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SPECIAL FOCUS: GOVERNANCE OF NANOBIOTECHNOLOGY

Recommendations for oversight of nanobiotechnology: dynamic oversight for complex and convergent technology

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Abstract Federal oversight of nanobiotechnology in the U.S. has been fragmented and incremental. The prevailing approach has been to use existing laws and other administrative mechanisms for oversight. However, this "stay-the-course" approach will be inadequate for such a complex and convergent technology and may indeed undermine its promise. The technology demands a new, more dynamic approach to oversight. The authors are proposing a new oversight framework with three essential features: (a) the oversight trajectory needs to be able to move dynamically between "soft" and "hard" approaches as information and nano-products evolve; (b) it needs to integrate inputs from all stakeholders, with strong public engagement in decision-making to assure adequate analysis and transparency; and (c) it should include an overarching coordinating entity to assure strong inter-agency coordination and communication that can meet the challenge posed by the convergent nature of nanobiotechnology. The proposed framework arises from a detailed case analysis of several key oversight regimes relevant to nanobiotechnology and is informed by inputs from experts in academia, industry, NGOs, and government.

The views expressed are those of the authors and do not necessarily reflect the views of NSF.

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Introduction

Nanoscale science and technology operate at the scale of approximately 1–100 nm, where structures, devices, and systems have novel functions and properties because of their size (EPA 2009b). Nanotechnology grows out of a number of scientific fields including chemistry, biology, physics, optics, and mechanics and is seen by many as the "next industrial revolution" (Maynard 2006). While commercial applications of the current generation of nanotechnologies have mostly focused on so-called "passive" nanostructures (including nanostructured materials, coatings, and paints), the next generation of increasingly sophisticated and "active" nanotechnologies and nanostructures (Subramanian et al. 2010) is leading to increased convergence between nanotechnology, biotechnology, information technology, and cognitive science (such as nanobiological sensors, nano-mechanisms for drug delivery, and nanoelectronics).

Nanobiotechnology specifically refers to nanotechnology designed for use within biological systems, in which nanomaterials are biologically active, integrate biological entities (e.g., large molecules such as proteins or DNA), or mimic biological systems. Many nanobio materials and systems will exhibit complex properties and interactions, as nanotechnology converges with biotechnology. Examples include nanoformulations of drugs (that may take advantage of nanomaterials' ability to cross the blood–brain barrier), nano-vectors in gene transfer research (often called "gene therapy"), and nanoparticles designed to seek out, bind to, and image cancerous micro-metastases and then ablate them with radiation.

These developments are expected in the next two decades. Such transitions will result in qualitative and quantitative changes in risk (Breggin and Carothers 2006). Therefore, the promise of nanobio will only be fully realized under responsible oversight regimes developed with inputs from all stakeholders to assure adequate analysis, safeguards, and transparency. If nothing else, we have learned from history that technologies and innovation suffer when there is a lack of confidence in oversight systems (as in the case of genetically modified foods) and when adverse environmental or health effects are reported (as in the case of gene therapy).

Nanobiotechnology challenges existing systems of oversight for laboratory research, occupational and environmental health, ecological systems, human subjects research, manufacturing, marketed products, and disposal. The diversity and complexity of nanobio materials, which may combine functionalities and integrate multiple technological domains, pose fundamental challenges. First, much remains unknown about nanobio materials characteristics and how those characteristics compare to bulk forms of the same materials. Further, nanobio materials are often engineered to perform certain tasks, such as drug delivery, gene delivery, sensing and signaling metabolic changes, making tissue visible on imaging, or enabling destruction of cancer cells using targeted radiation. Yet there is much we may not know about the unanticipated behavior of these materials in the human body, such as effects on laboratory workers, patients and research participants, their close contacts, and environmental effects.

Developing adequate toxicological assessment strategies is a challenge. Moreover, assessing risks of nanomaterials using conventional paradigms (such as chemical or microbial risk assessment) may not be sufficient to capture all the dimensions of risk of an active nanobio material, as risk may arise not only from its inherent material toxicity but also from its interactions with complex biological systems. A core challenge for nanobio oversight is finding the appropriate balance between supporting innovation and maintaining public health and safety. Scientists, policy makers, and the public are beginning to weigh in on measures to ensure responsible development of nanotechnology that protects public health and safety (Paradise et al. 2008).

The emergence of nanotechnology is challenging the capacity of the U.S. federal agencies to provide oversight. Key agencies including the Food and Drug Administration (FDA), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA), the National Institutes of Health (NIH), and the U.S. Department of Agriculture (USDA) are struggling to evaluate a wide range of nanomaterials and nanoproducts. Over 1000

products are already on the market and $2.6 trillion in global manufactured goods will incorporate nanotech by 2014 (Lux Research 2007). Yet adequate evaluation of the safety, human health effects, and environmental impacts of many of these materials and products is still in its infancy.

