may also be considered. Had the proposed revisions been adopted, such information relating to nanomaterials might have assisted in addressing current concerns surrounding their use in such applications in relation to nanoparticles (CEC, 2008b; Chaudhry et al., 2012).

The failure of the political parties to reach a compromise in regard to the Novel Foods Regulation should act as a warning sign of what to expect in regard to the likely negotiations around revisions to REACH, in which the stakes appear to be significantly higher for many parties. There is, we would argue, the potential for nanomaterials to be overlooked in the 2012 REACH revision discussion, with attention focusing instead on the myriad of other issues in play, including increasing dossier quality, limiting registration bureaucracy and lessening the impact of the regulation on small to medium enterprises.

Many of these issues are so controversial that the EU Commission is trying to downplay expectations for the 2012 REACH revision, arguing that no fundamental overhaul should be expected (EurActiv, 2011). In regard to nanomaterials, such efforts to maintain the status quo are worrying given the rapidly increasing evidence of risks as well as the swift growth of production and commercialisation

of nanomaterials and products. Such political statements are further worrying given the fact that the next formal REACH revision with relevance for nanomaterials is not scheduled before 2019 (EP and CEU, 2006). Substantial time is being wasted and effective regulation of nanomaterials is being pushed even further into the future although it is clear that immediate revisions are needed to address the most obvious and short-term limitations of the current legislative framework.

Against this background of legislative reform and associated debates, a number of other policy-related activities have occurred within the EU that have the potential to impact on the longer-term regulatory approach in relation to nanomaterials. For example, in 2009 the European Parliament's Environment Committee adopted a report on regulation of nanomaterials in general which calls for application of the no data, no market principle (as already incorporated in REACH) until safety assessments can be made (Schylter, 2009). While the fate of the proposal to implement this principle is unclear, it would appear to put additional pressure on the European Commission and the Council to address the potential risks of nanomaterials in the short to medium term.

Of arguably greater significance is the October 2011 recommendation of a definition of the term nanomaterial by the European Commission specifically for legislative, policy and research purposes. As set out in the Official Journal of the European Union (2011), a nanomaterial means:

'... a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.'

This definition differs considerably from the one in the Cosmetic Regulation (as articulated above) and was mooted in relation to the recast of the Novel Foods Regulation. It is therefore not surprising that this recommendation for a definition has not been without considerable controversy and global debate. According to Maynard (2011), the Commissions push for a one

size fits all policy-based definition has the potential to sideline the science and may fail to capture what is important for addressing risk. Others within the scientific community have similarly expressed concern about the fact that the definition fails to take into account the key physico-chemical characteristics associated with potential risks (see, for example, ChemSec, 2011). In response to such criticisms, Hermann Stamm of the European Commission Joint Research Centre Institute for Health and Consumer Protection has contended ...such a definition is urgently needed, especially for particulate nanomaterials. The aim should be to identify a general class of materials for attention — whether they are benign or hazardous (Stamm, 2011). It would seem that both camps have valid points; it is important that the crafting of such a definition does not act as a barrier to the effective regulation of nanomaterials.

The fact that existing legislation may have serious shortcomings when it comes to effectively regulating nanomaterials is not a new revelation. Government and independent reviews of the current regulatory frameworks and their applicability to nanotechnologies have now been published (see, for example, Chaudhry et al., 2006; Ludlow et al., 2007; European Commission, 2008). While the reports have varied in scope, method and the instruments that they have sought to evaluate, each has concluded that nanomaterials are currently captured under the existing regimes. However, the failure of such instruments to differentiate between nano-based products and their conventional counterparts has raised a number of concerns regarding the ongoing effectiveness of these regimes. A number of cross-cutting issues that appear to be common to most jurisdictions have now been examined through these reviews. The main areas of concern include that, as discussed above, the regimes do not differentiate between novel and known substances for the purposes of triggering regulatory oversight; that requirements for regulators to undertake safety evaluations on novel substances are triggered by mass or volume thresholds that are not tailored to the current production volumes of nanoscale materials; the lack of trust in the appropriateness of conventional risk assessment protocols and technical guidelines; and that risk thresholds and exposure limits established with existing methodologies are questionable (Ludlow et al., 2007; Baun et al., 2009).

In most countries, nanomaterials are still being treated within existing regulatory frameworks, under which the nanomaterials have inherited

the scope and features of the previous analogous regime (Stokes and Bowman, 2012). At this stage of development and commercialisation, countries such as the US, Australia, China and India, as well as the Organisation for Economic Co-operation and Development (OECD) and the EU, are proposing to treat nanomaterials primarily in the same manner as their conventional chemical counterparts (CEC, 2008; US EPA, 2007 and 2009b; OECD, 2009a and 2009b). In doing so, they have opted to retain the regulatory status quo despite the growing body of literature that suggests that some nanomaterials may cause harm to human and/or environmental health. This approach is not surprising given the current knowledge deficits in the evolving state of the scientific art and a general lack of express reliance on the precautionary principle in most jurisdictions.

Australia is one country that has explicitly moved to differentiate the requirements for some new industrial nanoscale chemicals. Recent administrative changes to its National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (which may be considered analogous to the TSCA), which came into effect in January 2011, have sought to remove several of the low-volume/low-concentration exemptions that usually apply to new industrial chemicals (NICNAS, 2010). While minor and incremental in nature, such a shift is indicative of how some countries may attempt to tweak their regulatory frameworks in the first instance rather than move towards more wholesale changes.

