

## Emerging methods and tools for environmental risk assessment, decision-making, and policy for nanomaterials: summary of NATO Advanced Research Workshop

Igor Linkov · Jeffery Steevens · Gitanjali Adlakha-Hutcheon · Erin Bennett · Mark Chappell · Vicki Colvin · J. Michael Davis · Thomas Davis · Alison Elder · Steffen Foss Hansen · Pertti Bert Hakkinen · Saber M. Hussain · Delara Karkan · Rafi Korenstein · Iseult Lynch · Chris Metcalfe · Abou Bakr Ramadan · F. Kyle Satterstrom

Received: 24 May 2008 / Accepted: 6 September 2008 / Published online: 8 October 2008  
© Springer Science+Business Media B.V. 2008

**Abstract** Nanomaterials and their associated technologies hold promising opportunities for the development of new materials and applications in a wide variety of disciplines, including medicine,

environmental remediation, waste treatment, and energy conservation. However, current information regarding the environmental effects and health risks associated with nanomaterials is limited and

---

I. Linkov (✉)  
Environmental Laboratory, U.S. Army Corps of Engineers, 83 Winchester Street Suite 1, Brookline, MA 02446, USA  
e-mail: Igor.Linkov@usace.army.mil

J. Steevens  
U.S. Army ERDC, 3909 Halls Ferry Road, Vicksburg, MS 39056, USA  
e-mail: Jeffery.A.Steevens@us.army.mil

G. Adlakha-Hutcheon  
Defense Research and Development Canada, 305 Rideau Street, Ottawa, Canada K1A 0K2  
e-mail: Gitanjali.Adlakha-Hutcheon@drdc-rddc.gc.ca

E. Bennett  
Intertox Inc. and Bioengineering Group, 18 Commercial Street, Salem, MA 01970, USA  
e-mail: ebennett@bioengineering.com

M. Chappell  
Environmental Laboratory, U.S. Army Corps of Engineers, 3909 Halls Ferry Road, Vicksburg, MS 39056, USA  
e-mail: Mark.a.chappell@usace.army.mil

V. Colvin  
ICON, Rice University, 141 Dell Butcher Hall, Houston, TX 77005, USA  
e-mail: colvin@rice.edu

J. M. Davis  
National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, USA  
e-mail: Davis.Jmichael@epa.gov

T. Davis  
Environment Canada and Department of Chemistry, University of Montreal, C.P. 6128, succursale Centre-Ville, Montreal, QC, Canada H3C 3J7  
e-mail: ta.davis@umontreal.ca

A. Elder  
Department of Environmental Medicine, University of Rochester, 575 Elmwood Ave., Box 850, Rochester, NY 14610, USA  
e-mail: Alison\_Elder@urmc.rochester.edu

S. Foss Hansen  
Department of Environmental Engineering, NanoDTU, Technical University of Denmark, Building 113, Kgs. Lyngby 2800, Denmark  
e-mail: sfh@er.dtu.dk

P. B. Hakkinen  
Science Fellow Ranco, Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH, USA  
e-mail: berthakkinen@gmail.com

sometimes contradictory. This article summarizes the conclusions of a 2008 NATO workshop designed to evaluate the wide-scale implications (e.g., benefits, risks, and costs) of the use of nanomaterials on human health and the environment. A unique feature of this workshop was its interdisciplinary nature and focus on the practical needs of policy decision makers. Workshop presentations and discussion panels were structured along four main themes: technology and benefits, human health risk, environmental risk, and policy implications. Four corresponding working groups (WGs) were formed to develop detailed summaries of the state-of-the-science in their respective areas and to discuss emerging gaps and research needs. The WGs identified gaps between the rapid advances in the types and applications of nanomaterials and the slower pace of human health and environmental risk science,

along with strategies to reduce the uncertainties associated with calculating these risks.

**Keywords** Nanomaterials · Risk assessment · Decision analysis · Regulatory policy · Uncertainty analysis · Nanotechnology governance · Societal implications

## Introduction

Many potential questions are associated with the current state of development and use of nanomaterials. For example, with the availability of over 600 consumer products worldwide claiming to contain nanomaterials, what information exists that identifies their risk to human health and the environment? What engineering and other personal and environmental protection controls can be deployed to minimize the potential human and environmental health and safety impacts of nanomaterials throughout the manufacturing and product lifecycles? How can the potential environmental and health benefits of nanotechnology be realized? To discuss and develop expert answers to questions, such as these, the NATO Advanced Research Workshop “Nanomaterials: Environmental Risks and Benefits and Emerging Consumer Products” brought together 70 scientists and engineers from 19 different nations and multiple fields, reflecting the global and interdisciplinary nature of nanotechnology and nanomaterials research. The workshop had five primary purposes:

- Describe the potential benefits of nanotechnology-utilizing commercial products.
- Identify and describe what is known about the environmental and human health risks of nanomaterials and the approaches to assess their safety.
- Assess the suitability of multicriteria decision analysis for reconciling the benefits and risks of nanomaterials and nanotechnology.
- Provide direction for future research in nanotechnology and environmental science to address issues associated with emerging nanomaterial-containing consumer products.
- Identify strategies for users in developing countries to best manage this rapidly developing technology and its associated risks, and to realize its benefits.

---

S. M. Hussain

Air Force Research Laboratory, Dayton, OH, USA  
e-mail: Saber.Hussain@wpafb.af.mil

D. Karkan

Health Canada, Ottawa, Canada  
e-mail: Delara\_karkan@hc-sc.gc.ca

R. Korenstein

Department of Physiology and Pharmacology, Faculty of Medicine, Marian Gertner Institute for Medical Nanosystems, Tel Aviv University, Tel-Aviv 69978, Israel  
e-mail: korens@post.tau.ac.il

I. Lynch

Irish Centre for Colloid Science & Biomaterials, School of Chemistry & Chemical Biology, University College Dublin, Dublin, Ireland  
e-mail: iseult@fiachra.ucd.ie

C. Metcalfe

Trent University, 1600 West Bank Drive, Peterborough, ON, Canada K9J 7B8  
e-mail: cmetcalfe@trentu.ca

A. B. Ramadan

National Egyptian Environmental and Radiation Monitoring Network, 3 Ahmed El Zomor St., Nasr City 11672, P.O. Box 7551, Cairo, Egypt  
e-mail: ramadan58@yahoo.com; ramadan85@yahoo.com

F. K. Satterstrom

Engineering Sciences Laboratory 224, Harvard School of Engineering and Applied Sciences, 40 Oxford Street, Cambridge, MA 02138, USA  
e-mail: satterst@fas.harvard.edu

State-of-the-science reviews of nanotechnology were presented during the plenary sessions by renowned experts in the field, and over 20 poster presentations provided insights regarding specific projects and issues of interest to the nanotechnology community. Discussion panels were held to debate the implications of this information and to begin clarifying gaps in current knowledge and four working groups (WGs) were formed to detail these gaps and propose solutions to address them. The WGs discussed methods and applications specific to the following areas: (i) technology and benefits, (ii) human health risks, (iii) environmental risks, and (iv) policy implications. Prior to the conference, WG chairs prepared and circulated topical white papers, providing a starting point for the detailed WG discussions during the meeting. This summary paper was initially drafted by the workshop organizers and WG chairs and rapporteurs during a one-day meeting immediately following the workshop. The conclusions described for each WG are based on a prioritized list agreed upon during the post-workshop session. These efforts highlight the significant challenges to professionals in assessing the risks associated with nanotechnology; such assessments will almost certainly require a highly integrative and adaptive process of decision-making for nanomaterial risk assessment. The full reports from each WG are published in Linkov and Steevens (2009), but the concepts discussed and conclusions made are summarized in the following pages.

