Nanoparticle Safety – A Perspective from the United States

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1 Introduction

Nanotechnology has variously been described as a transformative technology, an enabling technology and the next technological revolution. Even accounting for a certain level of hype, a heady combination of high-level investment, rapid scientific progress and exponentially increasing commercialisation point towards nanotechnology having a significant impact on society over the coming decades. However, enthusiasm over the rate of progress being made is being tempered increasingly by concerns over possible downsides of the technology, including unforeseen or poorly managed risk to human health.[1–4] Real and perceived adverse consequences in areas such as asbestos, nuclear power and genetically modified organisms have engendered increasing scepticism over the ability of scientists, industry and governments to ensure the safety of new technologies. As nanotechnology moves towards widespread commercialisation, not only is the debate over preventing adverse consequences occurring at an unusually early stage in the development cycle, but it is expanding beyond traditional knowledge-based risk management to incorporate public perception, trust and acceptance.[5–8]

Within this context, the long-term success of "nanotechnologies" (referring to the many specific applications and implementations of nanotechnology) will depend on rational, informed and transparent dialogue aimed at understanding and minimising the potential adverse implications to human health and the environment. A central question within this dialogue, and one that has been raised in the popular media as well as in the peer-reviewed press, is "how safe is nanotechnology?".[2,3,9–13,] Of course, "safe" is relative, and needs to be understood in the context of specific nanotechnologies and their applications. Nevertheless, there is an increasing desire to understand the potential risks associated with emerging technologies, and how they might be managed to ensure the benefits outweigh any downsides. This paper provides a perspective on current

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activities within the USA addressing "safe" nanotechnology – including potential risks associated with the production and use of engineered nanoparticles.

2 The US National Nanotechnology Initiative

In many ways, the USA has been a leader in international interest in nanotechnology. Through the late 1990s an Interagency Working Group on Nanotechnology (IWGN) was active in promoting research and development in this area.[14,15] In 2001, the Clinton administration raised nanoscience and technology to the level of a national initiative, and the US National Nanotechnology Initiative (NNI) was formally established. Under the auspices of the National Science and Technology Council (NSTC), the NNI was to coordinate nanotechnology-related research across federal agencies. Although the NNI lacked (and still lacks) authority to allocate research funding, its formation stimulated research across the federal government, and has led to an increase in nano-specific research and development funding, from \$464 million in 2001 to an estimated \$1301 million in 2006.[16]

The role of the NNI was further formalised in 2003 through the signing of the 21st Century Nanotechnology Research and Development Act.[17] Through the Nanoscale Science, Engineering and Technology (NSET) subcommittee of NSTC, specific charges were given to agencies operating within the NNI. As well as addressing new research underpinning the application and commercialisation of nanotechnology, the Act also raised the issue of societal impact. Section 2(B) 10 of the Act covers responsibility for

> "ensuring that ethical, legal, environmental, and other appropriate societal concerns, including the potential use of nanotechnology in enhancing human intelligence and in developing artificial intelligence which exceeds human capacity, are considered during the development of nanotechnology".

This is to be achieved through establishing appropriate research programs and interdisciplinary research centres, integrating research on societal, ethical and environmental concerns with nanotechnology research and development, and providing for public input and outreach.[17] Although there is a heavy emphasis on ethical, legal and other social implications, the Act does encompass environmental, safety and health implications of emerging nanotechnologies.

A commitment to addressing potential societal impacts of nanotechnology within the US federal government was further emphasised with the publication of the NNI strategic research plan in 2004.[18] The plan outlined four broad goals, and seven Program Component Areas, forming the basis of a strategic and reviewable plan. While fundamentally focused on the development and applications of nanotechnology, a commitment to address the

> "societal dimensions related to the development of new technologies, including the potential implications for health and the environment, and the importance of dialogue with the public"

was emphasised by John H. Marburger III, the Director of the Office of Science and Technology Policy.[18] In the plan, this commitment was supported by one specific goal addressing the responsible development of nanotechnology, and a broader Program Component Area addressing societal dimensions of nanotechnology.