A number of features related to engineered nanomaterials indicate that the identification of hazards may deviate from what is known about regular chemicals. While our current approach to toxicity-driven risk is based on the paradigm attributed to *Parcelsus*, that it is the dose that makes the poison, and most extrapolations from toxicity tests assume that there is a correlation between mass and toxicity, this may not hold true for engineered nanoparticles (Baun and Hansen, 2008). As pointed out in a number of studies, other properties such as surface area and surface chemistry may be better indicators of the toxicity of some nanoparticles. This raises the question of how to determine the relevant exposure concentrations in laboratory studies and in occupational and environmental settings. In response to this concern, SCENIHR has stated that amendments have to be made to the existing technical guideline for risk assessment of chemicals since: due to the physico-chemical properties of nanoparticles, their behaviour and their potential adverse effects are not solely dependent on exposure in terms of the mass concentration ... (SCENIHR, 2007).

Another issue that makes engineered nanomaterials, especially nanoparticles, different from conventional industrial chemicals is their ability to agglomerate (form clusters of weakly bound particles) or aggregate (form clusters of strongly bound particles) into stable particles. Aggregated particles are generally considered to be less prone to biological uptake, however it is not correct to assume that they are inherently safe. While the aggregation and agglomeration behaviour of engineered nanoparticles is only partly understood, it is known that their formation is concentration-dependent and that smaller aggregates/agglomerates may be formed at lower initial concentrations. If toxicity is inversely associated with aggregation/agglomeration size, our traditional understanding of concentration-response relationships may have to be altered for nanoparticles since higher concentrations may not necessarily result in higher toxicity. Furthermore, it is not known whether larger benign agglomerates may be broken down after inhalation or ingestion, resulting in smaller, and perhaps less benign, agglomerates or single particles. For these reasons the statement that lower exposure equals lower effects should be seriously scrutinised before it can be considered valid for engineered nanoparticles (Baun and Hansen, 2008; Baun et al., 2009).

In environmental hazard identification it is not only the toxicity, but also the degradability and potential for bioaccumulation that are used as parameters to identify chemical compounds that are environmentally hazardous. Very few studies have addressed these two parameters for engineered nanomaterials (Stone et al., 2010; Mikkelsen et al., 2011) and, as described above, serious concerns have been raised about whether the knowledge built up for regular chemicals can be transferred to nanoparticles. This led the SCENIHR (2007) to conclude that: The criteria used for persistence, bioaccumulation and toxicity (PBT) assessment applied for substances in soluble form should be assessed for applicability to nanoparticles.

Finally, in order to take the unique properties of any type of nanoparticles into consideration, it has often been argued that risk assessments of nanoparticles need to be completed on a case-by-case basis (see for example, SCENIHR, 2007 and 2009; Stone et al., 2010). Past experiences with case-by-case risk assessment of regular chemicals indicates that such an approach can be very time- and resource-intensive even with well-defined data demands and hence one has to wonder whether this is the most appropriate approach when it comes to risk assessment of nanoparticles. The

situation for these is further complicated by the fact that the hazard characteristics will be linked not only to the chemical identity but also to a number of other characteristics and their combinations. For example, it has been claimed that there are up to 50 000 potential combinations of single-walled carbon nanotubes (SWCNTs), depending on their structural type, length, surface coating, manufacturing processes and purification method (Schmidt, 2007). Each of these 50 000 SWCNTs may have different chemical, physical and biological properties that determine their overall hazard. Although not all of them are expected to be of commercial relevance, there are many kinds of nanoparticles, such as fullerenes, quantum dots, and metal and metal oxide nanoparticles, which imply a great complexity in performing case-by-case risk assessments for nanoparticles.

22.6 Late lessons from early warnings for nanotechnology

A comparison between the EEA recommendations made in 2001 and the current situation for nanotechnology shows that stakeholders are doing some things right, but we are still in danger of repeating old, and potentially costly, mistakes. In this section we briefly discuss the current development of regulation and environmental, health and safety research in view of the late lessons from early warnings learned by the EEA in 2001.

22.6.1 Lessons 1–3: heed the 'warnings'

According to *Late lessons from early warning* Volume 1. 'No matter how sophisticated knowledge is, it will always be subject to some degree of ignorance (i.e. inevitable surprises, or unpredicted effects). To be alert to — and humble about — the potential gaps in those bodies of knowledge that are included in our decision-making is fundamental' (EEA, 2001).

Perhaps more than any preceding technology, the early development of nanotechnology has been characterised by discussions of potential risks and the need for regulatory reform (Grieger et al., 2009; Fiedler and Reynolds, 1994). Such discussions have always been an integral part of the government-led National Nanotechnology Initiative (NNI) in the US, for example, while in the EU the landmark report published by the Royal Society & Royal Academy of Engineering (RS and RAE) in 2004 emphasised the need to address uncertainties regarding the risks of nanomaterials (RS and RAE, 2004). Levi-Faur and Comhanester (2007) have observed that unlike other

cases where the discussion of the associated risks has followed the development of new technologies, the discussion on the proper regulatory framework for the governance of nanotechnology risks is accompanying the development of the technology and the associated products themselves. While hard government action may still be limited, we have however seen the emergence of a number of nano-specific self-regulatory activities within industry, including codes of conduct, guidance documents and risk assessment/management frameworks (Bowman and Hodge, 2009; Meili and Widmer, 2010). Voluntary in nature, they sit within the shadow of formal regulatory obligations and do not seek to usurp legislative requirements.