### **Nanotechnology, its applications, consumer products, and benefits**

#### *State of the field*

Nanotechnologies already provide new exciting applications in materials science, communications, electronics, medicine, energy, and the environment, to name just a few areas. Nanotechnology represents a platform technology that utilizes the properties of matter that arise at the nanometer scale. Many nanomaterials are currently being produced (some have been for many years), such as carbon black, fumed silica, carbon nanotubes, fullerenes, silver nanoparticles, polymer nanocomposites, dendrimers, metal oxides, organic and inorganic semiconductors,

and nanocatalysts. Nanomaterials are used, for example, in coatings, emulsions, dispersions and films in automobile components, paper, cosmetics, textiles, and electronic displays. The unique physicochemical characteristics of nanomaterials, particularly the high surface-to-volume ratio (influencing solubility, chemical reactivity, and catalytic activity) and quantum effects (influencing colour, magnetism, hardness, and electronic properties), make them important drivers of innovation with the potential to benefit the world's entire population. Nanotechnology can thus be viewed as a cross-sectional and enabling technology.

#### *Nanomedicine*

The application of nanotechnology in health care, termed nanomedicine, offers new opportunities to significantly improve medical diagnosis and treatment of diseases, such as cardiovascular disease, cancer, diabetes, musculoskeletal disorders, and neurodegenerative diseases (European Technology Platform 2006). The main areas of activity are nanotechnology-based diagnostics and imaging, targeted delivery of multi-tasking medicines, and regenerative medicine. In vivo diagnostic technology is based on nanoparticle contrast agents, particularly for MRI and ultrasound. In vitro diagnostic technology attempts to develop novel sensor concepts that are based on nanotubes, nanowires, cantilevers, or atomic force microscopy, with an aim to improve sensitivity, reduce production costs, or measure novel analytes. Development of multifunctional nanocarriers associated with drugs and possessing targeting capabilities offers new opportunities for cancer therapy. Regenerative medicine employs novel cell culture techniques combined with the design of biocompatible polymers, enabling advanced therapeutic tissue engineering (European Technology Platform 2006).

#### *Environment*

Environmental nanotechnology applications can be divided into two groups: (1) environmental technology applications that will reduce pollution, and (2) technologies that will remediate pollutants that accumulate in the environment. The first category consists of environmentally beneficial approaches, such as

green design, green chemistry, and green manufacturing. The second category includes a group of different nanomaterials that, due to their chemical reactivity and high surface area, are being applied to soil and water for decontamination. For example, iron nanopowders are already in use for effective detoxification of soils for a variety of organic contaminants.

Nanotechnology also offers the potential of novel materials for treatment of surface water, groundwater, and wastewater contaminated by toxic metal ions, organic and inorganic contaminants, and pathogenic microorganisms. Due to their unique activities toward recalcitrant contaminants, many nanomaterials are under active research and development. Accordingly, literature about current research on different nanomaterials (nanostructured catalytic membranes, nanosorbents, nanocatalysts, and bioactive nanoparticles) and their application in water treatment, purification, and disinfection has been recently reviewed (Theron et al. 2008).

### *Energy*

To meet the energy demands of a future world with a larger population and a growing dependence on power, technological breakthroughs that advance energy conversion, storage, and savings are needed. A report of the National Nanotechnology Initiative (NNI 2004) identifies a number of strategic research targets in which nanotechnology is likely to have the greatest impact by forming alternatives to fossil fuels. These targets include:

- Hydrogen production from sunlight and water,
- Solar cells with 20% power efficiency and 100 times lower cost than current cells,
- Solid-state lighting requiring half the power consumption of current technologies, and
- Super-strong, light-weight materials to improve the fuel efficiency of the transportation sector.

The use of nanotechnology is expected to cut costs both of solar cells and of the equipment needed to deploy them, making solar power economical and hence a more usable alternative to fossil fuels. Nanotechnology may also contribute to reductions in energy demand through lighter materials for vehicles, materials and geometries that contribute to more effective temperature control, technologies that improve manufacturing process efficiency, materials

that increase the efficiency of electrical components and transmission lines, and materials that could contribute to a new generation of fuel cells and a potential hydrogen economy.

### *Consumer products*

As noted in the above sections, nanotechnology heralds a world of better and more durable consumer products. In 2006, nanotechnology was incorporated into more than \$50 billion worth of manufactured goods. The Project on Emerging Nanotechnologies (PEN) maintains an inventory of consumer products that claim to utilize nanomaterials. As of May 15, 2008, this inventory contained 610 products or product lines produced by 322 companies located in 20 countries. This online list of company-identified nanotechnology consumer products includes merchandise from such well-known brands as Samsung, Black & Decker, Eddie Bauer, and others (PEN 2008). Since this list relies on manufacturers self-identifying products that may contain nanomaterials or use nanotechnologies in the manufacturing process, it is not an all-inclusive inventory. Other inventories are maintained, for instance, in Japan, although language differences may hinder their utilization (e.g., AIST 2008).

### *Benefits and implications*

Rapid advances in materials science and technology that enable the manipulation of matter at the nanometer scale will continue to allow the realization of many benefits of nanotechnology. Foremost among these will be a new manufacturing paradigm.

While techniques for manufacturing nanomaterials are as varied as the materials themselves, they can be divided into 2 main types of approaches: “bottom-up” and “top-down.” The building of structures atom-by-atom or molecule-by-molecule forms the basis for bottom-up manufacturing and can be split into three categories: chemical synthesis, self-assembly, and positional assembly (The Royal Society and Royal Academy of Engineering UK 2004). Bottom-up methods are widely used for manufacturing of metal nanoparticles, nanofilms, fullerenes, nanotubes, and quantum dots. Top-down manufacturing, meanwhile, involves starting with a micrometer- to millimeter-sized piece of material and etching, milling, or

machining nano-sized structures from it by removing material using precision engineering or lithography techniques. Top-down manufacturing can be used for creating computer chips, precision-engineered surfaces, and metal oxanes (Wiesner et al. 2006).