Since 2003, activities within the NNI addressing the environmental and health implications of nanotechnology have largely been coordinated through the Nanotechnology Environmental and Health Implications (NEHI) working group. The working group aims to support federal activities to protect public health and the environment through exchanging information across federal agencies, facilitating the identification, prioritisation and implementation of research and promoting the communication of information on the environmental and health impact of nanotechnology to other government and non-government groups. Agencies participating in NEHI include risk-based research and regulatory agencies such as the National Institute for Occupational Safety and Health (NIOSH), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the Consumer Product Safety Commission (CPSC). A number of other agencies with research capabilities in addressing potential risk, or an interest in risk management, also participate, including the Department of Energy (DOE), the Department of Defense (DOD), the National Institutes of Health (NIH) and the National Science Foundation (NSF).

3 Federal Government Activities in Support of "Safe" Nanotechnology

While the NEHI has provided an effective forum for government agencies to exchange notes and experiences, there has been little direct output visible from the working group since its inception. In the light of the NEHI's coordinating function, much of the group's work is reflected in agency plans and initiatives. Certainly, a number of US federal agencies have developed a position on nanotechnology and have instituted internal nanotechnology programs since joining NEHI. What the working group has contributed to directing strategic risk-related research across the federal government is harder to judge. The first overt step in this direction was anticipated later in 2006, when the NEHI planned to release a report on strategic research needs and directions.[†]

One area that NEHI has contributed to is collating information on nanotechnology risk-based research funding levels. As reported in the 2006 NNI supplement to the President's budget,[16] federal agencies were planning to spend \$38.5 million on research into the environmental, safety and health impact of nanotechnology between 2005 and 2006 (Table 1). Over 60% of this funding resides in agencies focused on basic research, with approximately 25% being

[†] In September 2006, NSET published the report "Environmental, health and safety research needs for engineered nanomaterials"

Table 1 Estimated US annual investment in research and development with relevance to the environmental, safety and health implications of engineered nanomaterials (in millions of dollars). Comparing estimated from the National Nanotechnology Initiative,[a] and the Project on Emerging Nanotechnologies (PEN)[b].

Agency	*NNI-estimated investment 2005/2006*	*PEN-estimated investment, 2005 (any relevance)*	*PEN-estimated investment, 2005 (highly relevant)*
NSF	24.0	19.0	2.5
DOD	1.0	1.1	1.1
DOE	0.5	0.3	0
HHS (NIH)	3.0	3.0[c]	3.0[c]
DOC (NIST)	0.9	1.0	0
USDA	0.5	0.5	0
EPA	4.0	2.6	2.3
HHS (NIOSH)	3.1	3.1[d]	1.9[e]
DOJ	1.5	0	0
Totals	38.5	30.6	10.8

[a]NSET, The National Nanotechnology Initiative, Research and development leading to a revolution in technology and industry. Supplement to the President's FY2006 budget, Nanoscale Science Engineering and Technology subcommittee of the NSTC, 2005.
[b]PEN, Inventory of research on the environmental, health and safety implications of nanotechnology, Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, 2005.
[c]Estimate, based on research within the National Toxicology Program.
[d]Based on aggregated funding. Reported by NNI.
[e]Estimated from the percentage of projects highly relevant to engineered nanomaterials.

associated with agencies directly addressing risk evaluation and management. These figures are somewhat lower than initial estimates of $100 million per year[19], which included research having incidental relevance to risk.

Three agencies within this list have coordinated research programs addressing the health, safety and environmental implications of nanotechnology: NIH, NIOSH and EPA. Risk-related research within NIH is predominantly administered within the National Institute of Environmental Health Sciences (NIEHS), which oversees the national Toxicology Program (NTP) – a collaboration between NIEHS, NIOSH and FDA.[20] In 2003, a group of nanoscale materials was nominated to the NTP for testing. Research is currently underway within the NTP Nanotechnology Safety Initiative to address the potential human hazards associated with the manufacture and use of nanoscale materials. The intent is to conduct studies that test hypotheses focused on the relationship of key physicochemical parameters of selected nanomaterials on their toxicity. These currently include the dermal toxicity of materials such as titanium dioxide and zinc oxide, the pulmonary toxicity of single-walled carbon nanotubes and systematic studies of the toxicity of quantum dots, fullerenes and related compounds.