Currently, most economies investing in nanotechnology season discussions about future directions in research with questions concerning potential risks and how to manage them. Yet despite some moves (for example, the funding of early investigations into environmental, health and safety risks) to respond to ignorance and uncertainty rather than simply discuss them, coordinated action seems slow to emerge. The EEA report recommends looking out for warning signs such as materials that are novel, bio-persistent, readily dispersed or bioaccumulative, and/or materials that lead to irreversible action (such as mesothelioma caused by the inhalation of asbestiform fibres).

These warning signs are clearly relevant to many nanomaterials, some of which have novel properties, may be capable of being incorporated in highly diverse products, may be transported to places in the human body in new ways, such as across the blood, brain or placental barriers, and may be designed to be persistent. Too little is known at this early stage of the technology's development trajectory to predict the environmental fate of many nanomaterials, and appropriate documentation of environmental dispersion through monitoring is not expected in the short term (SCENIHR, 2007). The extent to which specific nanomaterials are bioaccumulative or lead to irreversible impact is largely unknown, but the current state of knowledge suggests that the potential exists for such behaviour under some circumstances (Moore, 2006; Stone et al., 2011; Mikkelsen et al., 2011) (see Box 22.1 on how EEAs warning signs apply to C60 and CNTs).

The global response to these warning signs may be described, at least in our view, as patchy at best, with governments being slow, and sometimes complacent, regarding the need to gather essential data, for example on production, use patterns and the effectiveness of current types of personal protection

equipment (see Section 22.5 on the current regulation of nanomaterials). Saying this, it is important to acknowledge that efforts to date have been better than those seen in response to the emergence of earlier technologies, but they are still far from ideal.

A number of reports have made specific recommendations on developing responsive research strategies (see for instance Oberdorster et al., 2005b; Maynard et al., 2006; Tsuji et al., 2006; SCENIHR, 2006; National Academy of Sciences, 2012). For example Maynard et al. (2006) called for:

- the development of strategic programmes that enable relevant risk-focused research, within the next 12 months;
- the development of instruments to assess exposure to engineered nanomaterials, within the next 3–10 years;
- the development of robust systems for evaluating the health and environmental impact of engineered nanomaterials over their entire life, within the next 5 years;
- the development and validation of methods to evaluate the toxicity of engineered nanomaterials, within the next 5–15 years;
- the development of models for predicting the potential impact of engineered nanomaterials on the environment and human health, within the next 10 years.

Calls for research proposals in the European seventh framework programme reflect some of these recommendations, and a number of countries are beginning to develop integrated environment, health and safety (EHS) research programmes, such as the cross-agency risk-research strategy published by the NNI (2008). However, there are still critical gaps in our knowledge that need to be addressed in EHS research programmes. These include, but are not limited to, epidemiological investigation of exposed populations; the behaviour and impact of ingested nanomaterials; investigation of the fate, behaviour and (eco)toxicity of nanomaterials throughout the life cycle; and interactions between nanomaterials and environmental matrices such as natural organic matter and sediments and other pollutants already present in the environment (Maynard 2006; Baun et al., 2008; Grieger et al., 2009; National Academy of Sciences, 2012).

Research strategies that target recognised areas of uncertainty (including the applicability of current

testing procedures and equipment, how to assess human and environmental effects, and how to do exposure assessments and characterisation of nanomaterials) should be relatively easy to develop, as the critical questions to be addressed are generally agreed (Maynard et al., 2006; Grieger et al., 2009). But the EEA report highlights the dangers of entirely missing important areas because the right questions have not been identified, leading to blind spots in our understanding. The report cites the widespread use of anti-microbials as growth promoters in food animals, methyl tert-butyl ether (MTBE) and tributyltin as three examples where conventional thinking led to inappropriate assumptions and a lack of recognition of broader issues. At present it is not clear whether the recognition of ignorance in the field of nanomaterial-related EHS risks is sufficient to avoid blind spots, or whether the novel properties of nanomaterials inherently will generate blind spots because of their novelty (see Box 22.1).

22.6.2 *Lessons 4 and 11: reduce obstacles to action*

Even when research throws up useful information, it may be ignored and overlooked through what the EEA authors call institutional ignorance. They cite cases where regulators have made inappropriate appraisals because of the blinkers imposed by their specific disciplines — such as the preoccupation of medical clinicians with acute effects when dealing with radiation and asbestos. There is a real danger of similar errors being made with nanotechnology, which crosses many fields of expertise. One needs to draw on physics, chemistry, computer sciences, health, environmental sciences and law to understand nanomaterial properties and risks (Karn et al., 2003). A number of multidisciplinary centres for nanoscience and nanomanufacturing have been established around the world, but only a few of these address health, environmental and social aspects. It is critical to set aside resources to create an infrastructure that gets people working together across disciplines (Lynch, 2006).

Interdisciplinary obstacles also affect regulatory oversight in decision-making (EEA, 2001). In a discussion on how nanomaterials were covered under the TSCA, the US EPA appeared to be constrained by a world-view rooted in chemistry, stating that the sole factor that determines whether a nanomaterial is legally classified as new depends on whether it has a unique molecular identity (US EPA, 2007). However, it is now clear that characteristics other than molecular identity — such as particle size and shape — can affect exposure and response to engineered nanomaterials (SCENIHR, 2007).

Box 22.1 EEA's warning signs applied to fullerenes and carbon nanotubes

To acknowledge and respond to ignorance, i.e. potential risks that you do not know (EEA, 2001), seems almost impossible when it comes to a rapidly emerging technology such as nanotechnology. In cases of ignorance, the EEA recommends being proactive, alert and humble about the state of the scientific evidence indicating harm as well as looking for warning signs such as novelty, persistence, ready dispersion, bioaccumulation, leading to potentially irreversible action. These lessons bear an uncanny resemblance to many of the concerns now being raised about various forms of nanomaterials such as the two types of nanoparticles: C60-fullerenes and carbon nanotubes (CNTs).