In addition to enabling a new manufacturing paradigm, another benefit of nanotechnology would be its potential to help sustain the world's resources. At the workshop, this benefit was discussed along with the view of Petersen and Egan (2002), who believe that nanotechnology is a technology which, for the first time in history, holds the promise of providing inexpensive energy, food, and clean water for everyone on the planet; it could thus be used also in innovative ways to encourage political stability and responsibility.

Economically, current projections put the global market for nanotechnology and nanomaterial-containing products at an estimated \$2.6 trillion by 2014 (Lux Research 2004). A more recent forecast by Business Communications Co. Research predicts the market for nanomaterials, nanotools, and nanodevices to be worth \$12.7 billion by the end of this year. While being more conservative than Lux Research, this estimate calls for a doubling of the \$12.7 billion market value in the next 5 years (BCC Research 2008). It should be noted here that the public sector leads the private sector in terms of investing in nanotechnological advancements worldwide and that the developed nations are the primary investors (Lux Research 2004). Therefore, a very significant challenge is ensuring an even distribution of benefits throughout the world community.

#### Ways to overcome problem

Given the large number of applications being designed that utilize nanomaterials and nanotechnologies, and the perception that nanotechnology is, or will be, a panacea for the world's problems, questions arise regarding who benefits from these technological advances. The popular press generally touts nanotechnology products as beneficial to society, while not necessarily distinguishing between the real and potential benefits of the technology. The Technology and Benefits WG acknowledged that the promise of economic returns drives investments, which in turn lead to technological advances. Taking three examples, one each from applications of nanotechnology

to medicine, the environment, and energy, we evaluated the health risks, environmental risks, total investment, health and environmental benefits, return on investment, and size of population impacted. The estimates for these parameters were best estimates based on information available from the NanoRoad-Map (NRM) project of the EU 6th Framework. This preliminary prediction showed that benefits were indeed not evenly distributed across the world. There was also a clear recognition among all workshop participants that resolving the question of who benefits from nanotechnology lies in pulling together multidisciplinary expertise from multiple nations. Issues of technical or economic capacity would have to be addressed through collaboration not just across disciplines but between the developed and developing nations to level the playing field. Just as market pressures drive investment, it is hoped that ethical and social imperatives would drive fair access to benefits of nanomaterials. Concurrent advances in methods to protect human and environmental health will have to lead the initiative on facilitating accessibility so that asymmetric benefits are not created. Although interdisciplinary collaboration was not the focus of this WG's deliberations, it was brought up as a subject addressed by the WG on policy. Finally, it was observed that one of the strengths of nanotechnology is its cross-disciplinary approach. Simply put, ideas and products originally developed for medical and biological purposes find applications in electronics or energy industries. This has in turn pushed scientists, medical doctors, and engineers to significantly revise and modify their approach to problem solving to rapidly adopt new ideas and techniques. The ultimate beneficiary of such a shift in thinking will be humanity.

#### Human health risk and implications

##### State of the field

There are several articles in the literature that review current concepts of nanomaterial toxicology and risk assessment (Balbus et al. 2007; Borm et al. 2006; Holsapple et al. 2005; Nel et al. 2006; Oberdörster et al. 2005; Stone et al. 2007). The purpose of the Human Health WG was not to re-review the literature, but to consider important findings in the context of a



rapid reduction in the uncertainties of the risk assessment process. Participants discussed mechanisms by which nanomaterials might pose a risk to human health, including nanosized particles penetrating epithelial barriers at the portal of entry and inducing oxidative stress. Both of these processes are fundamentally tied to the physical and chemical nature of the material itself. An important point is that there is no such thing as a generic “nanomaterial,” as factors, such as size, shape, chemistry, and solubility affects the biological interactions and consequences of exposure to a specific nanoparticle. This is highlighted by recent reports of impacts from carbon nanotubes (Poland et al. 2008) and nano silver (Benn and Westerhoff 2008). The goal that should be kept in sight, similar to a recent commentary (Hansen et al. 2008), is to facilitate actions taken by regulatory bodies that are charged with protecting human and environmental health through the reduction in uncertainties and prioritization of health-based research.

It is neither feasible nor sensible to conduct safety evaluations for all nanomaterials in current or future production; therefore, a risk assessment paradigm should be flexible and based on current knowledge of similar materials (Linkov et al. 2008). Along these lines, people are regularly exposed to nanosized particles in ambient air (i.e., ultrafine particles) that are derived from combustion processes. Although there are physicochemical differences between engineered nanomaterials and ambient ultrafine particles, the large body of toxicological literature regarding the latter provides a framework for understanding nanomaterial risks. In addition, large-volume production of nanosized titanium dioxide and carbon black particles has been carried out for several years, and it is possible that aspects of the risk assessment paradigms for these materials could be applied more generally to nanomaterials. Useful predictive guidance can also be gained from the literature regarding interactions of nanosized particles with skin, focusing on penetration of the stratum corneum and drug delivery. Although this approach focuses mainly on the respiratory tract and skin, such simplification is reasonable because of the ways in which humans are likely to be exposed to nanomaterials, namely in occupational and environmental settings and via consumer products.

An area that is gaining considerable interest and attention is the role of biomolecules, such as proteins

as mediators in the interactions of nanoparticles with living systems (Cedervall et al. 2007a, b; Lynch et al. 2006, 2007). For example, apolipoprotein E has been associated with transport to the brain, and recent evidence has indicated that nanoparticles coated with apolipoprotein E can reach the brain (Michaelis et al. 2006). Thus, one can begin to see how identification of proteins bound to nanoparticles could predict uptake and distribution, target organs, and cellular and tissue responses. Such predictive information linked with mechanistic knowledge could significantly contribute to reductions in the uncertainties of nanomaterials risk assessment.

#### Impediments to risk assessment

Several impediments to successful risk assessment of nanomaterials were discussed, including lack of adequate information regarding (i) external and internal dose and disposition, (ii) standardized testing strategies (methods, nanomaterials, characterization, and identification), and (iii) mechanistic uncertainties. The WG had a sense that the current focus on mechanistic aspects of responses to nanomaterials is not connected to information about the relevance to human health due to a lack of knowledge regarding exposure and target organ doses. Critical information is needed about exposure doses, target organs (kinetics, disposition), and uptake pathways. The lack of clarity as to the specific challenges associated with nanomaterials, coupled with the fact that this class covers such a diverse range of material types, solubilities, reactivities, sizes, and other properties, presents difficulties in designing suitable studies and interpreting the data from these studies. There is also concern about the validity of the assumption that existing endpoints are sufficient for nanoparticles (e.g., even after 20 years of research, there is no broad agreement on a test to predict biopersistent fiber-induced mesothelioma). Indeed, recent reports have highlighted interferences in cytotoxicity assays related to specific nanomaterial properties (Casey et al. 2007; Ryman-Rasmussen et al. 2007; Wörle-Knirsch et al. 2006). Response pathway analysis using gene chip technology is promising. However, direct application of the genomic technologies to nanoparticles is not straightforward, as many issues remain to be resolved, such as potential interactions of nanoparticles with mRNA. There is also considerable debate about relevant exposure

metrics, such as mass, surface area, and particle number.