The National Institute for Occupational Safety and Health has been active in disseminating information on nanotechnology in the workplace and it has been actively addressing research and information needs for some years. Current research within the agency that has some relevance to nanotechnology is estimated at approximately \$3 million per year.[16] This research covers the toxicity and health impact of nanomaterials (including carbon nanotubes), exposure evaluation, exposure control and good working practices. In 2005, the agency published a draft strategic research plan for nanotechnology in the workplace that outlined current needs and the agency's plans to address those needs.[21] At the same time, the agency published a draft document entitled "Approaches to safe nanotechnology. An information exchange with NIOSH".[22] This document outlines many of the concerns over engineered nanomaterials in the workplace and the current state of knowledge regarding potential risk and risk assessment/reduction. The National Institute for Occupational Safety and Health has also demonstrated a commitment to studying exposure to engineered nanomaterials in the workplace, and at the end of 2005 the agency announced a program of field studies to be conducted in partnership with industry.[23]

The Environmental Protection Agency started to fund extramural research into the environmental applications and implications of nanotechnology in 2001. Under the Office of Research and Development Science To Achieve Results (STAR) program, the agency has awarded over 32 grants addressing the environmental applications and implications of nanotechnology, worth over \$10 million.[24] In recent years, EPA has been partnering with agencies such as NIOSH, NSF and NIEHS to increase the scope and extent of this research program. As of 2005, estimated funding within EPA into the environmental applications and implications of nanotechnology was \$4 million per year.[16] In 2006, a further \$4 million per year was requested by EPA to support intramural research into nanotechnology and the environment.[25] A draft white paper was published by EPA in December 2005, which provides an idea of the issues the agency considers important and which may receive attention through this new funding.[24]

Gaining further insight into the nature and extent of the research represented in Table 1 is not easy, as the NNI does not release information on specific research projects. One reason cited for not releasing specific information is the difficulty and complexity in identifying research that might have some relevance to risk, and the danger of either over- or under-estimating the extent to which relevant research is being funded. However, information on what is and is not being done is clearly essential to strategic research planning, especially if future risk-related research is to target critical knowledge gaps. In 2005, the Wilson Center Project on Emerging Nanotechnologies (PEN) sought to clarify the research landscape by compiling a publicly accessible on-line inventory of current risk-related research relevant to nanotechnology.[26] Published information on federally funded research was classified by relevance to an understanding of risk, category of nanomaterials (engineered, incidental or natural) and impact sector (human health, environment or safety). This enabled a sophisticated analysis of current research of relevance to the implications of engineered nanomaterials. It also allowed research trends to be explored, and research gaps to be identified.

In Table 1, estimates of annual federal funding for nanotechnology environmental, safety and health research from the PEN analysis are compared with the NNI figures. The comparison is confounded by slightly different reporting periods and a reticence within some agencies to provide detailed information on current research. However, the figures provide a reasonable indication of current activity. Research with some relevance to risk includes research into nanotechnology applications which might also be relevant to understanding health, safety and environmental impacts, while highly relevant research only includes projects specifically focused on understanding risk. Reported funding of research with some relevance to risk matches NNI figures reasonably well. However, identified funding for research that is highly relevant to risk is only \$11 million per year – less than 1% of the annual US nanotechnology R&D budget. Although not conclusive, comparison of the NNI and PEN figures suggests only one third to one quarter of reported NNI funding into the environmental safety and health implications of nanotechnology has a high degree of relevance to these specific risk issues.