No single exhaustive taxonomy exists for novel materials and, as noted by the Royal Commission on Environmental Pollution (RCEP, 2008), it is unlikely that one is possible or even necessarily desirable. That said, one could argue that nanomaterials are novel by definition in the sense that many of the definitions of nanotechnology require either novel applications, whatever they might be, and/or that nanomaterials exhibit novel properties compared to bulk materials (see for example the definitions cited earlier in the chapter). In the following, C60 and CNT will be used as illustrative examples of nanomaterials that are novel in their use pattern and properties.

At present, very few studies have addressed the degradability of engineered C60 and CNT, but, because of their structure, they are expected to be persistent in the environment. Both C60 and CNT are often seen as anthropogenic, however they may also be formed in forest fires or volcanic eruptions. Although the sources of naturally occurring carbon-containing nanoparticles are different from the engineered ones, the particles are, from a chemical point of view, identical, and geological studies have shown that both C60 and CNT may be very resistant to degradation. Thus, Becker et al. (1994) observed C60 in 1.85 billion year-old shock-produced breccias of the Sudbury impact structure in Ontario, Canada and C60 has also been found in a 70 million-year-old fossil dinosaur eggshell from Xixia, China (Zhenxia et al., 1998). CNT and fullerenes have been extracted from 10 000-year-old ice-core melt samples (Murr et al., 2004).

Whether C60 and CNT are readily dispersed depends on a number of factors such as the environmental compartment considered (e.g. air, water, soil). Little is known about the fate and transport of C60 and CNT in air and soil, but under laboratory conditions hydrophobic nanoparticles such as C60 and CNT have been found to aggregate rapidly (Fortner et al., 2005; Baun et al., 2008). As a result of sedimentation, they may therefore not be readily dispersed after emission to the aquatic environment. However, the dispersivity of nanomaterials can be altered, for example by changing the surface chemistry, and hydroxylated C60, for example, is much more soluble in water (Sayes et al., 2004). What happens in the environment, and how interaction with natural substances (e.g. humic substances) and water-living organisms influence dispersion, are however unclear (Roberts et al., 2007; Hansen et al., 2009).

The potential bioaccumulation of nanomaterials is believed to depend on a combination of the specific properties of the nanomaterial (such as biodegradability, lipophilicity, aqueous solubility) that influence overall bioavailability. For example carbon nanotubes are known to be non-biodegradable, insoluble in water and lipophilic, which indicates that carbon nanotubes have a potential to bioaccumulate. However, there is a profound lack of studies addressing the issue of bioaccumulation of engineered nanomaterials (RCEP, 2008).

Because of the lack of scientific research, it is currently almost impossible to say whether or not the production and use of nanomaterials could lead to potentially irreversible action. Some studies have indicated that some CNTs might be able to cause effects that would be classified as irreversible (e.g. Poland et al., 2009; Smith et al., 2007). Widespread production and use of C60 and CNT will inevitably lead to the release of these materials into the environment, and hence an irreversible action, as they would be practically impossible to locate and recover after release (Hansen et al., 2009).

22.6.3 Lessons 5 and 8: stay in the real world

The EEA panel assertion from 2001 (EEA, 2001) that it is often assumed that technologies will perform to the specified standards. Yet real life practices can be far from ideal echoes claims made of nanotechnology. In 2006, Rick Weiss of the Washington Post visited a

nanomaterial company expecting to see a high-tech work environment. Instead, he found the future looked a lot like the past with men in grease-stained blue coats [...] story-tall spray-drying machines [...] noisy milling operations and workers with face masks covered by a pale dust stemming from emptying buckets of freshly made powders (Weiss, 2006).

It is often assumed that nanotechnology will be conducted with small quantities of material, within sealed processes. Reality can be very different and the past tells us that persistent substances used in closed settings or incorporated in solid matrices (like PCBs) will eventually end up in the environment. Moreover, there is evidence that the R&D community is entrenched in the philosophy that basic research will ultimately solve real-world problems through a one-way process of knowledge diffusion, and that they do not need to worry about EHS issues. A study by Powell (2007) found that many scientists who are developing new nanotechnologies do not think that nanotechnologies pose new or substantial risks and that concerns about risks are based on invalid science (Powell 2007). This is a mistake in our view, and there is plenty of historical evidence to support this view in the first EEA report *Late lessons from early warnings* (EEA, 2001), including the sorry tale of asbestos. Clearly, applied researchers and the EHS community need to be involved in informing policy decisions. According to the EEA, this includes making use of the information that workers and users can bring to the regulatory appraisal process, although such knowledge of course needs as much critical appraisal as specialist knowledge.

Nanotechnology is complex, and it can be argued that non-experts have little to contribute to its safe development and use currently. But non-specialists intimately involved with a technology can bring unique insight to the table since they may have some of the clearest ideas about what is important, what has the potential to work and what may not (Gavelin et al., 2007).

22.6.4 Lessons 6 and 9: consider wider issues

Concerns have often been raised that speculation on risks overshadows real benefits, or that an unbalanced promotion of possible benefits will prevent potential risks from being critically scrutinised.

Nanotechnology is in such a position (Maynard et al., 2011). Pros include economic benefits, improved materials, reduced use of resources and new medical treatments (RS and RAE, 2004; Roco and Bainbridge, 2005), while cons mainly revolve around worker health, consumer exposure and environmental impacts. Comparisons have also been made between ultrafine particles in the atmosphere — which are known to cause health problems — and specific types of nanoparticles (RS and RAE, 2004, Oberdorster et al., 2005b; Maynard et al., 2006).