Thousands of different nanomaterials are currently under development, with many more already in use, and it is not possible to test each individually. Screening assays are therefore needed. A key challenge is determining what should form the basis of such assays. Focusing on physicochemical properties alone is insufficient, as these may change (e.g., agglomeration, oxidation, and interaction with biomolecules) upon contact with liquid or gaseous media and with biological fluids. Second, screening tests that focus on toxicological mechanisms without any connection to plausibility or real-world exposure concentrations are of little use. Thus, the working group felt that these two approaches should be combined with each other and also with dosimetric information.

A lack of standardization is also a problem in many aspects of nanomaterials research. For example, characterization would be helped by the existence of standard nanoparticles with full physical, chemical, and “biological” characterization (the only current standard is the United States National Institute of Standards and Technology’s gold in three sizes which have been characterized physically). Current characterization techniques have size limitations (e.g., nanoparticles are at the limits of applicability for the equations used as the basis for size characterization) and are also affected by the states of aggregation or agglomeration. Standards are also lacking for characterizing nanoparticles in the aqueous and gaseous media used in test systems.

#### Strategies for addressing risk assessment needs

As the working group was asked to address the key research gaps affecting our ability to make realistic assessments of the potential risks associated with nanomaterials, our discussions focused on the types of studies that would reduce current uncertainties the fastest. The round-table discussions of the Working Group resulted in the conclusion that short-term research should focus on the following three key areas:

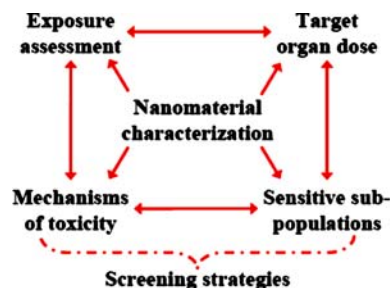
1. External exposure assessment (i.e., concentrations and characteristics of nanomaterials suspended in air or liquid),
2. Target organ dose (internal concentration, characteristics), and

3. Potential screening strategies (mechanistically relevant).

Long-term issues include the need for mechanistic studies once the susceptible organs are identified and addressing methodological gaps. Figure 1 summarizes the Working Group’s views regarding prioritization of future research, as described in more detail below.

Nanomaterial characterization is of key importance and new methodologies may be needed in support of this endeavor to characterize exposure-associated risks. Characterization efforts underlie all phases of the assessment and help to define, in particular, both the external and internal doses and exposures. This information also contributes to the development of rapid screening tests of the intrinsic properties of nanomaterials. In the descriptions below, “environment” refers broadly to the settings in which humans are exposed to nanomaterials, i.e., in the workplace or as consumers.

In addition to research on the mechanisms by which nanomaterials may cause adverse health effects, including to potential subpopulations with unique sensitivity, a research area that should be given high prioritization is that of exposure assessment. This includes the characterization of how exposure concentrations change in the environment due to particle agglomeration/deagglomeration, solubilization, and accretion of molecules in the gas or liquid carrier. Such processes could conceivably increase or decrease the clearance times of particles suspended in air or water. These studies focus on the physical behavior of particles in a carrier. However, information is also needed about how single particles can change in terms of size, shape, and surface



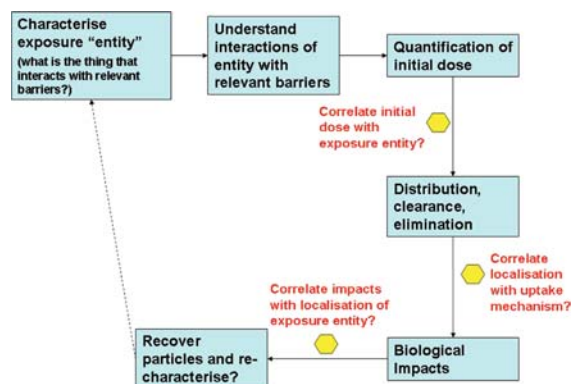
**Fig. 1** Overview of research needs for human health risk assessment of nanomaterials

chemistry due to exposure conditions and adsorptive processes. Finally, there is a need to develop standards for exposure characterization.

Since knowledge of the internal (target organ) dose should inform mechanistic studies, priority should also be given to filling the critical knowledge gaps in this area. To reach target tissues, nanomaterials must first penetrate one or more physiological barriers. Therefore, more needs to be understood about the characteristics of those barriers (such as the respiratory tract, skin, gut, and blood-brain barrier) with respect to penetration and subsequent distribution of nanomaterials. Second, the kinetics of nanoparticle uptake, transport, and clearance in the body and target organs need to be characterized. This goal could be impeded by the limitations of current technology, so there may be an opportunity to develop new methodologies to achieve in situ quantitation and visualization of nanosized particles. Similar to the need to understand more about the physical changes that nanoparticles undergo in the environment, this information is also needed with regard to size, shape, and agglomeration changes during transport in the body. Finally, it will be necessary to characterize changes in the “biological identity” of the nanoparticles (i.e., the biomolecule corona), surface chemistry, and solubility of the materials as a consequence of biodistribution.

The third high-priority research area that was identified by the WG was the development of screening strategies to assess the potential for health risks related to nanomaterials exposure. Such strategies should address, for one, the correlation of uptake dose, uptake mechanism, and target organ dose with the biomolecule corona. In addition, key aspects of nanomaterials reactivity from a physicochemical perspective should be addressed, including a focus on toxicological mechanisms and dose. As both the nanomaterials characterization efforts and mechanistic studies evolve, the data can be used to develop more meaningful screening tests.

The interplay between these three research topics and the logical progression and information flow can be conceptualized as shown in Fig. 2. In the longer term, again it is understood about external and internal dose and how to characterize these; it will be possible to identify in a meaningful way the key pathways of response to engineered nanomaterials. Likewise, dosimetric aspects of response can be



**Fig. 2** Flow chart of research topics

clarified. In parallel to these investigations, it will be important to identify disease processes (e.g., acute or chronic inflammation) or vulnerabilities (e.g., senescence or pregnancy) that might impact internal dose and/or mechanisms of response to nanomaterials.

## Ecological risk

### State of the field

This WG recognized that traditional risk assessment procedures are inadequate for predicting the ecological risks associated with the release of nanomaterials. The WG discussed a number of past case studies, where the traditional approach to risk assessment failed to reveal unforeseen risks, including recent developments with perfluorinated surfactants (PFOA/PFOS), where unexpected fate and biological effects became evident only after approval and inclusion of these compounds in a variety of consumer products (e.g., Teflon<sup>®</sup> coatings for cookware and other products).