Although funding levels are a useful indicator of activity, an analysis of how these funds are being used provides greater insight into the relevance of current research. Research listed in the PEN inventory indicates that there is little to no strategic direction to risk-based research in the USA. For example, an analysis of research into impact according to different exposure routes indicated a heavy emphasis on inhalation and a negligible emphasis on ingestion – even though inhaled and intentionally eaten nanomaterials will enter the gastrointestinal tract.[27]

The concern that engineered nanomaterials might behave differently from conventional materials has sparked debate over the applicability of oversight and regulatory mechanisms in the USA. The established position of the US government is that the current regulatory framework is sufficiently robust to accommodate emerging nanotechnologies and engineered nanomaterials, although some changes at an operational level may be required.[28] However, individual regulatory agencies are beginning to consider their response to emerging nanotechnologies, engineered nanomaterials and nano-enabled products. The Environmental Protection Agency began development of a voluntary program for industry in 2005,[24] which would require participants to provide existing information and generate new information on the potential health and environmental impact of engineered nanomaterials. The Food and Drug Administration held a public meeting in October 2006 to gather information about current developments in uses of nanotechnology materials regulated products. The Consumer Product Safety Commission released a statement in 2005 outlining the agency's mission and authority and highlighted some of the challenges facing the regulation of nanotechnology-based products.[29]

An independent report published in 2006 by J. Clarence Davies calls into question the robustness of current regulatory frameworks in the USA when applied to nanotechnology.[4] Written with the aim of stimulating dialogue at a critical time for nanotechnology, Davies cites the inability of chemical or physical properties alone to predict the behavior of nanomaterials as a rationale for considering new nano-specific regulation. He concludes that nanotechnology is difficult to address using existing regulations, that a new law may be required to manage potential risk and that new mechanisms and institutional capabilities are required.

While it is still uncertain how the oversight of nanotechnology will develop within the USA, it remains a focus of serious consideration within the federal government. Hearings of the House Science Committee in November 2005 and the Senate Committee on Commerce, Science and Transportation in February and May 2006 have all addressed nanotechnology oversight, and further hearings addressing the implications of nanotechnology are planned.

4 Industry and Other Non-government Activities in Support of "Safe" Nanotechnology

The non-government community in the USA continues to be active in addressing the safety of nanotechnology. Some activities – such as the development of standards, information dissemination and research coordination – are proceeding within an international context. Others are more focused on what is happening within the USA, but which will also have an international impact. In general it is clear that different stakeholders recognise a need to ensure the risks of new nanotechnologies are minimised.

A 2006 report from the RAND Corporation on nanomaterials in the workplace synthesised the perspectives of many nanotechnology stakeholders, concluding that "public and private resources and funds being allocated to understanding the occupational, health, and environmental risks of emerging nanomaterials are not commensurate with the development of new nanomaterials".[30] The same report underlines the need to address risk in a coordinated and strategic manner if nanotechnology-based enterprises are to succeed. Industry-led groups, such as the Chemical Industry/Semiconductor Industry Consultative Board on Advancing Nanotechnology, have outlined research gaps that need to be filled in support of "safe" nanotechnology.[31] Environmental Defense – a non-profit organisation seeking scientifically sound and sustainable solutions to environmental issues – has called for substantially increased and sustained government support of environmental, safety and health research and development in the field of nanotechnology.[32]

The group has also been working with industry to develop sustainable solutions to "safe" nanotechnology. For instance, in October 2005 they announced a collaboration with DuPont to develop a framework for the "responsible development, production, use and disposal of nano-scale materials". DuPont is also actively supporting research into assessing and managing potential risks associated with engineered nanomaterials. As well as a productive in-house research program, they are leading an industry-based research collaboration to develop a better understanding of the behaviour of airborne nanostructured particles, and how to measure and prevent exposure effectively.[33] Further non-government-led initiatives are emerging within multi-stakeholder groups such as the International Council On Nanotechnology (ICON). Bringing government and non-government stakeholders together, ICON is active in addressing relevant risk-related issues within the context of a broad community. In 2005 the Council published a web-based database of peer review publications relevant to nanotechnology and risk, with the intention of summarising and synthesising information into an easily accessible knowledge base.[‡] Research supported by ICON is currently examining good practices for working with engineered nanomaterials, including what is currently being done and what needs to be done.