This article addresses the oversight challenges posed by emerging nanobio materials, focusing on the challenges posed to those U.S. federal oversight authorities most directly implicated. While all face major challenges with the growth of nanobio, they vary considerably in their response to date. For example, while FDA, NIOSH, and EPA have addressed the challenge, albeit in different ways, USDA does not seem to be publicly examining their oversight authority although they are planning to fund some risk assessment research on nanotechnology.

The agencies most directly implicated by nanobio are only a subset of all agencies affected by developments in nanotechnology more broadly. The National Nanotechnology Initiative (NNI) (www.nano.gov), which began in 2001, operates under the aegis of the National Science and Technology Council (NSTC), a Cabinet-level entity. NNI coordinates among approximately 25 federal departments and agencies. NNI focuses on research and development, but has also examined societal implications of nanotechnology. The focus in this article will be on the "bio" portion of the nanotechnology challenge.

As the reach of the NNI suggests, nanobio challenges not only individual federal agencies, but also multiple agencies that should act together. A nano-vector to deliver genetic material in gene transfer research in human beings, for example, will involve the concerns of FDA, NIH, OSHA and NIOSH, and EPA. This raises significant jurisdictional and coordination problems. Yet we have no Coordinated Framework, as we do have for the multi-agency oversight of genetically engineered organisms (GEOs) in the food supply (OSTP 1986).

Some federal agencies are already grappling with the question of whether they should use existing oversight frameworks or create new ones. Agency oversight actions focused on nanobio to date have ranged from very little to voluntary approaches, and, in some cases, a gradual shift to more mandatory approaches. However, the response to the oversight challenge is in large part a "stay the course" approach that urges the use and adaptation of existing oversight mechanisms for nanobio products and has met with widespread criticism (Davies 2009). It also confuses certain stakeholders: how can nanotechnology, and nanobio more specifically, be touted as a revolutionary technology destined to help treat cancer, improve human health, change manufacturing, deliver chemicals with more precision, and remediate pollution, but, at the same time, be "nothing new" from a regulatory perspective?

This minimal response to the oversight challenge has been widely criticized; a number of organizations and academics have called for a more robust oversight approach with varying recommendations. Table 1 presents a roster of the key reports and articles, briefly encapsulating their recommendations. However, most of these recommendations have had little discernable impact on federal actions to date. In part this may be due to a lack of agency resources and the need for greater expertise in nanotechnology (and nanobio in particular). It may also reflect real agency uncertainty about how to generate the information needed on nanomaterials to evaluate them. The complexity of many nanomaterials, including those that combine multiple technologies and thus are convergent, will only increase the uncertainty. As noted above, convergent technologies may implicate multiple oversight agencies, creating confusion. Importantly, there have been no major public health disasters that could prompt an outcry for "reform."

This article presents recommendations that grew out of a 4-year project on "Evaluating Oversight Models for Active Nanostructures and Nanosystems: Learning from Past Technologies in a Societal Context," funded by the National Science Foundation (NSF). The authors are the project investigators plus two key researchers on the project team. The authors convened a multi-disciplinary group of experts, who served on the project's Working Group and Advisory Group. These individuals are listed alphabetically in Table 2 (with their institutions listed for identification only). They made vital intellectual contributions to this project. Note that listing an individual as a project member below does not necessarily mean that he or she agrees with the recommendations offered in this article.

Collaborating with the Working Group and Advisory Group, key criteria by which to evaluate oversight systems for emerging technology were