### Main problem

The WG emphasized their belief that the root of the problem lies in an inadequate application of solid phase chemical principles (e.g., particle size, shape, and functionality) in the risk assessment of nanomaterials. The group felt strongly that the “solubility” paradigm used to evaluate the risks associated with inorganic or organic contaminants must be replaced by a “dispersivity” paradigm for evaluating the risks associated with nanomaterials.



In the opinion of the WG, the pace of development of nanomaterials will exceed the capacity to conduct adequate risk assessments using current methods and approaches. “New generation” products will include materials with targeted nanotechnology–biology interactions, DNA-scaffolded devices, composite materials with biological functions or photovoltaic properties, materials for new environmental remediation technologies, self-assembling devices, and polymer-based nanomaterials. These nanomaterials could be available in a variety of size classes and with different surface functionalizations, probably requiring multiple risk assessments for each material.

### Ways to overcome problem

The WG proposed that traditional risk assessment processes could be augmented by having the risk assessors play a more proactive role in evaluating all aspects of the nanomaterial lifecycle, allowing the assessor to better formulate the problem. Risk assessors should be integrally involved in both the manufacturing and material development, providing information relevant to risk assessments to the product developers, and involved in decisions to utilize appropriate lower-risk materials, without compromising the desired characteristics of the materials. In addition, risk assessors should obtain specific information regarding material properties for the development of new risk models.

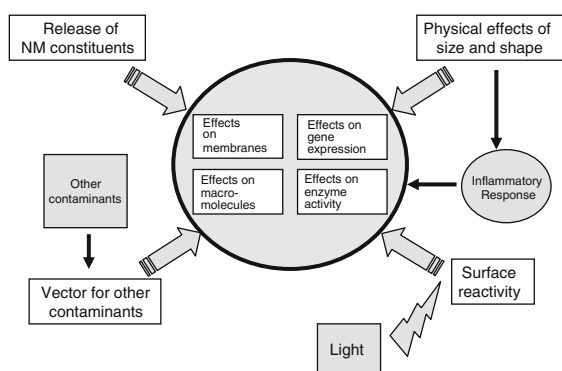
An improved problem formulation could come from consideration of the chemical and physical properties of nanomaterials; however, the WG attendees were uncertain which properties would be relevant or useful. Nonetheless, the WG agreed that solid phase properties, such as particle charge, species, or dispersion properties, or any combination of these may be relevant to predicting environmental fate and/or effects. Environmental fate should be considered in terms of all exposure pathways that are reasonable for solid phase particles.

The WG recommended that risk assessors should utilize new assessment technologies or techniques to assess effects. Methods are needed to assess cellular binding and uptake. Cellular uptake processes for nanoparticles are likely to be active (e.g., phagocytosis), or at least by facilitated diffusion (e.g., protein binding). Effects assessment methods should include biological assays that evaluate binding to

macromolecules or organelles, phagocytic activity, and active/passive uptake processes.

Once the nanomaterial enters the cell, toxicity can occur via one or a combination of up to four possible mechanisms (Fig. 3). The first mechanism involves the release of the chemical constituents from the nanomaterial, which leads to toxicity through more or less “conventional” processes, such as the release of toxic anions. The second mechanism of nanomaterial toxicity is related to the size and shape of the particle, which produces steric hindrances or interferences with macromolecules binding important sites. The third mechanism of toxicity involves the surface properties of the material, such as photochemical properties, local electric fields, charge densities, and electronic semi-conductance. The fourth mechanism of toxicity is related to the capacity for nanomaterials to act as vectors for the transport of other toxic chemicals to sensitive tissues. Tests should be developed to evaluate biological effects caused by each of these mechanisms. These tests should involve multiple species in different environmental systems, such as aquatic and terrestrial environments. Furthermore, these tests should be cross-validated in multiple laboratories in a coordinated international effort.

The WG recommended that risk assessors are flexible in their implementation of new models. Given the novelty of the nanotechnology field, the development of accurate risk assessment models is expected to be an iterative process. Despite best efforts to assess the risks associated with nanomaterials, previous experience indicates that we should expect that some products will enter the environment and cause biological effects. Therefore, risk assessors



**Fig. 3** Mechanisms of toxicity of nanomaterials in organisms

should support programs for reconnaissance and surveillance to detect the real world impacts of exposure to nanomaterials. The committee recognized the need for developing new tools and tests to accomplish this task, including sensors, active/passive collection systems, monitoring systems, and improved methods for separation and characterization of nanomaterials. Risk assessors should use this information, combined with information from analogous studies to further refine data quality objectives and to communicate interim conclusions to a wide group of stakeholders.

### **Considerations for implementation of manufactured nanomaterial policy and governance**

#### State of the field

The participants in this working group agreed to focus discussions on policy frameworks, rather than on the gaps of regulation which have been analyzed elsewhere. Further, the scope of discussion was narrowed to focus on guidance deemed helpful for developing policies, and on the information and tools (e.g., databases and web portals) that (i) support the development of policies by regulators, industry, and others, and (ii) disseminate information to the public and others.

The WG agreed that while many different policy frameworks for manufactured nanomaterials have been developed globally, a significant lag period remains between the development of nanotechnologies and the development and implementation of new policies. While policy initiatives range from voluntary measures to mandatory legislative frameworks, the WG recognized that governments and industry actually develop very few policies.

The document providing the foundation for the WG's discussions was a recent book chapter (Linkov and Satterstrom 2008) that reviewed current nanomaterial risk management frameworks. Linkov and Satterstrom took a global survey of risk assessment and risk management models and frameworks for manufactured nanomaterials developed by regulatory agencies, trade associations, not-for-profit organizations, academics, and companies, and selected 13 for in-depth review. Table 1 lists 11 documents reviewed

by the authors and, since publication of this chapter, one additional U.S. government multi-agency framework (National Nanotechnology Initiative, NNI) and the European Union's recently enacted Registration, Evaluation, Authorisation, and restriction of Chemicals (REACH) legislation were added by the WG participants. The documents reviewed included comprehensive state-of-the-science regulation framework documents, voluntary programs, documents on the regulation and ethics of nanomaterials, and position statements. Linkov and Satterstrom developed a list of criteria for comparing and contrasting these documents (i.e., aspects of a comprehensive nanomaterial risk management framework) based on work being undertaken by Health Canada on nanotechnology, under the categories of: (1) Science and Research Aspects; (2) Legal and Regulatory Aspects; (3) Social Engagement and Partnerships; and (4) Leadership and Governance. Within each category, Linkov and Satterstrom developed four comparison criteria per category, and the WG also reviewed the NNI and REACH in the same manner.

The WG agreed that developing regulatory tools is an important gap in the knowledge necessary for manufactured nanomaterial regulation. Further, the WG agreed with that the starting point for development of these tools is the set of policies and procedures already developed by regulatory agencies and industry for traditional industrial materials, e.g., surfactants and other chemical substances.