ICON members and others are also closely involved in nanotechnology standards development. While standards development is occurring at an international level, it is currently playing an important role in addressing "safe" nanotechnology within the USA. In 2005 the International Standards Organization (ISO) formally established Technical Committee 229 to address nanotechnology standards. This Technical Committee currently has three working groups addressing terminology and nomenclature, measurement and characterisation and health, safety and environmental aspects (the latter is being coordinated from the USA through the American National Standards Institute). In parallel with this effort, ASTM International Technical Committee E56 is developing international nanotechnology standards that include management of environmental occupational health and safety risk, and product stewardship. Prior to either technical committee being established, ISO TC146 began work on a Technical Report addressing the measurement of airborne exposure to nanostructured particles in the workplace. This report was approved for publication early in 2006.[34]

Taking a broader perspective on nanotechnology and science policy within the USA, the Project on Emerging Nanotechnologies was established in 2005 with the aim of bringing stakeholders together in a dialogue to develop sound policy, relevant research and safe practices. A partnership between the Woodrow Wilson International Center for Scholars (established in 1968 by Congress as a non-partisan living memorial to President Woodrow Wilson) and the Pew Charitable Trusts, the Project has been influential in raising awareness of the potential benefits and risks of emerging nanotechnologies and in enabling a broad dialogue on research and policies to underpin sustainable nanotechnologies. In 2006, the Project released the first publicly available on-line inventory of nanotechnology-based consumer products, to inform people about how this technology is entering their lives, and to support informed nanotechnology risk research and policy decisions (Figure 1). The Project on Emerging Nanotechnologies is currently one of the most widely cited sources of information in the USA on the responsible development and implementation of nanotechnology.

5 Looking to the Future – Ensuring the Development of "Safe" Nanotechnology

Reviewing current US activities in support of "safe" nanotechnology, it is clear that there is recognition of the need to address risk and a willingness to act to a

[‡] http://icon.rice.edu/research.cfm.

Figure 1 A cross-section of manufacturer-identified nanotechnology consumer products available now. An on-line inventory hosted by the Wilson Center Project on Emerging Nanotechnologies lists over 200 products globally[§,40] © 2006 David Hawkshurst/Woodrow Wilson International Center for Scholars.

certain degree on this recognition. However, there remains a dearth of information on risk and risk management. An analysis of nanotechnology risk research gaps from diverse organisations and sectors highlights how little is still known about the impact of the technology on human health and the environment and how much more research is needed.[3,21,24,31,32,35–38] The cross-disciplinary nature of nanotechnology requires risk-based research that transcends traditional boundaries. This in itself challenges conventional ways of doing science and suggests the need for an overarching strategic research framework. In addition, risk-based research must ultimately be applied to ensuring that people and the environment are not harmed, and this requires a close association between research and oversight. Finally, sufficient resources are required to carry out effective research, including facilities, personnel and research funds. An examination of current US activities suggests little or no strategic coordination, no clear link between research and oversight and insufficient resources to make a significant difference. While it is perhaps disingenuous to surmise that the current emphasis on getting the environmental safety and health aspects of nanotechnology right is little more than window dressing, it is clear that more needs to be

[§] www.nanotechproject.org/consumerproducts.

done if a serious attempt is to be made to understand and minimise risk early on in the technology's development and implementation.

Looking to the future of "safe" nanotechnology within the USA and globally, it is useful to consider what a viable strategic research framework might look like. An effective framework for strategic nanotechnology risk-based research is likely to have a number of attributes. It will provide a link between the implementation of nanotechnologies and the research necessary to ensure appropriate oversight of risk; it will ensure coordinated direction of research within different agencies and organisations at a national level; it will enable coordination and partnerships between international initiatives; it will allow resources to be allocated appropriately to address critical issues; and it will provide broad strategic research priorities for assessing and managing potential risk. A successful research framework that underpins sustainable nanotechnologies will also be responsive to the increasing sophistication of these technologies, and will evaluate progress against needs through review and revision.