It is generally difficult to evaluate whether proclaimed pros and cons are valid both in the short and the long term. However, the process of determining more likely scenarios is vital to the future development of sustainable nanotechnologies. As we emerge from the first flush of nano-enthusiasm and begin the hard work of translating good ideas into viable products, this is a lesson that is more relevant than ever if an appropriate balance between benefits and risks is to be struck (Maynard et al., 2011).

If proclaimed pros do not materialise in the foreseeable future despite heavy public investments, or if projected cons are not investigated, but later prove to be significant, decision-making processes will be undermined, and public trust may be compromised.

A key feature of the public reaction to the emerging evidence for bovine spongiform encephalopathy (BSE) in the late 1980s was the surprised revulsion that cows and other ruminants were being fed on offal and bodily wastes. The EEA panel in 2001 speculates that accounting for wider social values at an earlier stage might have limited the scale of BSE problems. The extent to which societal interests and values can prevent real risks with emerging technologies is debatable. Yet these interests and values influence what is considered acceptable, and consequently what is accepted or rejected. Nanotechnology is proclaimed to have a tremendous potential to address major global challenges like cancer, renewable energy and provision of clean water. Yet precisely because of the widespread applications of nanotechnology, citizens around the world are as much stakeholders in the technology as the governments, industries and scientists promoting it. But so far the deliberate engagement of citizens and the public in risk-related decisions on nanotechnology has been very limited.

22.6.5 Lesson 7: evaluate alternative solutions

This lesson may simply be summarised by saying, don't become so enamoured by a new technology, that you are blinded to alternative solutions. Past lessons have shown there is a tendency for proponents to justify heavy investment in a new technology by promoting its application to every conceivable problem, with the result that alternatives are insufficiently scrutinised, and the most appropriate solution not always selected.

While nanotechnology is diverse and widely applicable, this would seem a potential pitfall as

the number of nanoscale solutions looking for a problem continues to grow. And with international nano-fever running high, everyone wants to be at the forefront of the nanotechnology revolution. In many cases, nanotechnology will provide the means to overcome challenges — but the lesson to be learnt is the need to find the best solution to a given problem, rather than to squeeze a solution out of the latest technology. This means that, in some cases, while nanotechnology **could** be used, it may be questionable whether it **should**. In the context of such discussions, assessment of alternatives can be used to provide helpful guidance in case of doubt as it provides a structured approach to examining a wide range of alternatives (e.g. technologies, processes, social changes) to potentially hazardous activities (Rossi et al., 2006).

Alternatives assessment is normally a six-step process that includes:

- 1) identification of target(s) for action;
- 2) characterisation and prioritisation of end uses;
- 3) identification of alternatives;
- 4) evaluation and comparison of alternatives;
- 5) selection of preferred alternative(s); and
- 6) review of selected alternative.

The scope of any alternatives assessment should be broad enough to examine the service and function that it requires as opposed to just examining, for example, the opportunities of substituting a hazardous chemical with a less hazardous one. In the case of nanomaterials this means that alternatives need not simply be nanomaterials, but may include the process or administrative changes that reduce the need for the materials in the first place (Rossi et al., 2006; Linkov et al., 2009). While alternatives assessment is generally applied to existing technologies and problems, the thinking about alternatives can be applied at the design phase, which did not occur in the case of nanotechnology.

22.6.6 Lesson 10: maintain regulatory independence

The EEA panel found evidence in the case studies that interested parties are often able to unduly influence regulators. As a result, decisions that might reasonably have been made on the basis of available evidence were not taken. For example

according to the EEA panel one factor in the slow UK response to BSE was that the governmental regulatory body was responsible first to the industry and only second to consumers. In many countries, the organisations responsible for overseeing the development of nanotechnologies through R&D are the very ones that address health and environmental issues.

In testimony to the US Congress House Committee on Science and Technology, Richard Dennison of the Environmental Defense Fund, a non-profit environmental campaign group, wrote that:

'we have become convinced that a conflict of interest has arisen from the decision to house within NNI the dual functions of both seeking to develop and promote nanotechnology and its applications, while at the same time aggressively pursuing the actions needed to identify and mitigate any potential risks that arise from such applications. That conflict of interest is both slowing and compromising efforts by NNI and its member agencies and departments to effectively address nanotechnologies implications' (Denison, 2007a).

Concerns that such a conflict of interest could jeopardise effective environmental, health and safety research were most recently articulated by the US National Academies of Science in a research strategy for environmental, health and safety aspects of engineered nanomaterials:

'There is a concern that the dual and potentially conflicting roles of the NNI — developing and promoting nanotechnology and its applications while identifying and mitigating risks that arise from such applications — impede implementation and evaluation of the EHS risk research... To implement the research strategy effectively, a clear separation of management and budgetary authority and accountability is needed between the functions of developing and promoting applications of nanotechnology and of understanding and assessing potential health and environmental implications. Such a separation is needed to ensure that progress in implementing an effective nanotechnology-related EHS research strategy is not hampered' (National Academy of Sciences, 2012).

While an integrated approach to understanding the risks and benefits of nanotechnology is critical, when the promoters of nanotechnology, whether government or industry, have a strong

influence over oversight, independent regulatory decision-making becomes compromised. Perhaps more insidiously, research and development decisions end up being influenced by what will ultimately promote the technology, rather than what will protect producers, users and the environment.