#### Challenges

The working group agreed that the challenges for manufactured nanomaterial-related policies include the need to consider the risks and benefits of these materials and their uses. However, instead of focusing on estimating the exact risks and benefits, the WG noted that the efforts should be directed toward understanding tradeoffs and finding superior risk management alternatives.

Another challenge is the need to include an understanding of risk perceptions, which can depend on the applications in which the nanomaterials are being used, and then developing appropriate risk communication efforts. Public perception of the risks stemming from nanotechnology is important, not only with regard to an individual's own exposure, but also with regard to the individual's perception of risk

**Table 1** Elements of nanomaterial regulation frameworks discussed in each document

	Science and research aspects				Legal and regulatory aspects				Social engagement and partnerships				Leadership and governance			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
USEPA 2007	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
US FDA 2007	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Davies 2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
ED-DuPont 2007	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Québec Commission 2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
UK Royal Society 2004	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
UK DEFRA 2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Responsible NanoCode 2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
EC SCENIHR 2007	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
EC Action Plan 2005	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
IRGC 2005, 2006, 2007	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
US NNI 2008	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
REACH 2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Sub-criteria for the table are as follows

- |  |  |
|--|--|
| <p><i>Science and research aspects</i></p> <ol style="list-style-type: none"> <li>1. Development of methods for detection/characterization/data collection</li> <li>2. Assessment of environmental fate &amp; transport/impacts</li> <li>3. Assessment of toxicology/human health impacts</li> <li>4. Assessment of health and environmental exposure</li> </ol> <p><i>Legal and regulatory aspects</i></p> <ol style="list-style-type: none"> <li>1. Voluntary regulatory and best-practices measures</li> <li>2. Information-based regulatory tools (e.g., labeling)</li> <li>3. Economic-based regulatory tools (e.g., tax or fee for safety testing)</li> <li>4. Liability-based regulatory tools (e.g., penalty for pollution)</li> </ol> | <p><i>Social engagement and partnerships</i></p> <ol style="list-style-type: none"> <li>1. Promotion of education and distribution of information/use of risk communication tools</li> <li>2. Use of stakeholder engagement tools</li> <li>3. Development of partnerships with academia, industry, public organizations, provinces, and international regulators</li> <li>4. Emphasis of ethical conduct</li> </ol> <p><i>Leadership and governance</i></p> <ol style="list-style-type: none"> <li>1. Transparency in nanotechnology-related decisions</li> <li>2. Consideration of benefits of nanotechnology</li> <li>3. Adaptive modification of existing or development of new legislation</li> <li>4. Consideration of precautionary principle</li> </ol> |
|--|--|

Criteria are numbered 1 to 4 under each category; for each document and criterion, ■ = document discussed the criterion, ■ = document mentioned the criterion, and blank = document did not address the criterion; adapted from Linkov and Satterstrom 2008

to others (e.g., the family of a person) and to the environment. The WG recognized that public perceptions of nanomaterial risk may differ from the perceptions of policy makers and technical experts (including risk assessors), and that any differences in mental models for nanomaterial risk perceptions between general public and technical experts should be highlighted and used to inform communication efforts.

Several additional challenges were noted by the WG. For example, as with other substances in the environment, regulators involved with the development of nanomaterial-related policies need to consider the differences between manufactured nanomaterials and both engineered and non-engineered anthropogenic nanomaterials, and the associated scientific and legal challenges by separating these materials for risk assessment, risk management, and policy purposes. Another challenge discussed by the WG was the need to understand the complex relationships between sources and the related exposure pathways to many potential receptors.

Finally, the WG noted a need for a common, standardized taxonomy and terminology for nanomaterials which captures key aspects of their physical and chemical characteristics, together with the establishment of standardized use categories.

#### Strategies for addressing policy needs

The WG generally agreed with the strategies noted in the Linkov and Satterstrom (2008) book chapter. These include:

- A “regulatory pyramid” (with self-regulation at the pyramid’s base and prescriptive legislation at the apex) is needed. However, some members of the WG noted that the huge diversity of possible nanomaterials makes the pyramid approach very challenging, and that it would be impossible to develop a “one-way-to-go” methodology to support the development of policies. This is especially true in countries where more than one regulatory agency is involved in the regulatory process for manufactured nanomaterials.
- An adaptive management approach should be utilized to respond to new developments and gain additional information through policy.

- The framework should employ multiple tools at different levels of the regulatory pyramid, with specific tools chosen on a case-by-case basis.
- Information- or economics-based tools would help both bottom-up (i.e., self-regulation) and top-down approaches (i.e., prescriptive regulation) for the assessment, management, and regulation of nanomaterials.
- Multicriteria decision analysis, including stakeholder engagement, can be used to prioritize regulatory knowledge gaps, select specific regulatory tools, and also to allocate limited resources and focus follow-up activities.
- An adaptive, tiered integration of risk management with decision support would thus be ideal.

Further, the WG agreed that:

- A common, standardized taxonomy and terminology for nanomaterials, including the capturing of key aspects of their physical and chemical characteristics, together with the establishment of standardized use categories, should be the global goal. This would facilitate the development of information resources (e.g., publications and other documents, and databases) that provide easy access and sharing across countries as regulators attempt to understand and assess the properties of new materials compared to similar materials. Attempts could be made to have a leading global organization(s) for key aspects of this effort.
- The differences between the sources and intended uses of nanoscaled particles (naturally occurring versus manufactured) need to be acknowledged and considered when developing policies and frameworks.
- Interactions and collaborations among regulators, scientists, and other stakeholders should continue and be further encouraged to develop coherent, adequate policies to address such a dynamic field.
- The ideal policy should take a holistic viewpoint, considering the entire lifecycle of a nanomaterial, in addition to the production, transport, and disposal/recycling.
- The main exposure considerations for policy development include occupational, consumer, and general population exposures of humans, and environmental exposures of ecological receptors.

- Ecological and human health effects should be considered for all reasonably foreseeable exposures in multiple media.
- Attempts should continue to be made by both companies and regulatory agencies to communicate information about manufactured nanomaterials to the public. The WG noted the efforts of the not-for-profit organization GreenFacts ([www.greenfacts.org](http://www.greenfacts.org)) to provide information. See: <http://copublications.greenfacts.org/en/nanotechnologies/index.htm>
- Development of a crisis-/catastrophe plan for manufactured nanomaterials should be considered by both companies and regulatory agencies. The recent case of the Magic Nano consumer products in Germany being associated with respiratory problems was discussed by the WG as both a good and bad example of how such a crisis should be addressed by material suppliers, consumer product companies, and regulatory agencies (e.g., see [http://www.smalltimes.com/Articles/Article\\_Display.cfm?ARTICLE\\_ID=270664&p=109](http://www.smalltimes.com/Articles/Article_Display.cfm?ARTICLE_ID=270664&p=109) and [http://www.bfr.bund.de/cm/279/frequently\\_asked\\_questions\\_on\\_nanotechnology.pdf](http://www.bfr.bund.de/cm/279/frequently_asked_questions_on_nanotechnology.pdf)).