Table 1 Inventory of proposed approaches to nanotechnology oversight, 2003–2009

Year	Author/proponent	Basic approach	Core recommendations
2009	J. Clarence Davies	New department-level institution	• The government should develop a new Cabinet-level organization • The new body should combine the functions of and replace EPA, NOAA, NIOSH, and several other agencies • It should provide integrated oversight on products, pollution, and the workplace, plus risk research, technology assessment, and health and environmental monitoring • Oversight should be product-based and cover products' life-cycles
2008	Suellen Keiner	State and local oversight	• State and local governments should develop nanotech oversight initiatives using the legal authority granted them by federal laws such as the Clean Air Act
2008	Gary Marchant, Douglas Sylvester, Kenneth Abbott	Incremental regulation	• A flexible and evolutionary approach emphasizing decentralized regulatory measures, such as self-regulation, should be used for nanotech in the near term • As the public becomes familiar with nanotech, government can begin to implement some regulations through a transparent and participatory process
2008	Mihail C. Roco	Transforma-tional governance	• Use a transformational model of governance: organizations and processes should focus on the ways in which converging technologies (e.g., nanotech, biotech, cognitive science) can have more significant effects on the economy, health, and society when combined • This governance approach has four main components: investment policies, science/technology and business policies, education and workforce training, and transformational tools • Nanotech governance should focus on the transformational potential of converging technologies, account for unforeseen consequences, include multi-stakeholder participation, and combine real-time assessments with long-term planning
2008	Ahson Wardak, Michael E. Gorman, Nathan Swami, Shilpa Deshpande	Expert elicitation method-ology	• Framework to identify the potential risks of nano-products by eliciting experts in five fields (environmental sciences, toxicology, chemistry, material sciences, and technology policy) to determine the probability and severity of risks, identify risk-enhancing nanoparticle properties, and develop "use and disposal scenarios" to identify risk vectors • This expert elicitation methodology should be incorporated into an anticipatory risk governance approach to nanotech
2007	DuPont and Environmental Defense	Voluntary NanoRisk Framework	• Presents a voluntary system designed to provide organizations with guidance on the responsible development, use, handling, and disposal of nanoscale materials • The Framework also lays out a system for generating and communicating new risk data as they becomes available

Table 1 continued

Year	Author/proponent	Basic approach	Core recommendations
2007	Mark Greenwood	Product-specific oversight	• Government, industry, NGOs, researchers, and other stakeholders should take a systematic approach to nanotech oversight, initially focusing on products containing nanomaterials and related production processes • Risk criteria should initially be based on existing toxicology of bulk substances, with new testing methods developed over time for active nanostructures • Risk management practices should focus on products' life-cycles
2007	International Center for Technology Assessment and Friends of the Earth	NanoAction principles	• Developed by a coalition of civil society, environmental, labor, and public interest groups, these are eight fundamental principles for effective oversight of nanotech: use of the precautionary principle, mandatory nano-specific regulations, health and safety protections for workers and the public, environmental protections, transparency, public participation, attention to broad impacts, and manufacturer liability
2007	Igor Linkov, F. Kyle Satterstrom, Jeffery Steevens, Elizabeth Ferguson, Richard C. Pleus	Multi-criteria decision analysis	• Multi-criteria decision analysis (MCDA) is an approach for decision makers to reconcile conflict among stakeholder groups through a transparent process • First, policy decision makers and the public, industry, and interest groups participate in a process of identifying potential nanotech problems, management alternatives, and values/priorities. Management alternatives are ranked according to these priorities • Next, scientists and engineers join the policy makers and other stakeholders to methodically eliminate those alternatives that are not feasible due to costs, technical limitations, societal rejection, etc • If the decision groups' priorities or technical information change, they are fed into the process again for new outcomes
2006	Kenneth Abbott, Gary Marchant, Douglas Sylvester	Nanotech framework convention	• An international framework convention for nanotech should be adopted • The convention should include an intergovernmental scientific advisory committee charged with producing and assessing information in areas of uncertainty
2006	Diana M. Bowman, Graeme A. Hodge	Modified pyramid method	• Regulators should employ a variety of decentralized "soft law" mechanisms, such as guidelines grounded in public policy and international norms, to address nanotech concerns • This model is based on the Ayres and Braithwaite regulatory pyramid, a model that emphasizes self-regulation above command-and-control measures
2006	Foresight Nanotech Institute	Self-assessment scorecards	• These guidelines offer "self-assessment scorecards" to help researchers, industry, and regulatory agencies develop practices with sound scientific backing that address environmental, security, ethical, and economic issues

Table 1 continued

Year	Author/proponent	Basic approach	Core recommendations
2006	International Risk Governance Council	Integrated nanotech risk governance	• First distinguish nanotech products and processes by their level of complexity (e.g., passive versus active) • Next, evaluate risk for both groups, focusing on hazard and exposure for passive nanostructures and risk perception for active nanostructures • Third, assess the potential benefits and risks of each group based on current knowledge • Finally, select strategies to prevent and control risks
2006	Gary Marchant, Douglas Sylvester	Trans-national regulation	• Nanotech should be regulated transnationally through international agreements on environmental pollutants, non-proliferation and arms control agreements, global ethics treaties, framework contentions, and customary international law
2006	Mark E. Meaney	Integrated decision-making framework	• This model is based on the Integrative Decision-Making Framework, or D4P4, designed for decision-making in arenas where there are many stakeholder groups with diverse interests and unstable, changing conditions • First, stakeholders should select a nanotechnology issue that needs to be addressed • Second, stakeholders should explore the ethical principles of responsible nanotechnology development, starting with their own values • Third, identify the people and places connected to those principles (e.g., consumers or lake ecosystems) • Fourth, design a program that can positively affect those implications (e.g., education programs, testing protocols • Finally, have representatives from the five "knowledge cultures" (individuals, community leaders, specialists, organization strategists, and holistic thinkers) apply their skills to spur the development of practices for the responsible use of the nanotechnology
2006	ETC Group	Legally binding U.N. treaty	• Proposes a new, and the legally binding U.N. treaty to develop a participatory and transparent process for timely evaluation of new technologies • The treaty would support the development of national and regional frameworks consistent with the treaty
2003	ETC Group	Mandatory moratorium	• Calls for an international mandatory moratorium on use of engineered nanoparticles in laboratories and in products • The moratorium should be lifted only after researchers have collaboratively developed "the 'best practices' possible," in line with the precautionary principle