22.6.7 Lesson 12: avoid paralysis by analysis

In the face of uncertainty, a frequent response is to call for more research before action is taken. Yet, as the EEA panel note, Experts have often argued at an early stage that we know enough to take protective action (EEA, 2001). Good policy depends on identifying the right balance between information and action while keeping the end-point (preventing harm) in mind, and building in review procedures for course corrections.

Twenty years have elapsed since first indications of nanomaterial harm were published (Ferin et al., 1990; Oberdorster et al., 1990), and in the intervening time an increasing body of literature has been developed on how nanomaterials interact with cells, mammals and aquatic organisms (Hansen et al., 2007; Stone et al., 2010). Yet many governments still call for more information as a substitute for action; there are indications that understanding and managing the risks of engineered nanomaterials are being paralysed by analysis. While it is clear that more scientific information is needed, we need to act on what we know now, to enable industry to produce and market nanotechnology-enabled products that are as safe as possible. Engineered nanomaterials are already on the market, and in some cases the risks are poorly understood and may therefore be ineffectively regulated. Applying current knowledge to nanotechnology oversight will not solve every problem, but it will help prevent basic mistakes being made while the knowledge needed for more effective oversight is developed.

One way to facilitate decision-making on nanomaterials may be to develop design criteria to identify which nanomaterials are of higher or lower concern because of their intrinsic properties or use or exposure characteristics. For example, Maynard et al. (2011) have proposed principles of emergent risk, plausibility and impact to identify materials of high concern. Further, a thorough consideration of health and safety implications at the design phase of a nanomaterial, including consideration of possible safer production methods and alternatives to the material, will facilitate decisions as economic interests are not fully entrenched at that point.

22.7 So have we learnt the lessons?

Although the EEA panel was writing about existing technologies, and some of the 12 lessons learned are not directly applicable to all emerging technologies, many of the lessons are directly relevant to nanotechnology today. Yet the picture is not as bleak as it might be. Table 22.1 provides a qualitative analysis of 10 main EU Member State national and multilateral scientific reports that have provided input to the EU regulatory and political decision-makers on nanomaterials over the course of the last decade. For each of the late lessons from the first volume of this publication (EEA, 2001) we have provided an assessment of whether the lessons there have been mentioned in passing (+), have been substantially discussed and/or analysed (++), or whether a strategy to address a given lesson has been suggested (+++). Blanks means that no noticed was taken of these lessons.

While progress in developing sustainable nanotechnologies has been slow, the qualitative analysis above indicates that policy makers and relevant stakeholders seem to have learnt at least some of the lessons: they are asking more critical questions early on about health and environmental fate and effects; developing collaborations that cross disciplines, departments and international boundaries; beginning the process of targeting research to develop relevant knowledge; engaging stakeholders; and asking whether existing oversight mechanisms are fit for purpose.

But are we doing enough? The second half of Table 22.1 provides a qualitative analysis of the main EU regulatory actions taken over the course of the last decade in response to the twelve lessons.

The Cosmetic and the Biocides regulations acknowledge that there is a high level of scientific uncertainty regarding the risks of nanomaterials. They require industry to submit data and information about physical/chemical characteristics and the exposure and toxicological profile of a given nanomaterial, thereby providing some elements of a strategy toward long-term environmental and health monitoring to help identify and reduce scientific blind spots. The burden of providing health and safety data being placed on industry also helps to overcome the problem of paralysis by analysis since companies are in theory not able to market their products without proper data and information about risks. To some extent, regulatory independence is also ensured in the Cosmetic and the Biocides regulations in the sense that the scientific

Table 22.1 Late lessons learned, as indicated in 10 EU Member State nanomaterials reports

Lessons (EEA, 2001)	Royal S& RAE (2004)	DG Sanco (2004)	Chaundry et al. (2006)	IRGB (2006)	SCENIHR (2007)	RCEP (2008)	CEC (2008)	Stone et al. (2009)	RIVM (2009)	Aitken et al. (2009)	SCENIHR (2009)	Cosmetic Regulation	Biocides Regulation	Food Additives Regulation	RoHS * and WEEE **
Acknowledge and respond to ignorance, uncertainty and risk in technology appraisal	++	++	++	++	++	++	+	++	++	++	++	++	++	+	+
Provide long-term environmental and health monitoring and research into early warnings	++	++		++	+	++	+	++	+		++	++	++	+	+
Identify and work to reduce scientific blind spots and knowledge gaps	++	+		+	++	++	+	+			++	++	++	+	+
Identify and reduce interdisciplinary obstacles to learning	++			+	+	+									
Account for real-world conditions in regulatory appraisal		+										+	+		+
Systematically scrutinise claimed benefits and risks	+	+		+		+							++		
Ensure use of lay knowledge, as well as specialist expertise	++	+		++											
Evaluate alternative options for meeting needs, and promote robust, diverse and adaptable technologies															
Account fully for the assumptions and values of different social groups	++	+		++		+									
Maintain regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering	+											++			
Identify and reduce institutional obstacles to learning and action	++			+		+									
Avoid paralysis by analysis by acting to reduce potential harm when there are reasonable grounds for concern	+	+		+	++	+						+	+	+	+

Note: A empty cell indicates no notice taken
+ mentioned in passing; ++ substantially discussed and/or analysed; +++ strategy suggested/implemented
* Restriction of Hazardous Substances Directive; ** Waste Electrical and Electronic Equipment Directive.

committees such as the European Commissions Scientific Committee on Consumer Safety and the European Food Safety Agency that are responsible for evaluating the health and safety data and the information provided by industry are independent from the regulatory agencies that promote the use of nanomaterials in those same products. However, these agencies have recently come under attack for not being independent from industry interests (Muilerman and Tweedale, 2011).