## Conclusion

Workshop attendees shared basic agreements on policy and risk assessment needs across countries. Attendees identified the need for a common, standardized taxonomy and terminology for nanomaterials in which key aspects should include nanomaterial physical and chemical characteristics, with the view that such a system would facilitate the development of informational resources (e.g., publications, other documents, and databases) to provide easy access and sharing across international borders as regulators attempt to understand and assess the properties of these new materials. Attendees also agreed that assessments covering the entire lifecycle would best inform and guide risk assessment for engineered nanomaterials and related nanotechnologies, and that consumer and occupational health protection policies needed additional development as well. Given the proprietary nature of these rapidly evolving technologies, and current voluntary reporting requirements, a mechanism is needed for regularly providing and updating information to

scientists and policy makers regarding the safety profiles and characteristics of these current and emerging nanomaterials. Attendees were very aware that a serious nanomaterials-related health issue in one nation or region of the world would greatly promote a negative public perception of nanomaterials risk in every other nation or area.

Simultaneous advances in different disciplines are necessary to advance nanomaterials risk assessment and risk management. Risk assessment is an interdisciplinary field, but progress in risk assessment has historically occurred due to advances in individual disciplines. For example, toxicology has been central to human health risk assessment, and advances in exposure assessment have been important for environmental risk assessment and risk management. Nanotechnology, however, ideally involves the planned and coordinated development of knowledge across fields, such as biology, chemistry, materials science, and medicine.

Likewise, a risk assessment of nanomaterials and related technologies requires a lifecycle approach, meaning a comprehensive assessment of the impact of nanomaterials at different stages of production, use, and disposal/recycling. The current state of knowledge makes the identification of major risk drivers challenging. This includes understanding environmental pathways, fate and transport processes, and reasonably foreseeable exposures. An integrated, holistic approach is needed to consider an individual's total exposure from relevant environments expressed in different units across receptor groups. This would lead to risk characterizations that are systematic and more inclusive, accommodating non-traditional information sources, measures, and endpoints.

The attendees agreed that while existing chemical risk assessment and risk management frameworks may provide a starting point, the unique properties of nanomaterials adds a significant level of complexity to this process. The goals of this workshop included the identification of strategies and tools that could currently be implemented to reduce technical uncertainty and prioritize research to address the immediate needs of the regulatory and risk assessment communities. Such tools include advanced risk assessment, comprehensive environmental assessment, risk characterization methods, decision analysis techniques, and other approaches to help focus research and inform policymakers benefiting the world at large.



**Acknowledgments** We acknowledge the North Atlantic Treaty Organization (NATO) Science for Peace and Security Program, US Army Engineer Research and Development Center, US EPA Office of Research and Development, Rice University and Center for Biological and Environmental Nanotechnology, Copper Industry Association, American Chemistry Council, and University of Algarve, for providing financial and in-kind support for the Advanced Research Workshop. Permission was granted by the Chief of Engineers and NATO to publish this information. The views and opinions expressed in this paper are those of the individual authors and not those of the US Army, NATO, or other sponsor agencies.

## References

- AIST (2008) Research Center for Chemical Risk Management. A nanotechnology-claimed consumer products inventory in Japan. Available via DIALOG. [http://staff.aist.go.jp/kishimoto-atsuo/nano/e\\_link\\_text.htm](http://staff.aist.go.jp/kishimoto-atsuo/nano/e_link_text.htm)
- Balbus JM, Maynard AD, Colvin VL, Castranova V, Daston GP, Denison RA et al (2007) Meeting report: hazard assessment for nanoparticles—report from an interdisciplinary workshop. *Environ Health Perspect* 115:1654–1659
- BCC (2008) BCC research, nanotechnology—a realistic market assessment (Report identifier Nano31C). <http://www.bccresearch.com/report/NAN031C.html>
- Benn TM, Westerhoff P (2008) Nanoparticle silver released into water from commercially available sock fabrics. *Environ Sci Technol* 42(11):4133–4139. doi:10.1021/es7032718
- Borm PJA, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K et al (1996) The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol 3:1–35
- Casey A, Herzog E, Davoren M, Lyng FM, Byrne HJ, Chambers G (2007) Spectroscopic analysis confirms the interactions between single walled carbon nanotubes and various dyes commonly used to assess cytotoxicity. *Carbon* 45:1425–1432. doi:10.1016/j.carbon.2007.03.033
- Cedervall T, Lynch I, Foy M, Berggård T, Donnelly SC, Cagney G et al (2007a) Detailed identification of plasma proteins adsorbed on copolymer nanoparticles. *Angew Chem Int Ed* 46:5754–5756. doi:10.1002/anie.200700465
- Cedervall T, Lynch I, Lindman S, Nilsson H, Thulin E, Linse S et al (2007b) Understanding the nanoparticle protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc Natl Acad Sci USA* 104:2050–2055. doi:10.1073/pnas.0608582104
- Davies JC (2006) Managing the effects of nanotechnology. Woodrow Wilson International Center for Scholars Project on Emerging Nanotechnologies, Washington, DC 20004-3027. Available via DIALOG. [http://www.nanotechproject.org/process/files/2708/30\\_pen2\\_mngeffects.pdf](http://www.nanotechproject.org/process/files/2708/30_pen2_mngeffects.pdf)
- EC Scientific Committee on Emerging and Newly-Identified Health Risks (EC SCENIHR) (2007) Opinion on the appropriateness of the risk assessment methodology in accordance with the technical guidance documents for new and existing substances for assessing the risks of nanomaterials. B-1049 Brussels, Belgium. Available via DIALOG. [http://ec.europa.eu/health/ph\\_risk/committees/04\\_scenihhr/docs/scenihhr\\_o\\_010.pdf](http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_010.pdf)
- European Commission (EC) (2005) Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee: Nanosciences and nanotechnologies: an action plan for Europe 2005–2009. B-1050, Brussels. Available via DIALOG. [http://ec.europa.eu/research/industrial\\_technologies/pdf/nano\\_action\\_plan\\_en.pdf](http://ec.europa.eu/research/industrial_technologies/pdf/nano_action_plan_en.pdf)
- European Technology Platform (2006) Nanomedicine nanotechnology for health: strategic research agenda for nanomedicine. Office for Official Publications of the European Communities, Luxembourg. European Commission. <http://cordis.europa.eu/nanotechnology/nanomedicine.htm>
- Hansen SF, Maynard A, Baun A, Tickner JA (2008) Late lessons from early warnings for nanotechnology. *Nat Nanotechnol* 3:444–447. doi:10.1038/nnano.2008.198
- Holsapple MP, Farland WH, Landry TD, Monteiro-Riviere NA, Carter JM, Walker NJ et al (2005) Research strategies for safety evaluation of nanomaterials, part II: toxicological and safety evaluation of nanomaterials, current challenges and data needs. *Toxicol Sci* 88(1):12–17. doi:10.1093/toxsci/kfi293
- International Risk Governance Council (IRGC) (2005) White paper on risk governance: towards an integrative approach. By Ortwin Renn with Annexes by Peter Graham. CH-1219 Geneva, Switzerland. Available via DIALOG. [http://www.irgc.org/IMG/pdf/IRGC\\_WP\\_No\\_1\\_Risk\\_Governance\\_reprinted\\_version.pdf](http://www.irgc.org/IMG/pdf/IRGC_WP_No_1_Risk_Governance_reprinted_version.pdf)
- International Risk Governance Council (IRGC) (2006) White paper on nanotechnology risk governance. By Ortwin Renn and Mike Roco with Annexes by Mike Roco and Emily Litten. CH-1219 Geneva, Switzerland. Available via DIALOG. [http://www.irgc.org/IMG/pdf/IRGC\\_white\\_paper\\_2\\_PDF\\_final\\_version-2.pdf](http://www.irgc.org/IMG/pdf/IRGC_white_paper_2_PDF_final_version-2.pdf). (See publication: Renn O, Roco MC (2006) Nanotechnology and the need for risk governance. *J Nanopart Res* 8:153–191. doi:10.1007/s11051-006-9092-7
- International Risk Governance Council (IRGC) (2007) Policy brief: nanotechnology risk governance: recommendations for a global, coordinated approach to the governance of potential risks. CH-1219 Geneva, Switzerland. Available at: [http://www.irgc.org/IMG/pdf/PB\\_nanoFINAL2\\_2\\_.pdf](http://www.irgc.org/IMG/pdf/PB_nanoFINAL2_2_.pdf)
- Linkov I, Satterstrom K (2008) Nanomaterial risk assessment and risk management: review of regulatory frameworks. In: Linkov I, Ferguson E, Magar V (eds) Real time and deliberative decision making: application to risk assessment for non-chemical stressors. Springer, Amsterdam (in press)
- Linkov I, Steevens J (2009) Nanotechnology: risks and benefits. Springer, Amsterdam (in press)
- Linkov I, Satterstrom K, Corey L (2008) Nanotoxicology and nanomedicine: making hard decisions. *Nanomedicine* 4:167–171
- Lynch I, Dawson KA, Linse S (2006) Detecting cryptic epitopes in proteins adsorbed onto nanoparticles. *Science STKE* 327:pe14
- Lynch I, Cedervall T, Lundqvist M, Cabaleiro-Lago C, Linse S, Dawson KA (2007) The nanoparticle-protein complex as a biological entity: a complex fluids and surface science challenge for the 21st century. *Adv Colloid Interface Sci* 134–135:167–174. doi:10.1016/j.cis.2007.04.021