Who should be responsible for such an overarching framework? Industry stands to gain a lot from nanotechnology according to some sources.[39] It is certainly in industry's best interest to ensure that appropriate strategic research frameworks are put in place in order to maintain public and commercial confidence in their products, as well as to minimise the chances of adverse impacts. However the question that must be addressed first and foremost is: What is in the best interest of the society and environment in which we live? Conceptually, this does not seem an appropriate question for industry to take the lead on. Perhaps more pragmatically, while industry has been shown to be more than capable of directing and funding research that addresses product-specific risk, it is difficult to find an economic justification for having industry lead in developing a basic understanding of risk.

The most viable alternative to an industry-led strategic research framework is a government-led framework. A strategic research framework developed and administered by the government would combine societal accountability with a high-level overview of research needs, a capacity for addressing generic and applied issues and a facility for partnerships and coordination. It can also be argued that the federal government has a social responsibility for developing and implementing an effective strategic research framework. The US federal government is investing a lot of money into nanotechnology research and development – over $1 billion dollars a year.[16] With this investment comes a certain degree of social responsibility – to ensure new risks associated with resulting technologies are assessed and managed appropriately. This is a responsibility to people who may be directly or indirectly affected by new risks. It is also a responsibility to the business community, who need to know the social and technical risks associated with the technologies they are being encouraged to develop.

Assuming that the US government were to develop and implement a strategic research framework addressing the environmental, safety and health implications of nanotechnology, the central pillars of a workable strategy would most likely include:

Linking research to oversight. Ultimately, the aim of a strategic risk-related research framework will be to minimise and manage risk through applying existing knowledge and developing new knowledge. However, this work will be ineffective in the long term if research is not linked to oversight, whether this takes the form of regulation, voluntary programs, best practices or other risk management tools and approaches.

Balancing basic and applied research. Answers to short-term critical research questions require applied research, while understanding mechanisms of risk and risk management must be underpinned by basic (or pure) research. Both modes of research have their place. However, an effective strategic research framework will ensure that the types and models of research are employed to match real-world research needs.

Authority to direct and support research. An effective strategic research framework must have teeth. It will not be sufficient merely to suggest areas of research to respective agencies or to rely on agency resources to support the necessary research. While a certain level of autonomy must be directed to research organisations, an effective strategic research framework will include mechanisms that ensure work is done by the appropriate organisations, and that resource levels are adequate to the task.

Coordination and partnership. As well as directing and coordinating research within the federal government, a strategic research framework will only be successful if it includes provisions to coordinate and partner with industry, international governments and non-government organisations. With such provisions, international resources – both private and public – may be brought to bear with maximum effect and minimum redundancy in managing new risks associated with emerging nanotechnologies.

Whether such a strategic framework will emerge within the USA, or indeed globally, is not yet clear. However, it probably is not too great an exaggeration to say that the long-term health of nano-businesses, as well as the people they employ and who use their products, will depend on well-funded and appropriately directed research into understanding and minimising the risks of emerging nanotechnologies.

Update

Nanotechnology is a rapidly developing field and inevitably, any overview of activities is out of date almost before it is completed. Since this chapter was written, industry, government and other organizations based in the US have made significant strides to frame the challenges and opportunities being faced. Notable highlights include a list of environmental, safety and health research needs published by the NSET subcommittee in September 2006,[41] publication of the EPA white paper on nanotechnology in early 2007,[42] and publication of the DuPont/Environmental Defense Nano Risk Framework in 2007.[43] These and other activities are helping to clarify what needs to be done to ensure the success of nanotechnologies through understanding and avoiding potential risks. However, strategic action to ensure the safe use of engineered nanoparticles remains slow in coming. A report from the Project on Emerging Nanotechnologies published in July 2006 outlined a potential research strategy for the US to address short, medium and long-term challenges.[44] This was complemented by a paper published in Nature later in 2006, co-authored by 14 internationally recognized scientists, outlining five "grand challenges" to addressing potential nanotechnology risks.[45] In March 2007, the UK Center for Science and Technology urged the UK government to take "swift and determined action necessary to regain its leading position in nanotechnologies".[46] This is a message that seems as relevant to the United States as it is to any country hoping to reap the potential benefits of engineering particles at the nanoscale.

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