In the light of the 14 case studies in the first volume (EEA, 2001), the question here seems not to be whether we have learnt the lessons, but whether we are applying them effectively enough to prevent nanotechnology becoming yet another future case study on how not to introduce a new technology. Despite a good start, it seems that we have become distracted by the way that nanotechnology is being

overseen by the very government organisations that promote it; research strategies are not leading to clear answers to critical questions; collaboration continues to be hampered by disciplinary and institutional barriers; and stakeholders are not being fully engaged, or not being engaged early enough. In part this is attributable to bureaucratic inertia, although comments from some quarters, such as risk research jeopardises innovation or regulation is bad for business, only cloud the waters when clarity of thought and action are needed.

If we are to realise the commercial and social benefits of nanotechnology without leaving a legacy of harm, and to prevent nanotechnology from becoming a lesson in what not to do for future generations, perhaps it is time to go back to the classroom and re-learn these late lessons from early warnings.

22.8 Precautionary strategies for nanomaterials

Linkov et al. (2009) have pointed out that there seems to be a substantial time lag between the emergence of products containing nanomaterials, the generation of EHS data and their subsequent use by regulatory agencies (see Figure 22.2).

They argue that this results from these agencies having limited resources and that it will take time for regulatory agencies to adjust risk assessment procedures so that they are applicable to nanomaterials. The precise extent of the time lag is unclear, but there is historical evidence indicating that it will not be less than two decades. In 1977, Lawless and his team analysed 45 episodes of public alarm or strong concern over various technologies including reproduction and genetics, food and medicine, and environmental problems. A common theme identified by Lawless was that social institutions grapple with the problem for varying amounts of time while papers on effects increase in the technical literature. On average, this delay is one or two decades (Lawless, 1977). Volume 1 of this publication (EEA, 2001) found that the time gap between the first report of harm and effective regulatory action was decades, and in some cases, even over a century. Although the cases analysed by the EEA and Lawless may not reflect all emerging

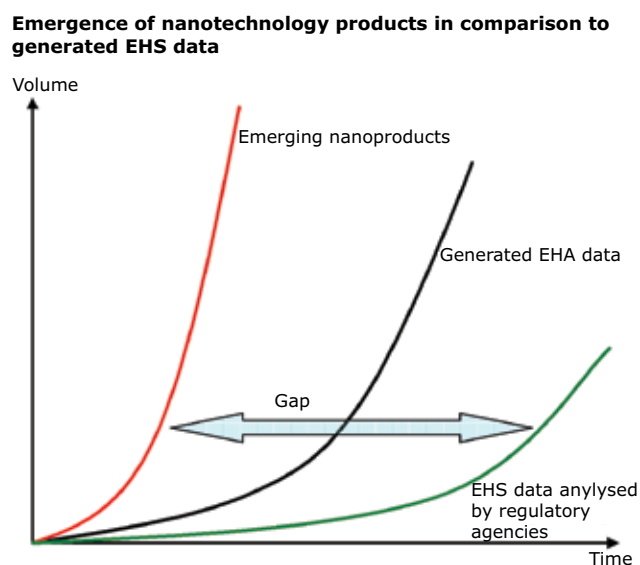
technologies, they do represent plausible worst-case scenarios. Given that the shelf life of specific new nanotechnology products is likely to be short because of continuous technology improvements, Linkov et al. (2009) argue that the approaches to regulating these materials should be adjusted to the evolving nature of the field. The question however is how this should be done.

RCEP (2008) has pointed out that existing regulatory approaches cannot be relied on to detect and manage problems before a novel technology such as nanomaterials has become ubiquitous. Although, this observation is rather bleak and discouraging, several precautionary strategies have nevertheless been suggested over the past decade. Some have focused on providing recommendations on how to adapt existing legislation, for example Chaundry et al., 2006; Fuhr et al., 2007; Franco et al., 2007; Ludlow et al., 2007 and Breggin et al., 2009. Specific recommendations include clarification of key terms and definitions of nanotechnology and material properties; ensuring the relevance of the scope and objectives of existing legislation; clear definition of thresholds relevant to nanomaterials; and risk assessment of nanomaterials prior to or after release into the environment.

Others have focused on providing recommendations on how to adapt existing risk assessment methods and risk management procedures such as the nano-risk framework jointly developed by the American non-governmental organisation Environmental Defense and the DuPont Corporation (ED and DuPont, 2007). This framework describes a process for ensuring the responsible development of nanoscale materials, and is designed to be used iteratively at different stages of development including basic R&D, prototyping, pilot testing, test marketing, and finally when new information becomes available. The suggested framework consists of six distinct steps:

- develop the nanomaterial and its intended uses;
- develop nanomaterial hazard and exposure profiles along the full life cycle;
- evaluate information generated to assess the probability of nanomaterial risks;
- evaluate risk management options and recommend a course of action;
- decide alongside key stakeholders whether to continue R&D and production;

Figure 22.2 Schematic representation of the emergence of nanotechnology products in comparison with generated EHS data



Source: Reprinted with permission from Linkov, I. et al., 2009.

- update and re-execute the risk evaluation regularly and share appropriate information with relevant stakeholders (ED and DuPont, 2007).

A third series of recommendations from various stakeholders and experts, for example the International Council on Risk Governance (2007) and RCEP (2009), have a much broader focus and have provided recommendations on issues more relevant to the governance of emerging technologies and innovation. In addition to a wide range of recommendations focused on restructuring risk research and regulation of chemicals and emerging technologies, RCEP (2009) has called for the development of flexible and resilient forms of adaptive management to allow us to handle such difficult situations and emergent technologies while recognising the high degree of ignorance and uncertainty and the time it will take to address these. According to RCEP (2009), key elements of such a framework should be structured around modification and extension of the existing regulatory framework as a matter of urgency, and development of an early warning system including robust arrangements for monitoring complemented (and informed) by the full range of perspectives on innovation.