- Michaelis K, Hoffmann MM, Dreis S, Herbert E, Alyautdin RN, Michaelis M et al (2006) Covalent linkage of apolipoprotein E to albumin nanoparticles strongly enhances drug transport into the brain. *J Pharmacol Exp Ther* 317:1246–1253. doi:10.1124/jpet.105.097139
- NanoRoadMap EU 6th Framework (2005) <http://www.nanoroadmap.it/>
- National Nanotechnology Initiative (NNI) (2008) Strategy for nanotechnology-related environmental, health and safety research. Available via DIALOG. [http://www.nano.gov/NNI\\_EHS\\_Research\\_Strategy.pdf](http://www.nano.gov/NNI_EHS_Research_Strategy.pdf)
- Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. *Science* 311:622–627. doi:10.1126/science.1114397
- NNI (2004) Nanoscience research for energy needs. Report of the national nanotechnology initiative grand challenge workshop
- Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 113:823–839
- Petersen JL, Egan DM (2002) Small security: nanotechnology and future defense. *Def Horiz* 8:1–6
- Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A et al (2008) Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol* 3(7):423–428. doi:10.1038/nnano.2008.111
- Project on Emerging Nanotechnologies (PEN) (2008) A Nanotechnology Consumer Products Inventory. Woodrow Wilson International Center for Scholars. Available via DIALOG. <http://www.nanotechproject.org/inventories/consumer/>. Accessed March 2008
- Québec Commission de l'éthique de la science et de la technologie (QC) (2006) Position statement: ethics and nanotechnology: a basis for action. Québec G1V 4Z2. Available via DIALOG. <http://www.ethique.gouv.qc.ca/IMG/pdf/Avis-anglaisfinal-2.pdf>
- Responsible NanoCode (RNC) (2006) Workshop report: how can business respond to the technical, social and commercial uncertainties of nanotechnology? Available via DIALOG. [http://www.responsiblenanocode.org/documents/Workshop-Report\\_07112006.pdf](http://www.responsiblenanocode.org/documents/Workshop-Report_07112006.pdf)
- Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA (2007) Variables influencing interactions of untargeted quantum dot nanoparticles with skin cells and identification of biochemical modulators. *Nano Lett* 7:1344–1348. doi:10.1021/nl070375j
- Stone V, Johnston H, Clift MJ (2007) Air pollution, ultrafine and nanoparticle toxicology: cellular and molecular interactions. *IEEE Trans Nanobiosci* 6(4):331–340. doi:10.1109/TNB.2007.909005
- Theron J, Walker JA, Cloete TE (2008) Nanotechnology and water treatment: applications and emerging opportunities. *Crit Rev Microbiol* 34:43–69. doi:10.1080/10408410701710442
- The Royal Society and Royal Academy of Engineering UK (2004) Nanoscience and nanotechnologies: opportunities and uncertainties. Available online at <http://www.nanotec.org.uk/finalreport.htm>. Accessed 27 July 2008
- UK Department for Environment Food and Rural Affairs (UK DEFRA) (2006) UK voluntary reporting scheme for engineered nanoscale materials. London SW1P 3JR. Available at: <http://www.defra.gov.uk/environment/nanotech/policy/pdf/vrs-nanoscale.pdf>
- US Environmental Protection Agency (USEPA) (2007) Nanotechnology white paper. Prepared for the US EPA by members of the nanotechnology workgroup, a group of EPA's Science Policy Council
- US Food and Drug Administration (US FDA) (2007) Nanotechnology: a report of the U.S. food and drug administration nanotechnology task force. July 25, 2007. Available via DIALOG <http://www.fda.gov/nanotechnology/taskforce/report2007.html>
- Wiesner MR, Lowry GV, Alvarez P, Dionysiou D, Biswas P (2006) Assessing the risks of manufactured nanomaterials. *Environ Sci Technol* 40(14):4336–4345
- Wörle-Knirsch JM, Pulskamp K, Krug HF (2006) Oops they did it again! carbon nanotubes hoax scientists in viability assays. *Nano Lett* 6:1261–1268. doi:10.1021/nl060177c