Similarly, ICRG (2006, 2007) has suggested an integrated analytic framework for risk governance, consisting of pre-assessment, risk appraisal, and judgment of tolerability and acceptability, with risk management and communication as integrated elements that provide connectivity between the other elements. Application of the framework to nanotechnologies has led to a number of recommendations that fall into five categories: improve the knowledge base; strengthen risk management structures and processes; promote stakeholder communication and participation; ensure social benefits and acceptance; and collaboration between stakeholders and nations.

Recently, the German Advisory Council on the Environment for the German Government has called for a multifaceted strategy that includes intensification of risk research, promotion of social dialogue, development of a single piece of nano-specific legislation based on the precautionary principle, establishment of a labelling and product register, and a reform of the current chemical, product and environmental legislation (SRU German Advisory Council for the Environment, 2011).

In many ways, these recommendations echo those made by the Royal Society and Royal Academy of Engineering in 2004 in areas such as health, safety and environmental impacts; regulatory, social and

ethical issues; stakeholder and public dialogue; and ensuring the responsible development of nanotechnologies. Key recommendations include:

- Research into possible adverse health, safety and environmental impacts of nanomaterials, which the RS and RAE (2004) argue should be an integral part of the innovation and design process of products including nanomaterials.
- Avoidance of the release of manufactured nanoparticles and nanotubes into the environment as far as possible.
- Regulatory authorities to consider whether existing regulations are appropriate to protect humans and the environment and inclusion of future applications of nanotechnologies in their horizon-scanning programmes to ensure timely identification of any regulatory gaps.
- Consideration of whether ethical and social implications of advanced technologies (such as nanotechnologies) should form part of the formal training of all research students and staff working in these areas.
- Comprehensive qualitative work involving members of the general public as well as members of interested sections of society, and government funding of public dialogue around the development of nanotechnologies.
- Establishment of a group that brings together representatives of a wide range of stakeholders to look at new and emerging technologies and identify, at the earliest possible stage, areas where potential health, safety, environmental, social, ethical and regulatory issues may arise and advise on how these might be addressed.

While a regulatory, stakeholder engagement and R&D strategy are critical elements of a precautionary approach to nanomaterials, one must not forget the critical role of design in ensuring that technology development occurs in parallel with technology assessment. Nanotechnology development has occurred in the absence of clear design rules for chemists and materials developers on how to integrate health, safety and environmental concerns into the design of nanomaterials. This is not surprising given that most chemists and materials designers are not trained to recognise these issues. The emerging area of green nanotechnology offers promise for the future. For this type of focus on preventive design to occur, we will need a cultural transition: that chemists and materials developers

are educated on health, safety and environment; that environment, health and safety become quality concerns in the development of new materials, equal to economic and performance considerations; that research on the sustainability of materials is funded at levels significant enough to identify early warnings; and that regulatory systems provide incentives for safer and sustainable materials.

When it comes to addressing R&D gaps, specific legislative gaps, limitations in current risk assessment and risk management approaches

as well as risk governance of nanotechnologies and other emerging technologies, a common denominator of all of these recommendations is that many of them are not or have yet to be successfully implemented by political decision-makers. As a result, there remains a developmental environment that hinders the adoption of precautionary yet socially and economically responsive strategies in the field of nanotechnology. If left unresolved, this has the potential to hamper our ability as a society to ensure the responsible development of nanotechnologies.

Table 22.2 Early warnings and actions

1974	Taniguchi first uses the term nanotechnology referring to the ability to engineer materials precisely at the nanometre (nm) level
1981	Scanning tunnelling microscope developed
1985	Atomic force microscope developed
1985	Fullerenes discovered at Rice University
1986	Drexler raises concern about potential risks of nanotechnology
1991	Iijima discovers carbon nanotubes
1992	Surface area found to be a better descriptor than mass for the adverse effects observed in rats exposed to TiO ₂
2000	National Nanotechnology Initiative (NNI) established by the US Government
2003	Making analogies with ultrafine particles and asbestos, the Royal Society and Royal Academy of Engineering in the UK calls for more research and for avoidance of the release of manufactured nanoparticles and nanotubes into the environment
2004	Single-walled carbon nanotubes of different purity found to induced dose-dependent granulomas and interstitial inflammation in the lungs of mice
2006	Project for Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars launches online consumer nanoprodut inventory totalling 212 products
2006	2 year voluntary reporting program set up in the United Kingdom by DEFRA
2007	Publication of Nano-risk framework jointly developed by the American non-governmental organisation Environmental Defense and the DuPont Corporation
2007	Voluntary reporting program set up in the US by the US EPA
2008	Long multi-walled carbon nanotubes are found to produce adverse effects qualitatively and quantitatively similar those caused by long asbestos
2009	Voluntary reporting program end in the US receiving only 31 submissions
2009	Cosmetic Regulation in Europe adopted that requires labelling and safety assessment of nanomaterials
2009	European Parliaments Environment Committee call for application of the no data, no market principle in regard to regulation of nanomaterials
2011	Australia explicitly moves to differentiate the requirements for some new industrial nanoscale chemicals in its National Industrial Chemicals Notification and Assessment Scheme
2011	NIOSH (2011) has determined that ultrafine TiO ₂ should be considered a potential occupational carcinogen
2011	European Commission publishes proposal of a definition of nanomaterials

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