The publications listed below offer recommendations for nanotechnology oversight. The publications included propose a course of action or conceptual methodology to inform the decision-making of government agencies, industry, and other relevant stakeholders. Approaches dealing with only a narrow subset of issues (e.g., just patent rights) or very specific aspects of nanotechnology (e.g., just carbon nanotubes) were not included. The list is organized in reverse chronological order (the most recent to the least recent). All are cited in full in the References

Table 2 Members of the project's Working Group and Advisory Group

Stephen Ekker, Ph.D. (Mayo Clinic College of Medicine)
Susan Foote, J.D. (University of Minnesota)
Christy Haynes, Ph.D. (University of Minnesota)
Robert Hoerr, M.D., Ph.D. (Nanocopoeia, Inc.)
Terrance Hurley, Ph.D. (University of Minnesota)
Robbin Johnson (Cargill Foundation)
Jeffrey Kahn, Ph.D., M.P.H. (University of Minnesota)
Bradley Karkkainen, J.D. (University of Minnesota)
George Kimbrell, J.D. (International Center for Technology Assessment and Center for Food Safety)
Andrew Maynard, Ph.D. (Woodrow Wilson International Center for Scholars; now, University of Michigan)
Kristen Nelson, Ph.D. (University of Minnesota)
Susanna Priest, Ph.D. (University of Nevada)
David Pui, Ph.D. (University of Minnesota)
T. Andrew Taton, Ph.D. (University of Minnesota)
Elizabeth J. Wilson, Ph.D. (University of Minnesota)
Members of the project's Working Group
Dave Chittenden (Science Museum of Minnesota)
Judy Crane, Ph.D. (Minnesota Pollution Control Agency)
Michael Gorman, Ph.D. (University of Virginia)
Linda Hogle, Ph.D. (University of Wisconsin, Madison)
Milind Kandlikar, Ph.D. (University of British Columbia)
William D. Kay, Ph.D. (Northeastern University)
Maria Powell, Ph.D. (Madison Environmental Justice Organization)

identified, and were used in qualitative and quantitative evaluations of five past oversight experiences in the United States (i.e., for GEOs in the food supply, pharmaceuticals, medical devices, chemicals in the workplace, and gene transfer research or "gene therapy"), and compared those oversight experiences to devise forward-looking lessons for oversight of nanobio (See symposium, Wolf et al. 2009b). This article offers resulting recommendations for nanobio oversight in the United States. The article benefits from our previously published analyses of oversight case studies (Kuzma et al. 2009; Paradise et al. 2009a, b; Choi and Ramachandran 2009; Wolf et al. 2009a); review of recommendations made by other groups for nano oversight; select interviews with experts involved in nanotechnology oversight; scenario analysis of existing and future products; and project group dialogue.

Our recommendations break new ground, going beyond what is already in the literature to offer recommendations that can be put into practical use. This is achieved in five ways:

A. We go beyond passive to active nanomaterials. Most recommendations and oversight efforts to date have focused on passive nanostructures, that is, materials with static functionalities. The authors offer recommendations to improve oversight of these materials but then look forward to offer oversight recommendations for active nanomaterials with bioactive properties, as well as complex materials utilizing multiple, convergent technologies.

B. We focus on nanobiotechnology. Looking at active nanomaterials and convergent technologies is all the more important when focusing on nanobio. These materials are designed to affect biological materials and systems. Analyzing their effects on organisms and systems, including human beings and our environment, raises complex health, safety, and environmental concerns.

C. We anticipate convergence. While many authorities anticipate increasing convergence of nanotechnology, biotechnology, information technology, and cognitive science, few have offered oversight recommendations to deal with this enormous oversight challenge. The authors specifically present an oversight approach to deal with this growing convergence.

D. We address dynamic oversight and regulation. While some commentators have looked beyond traditional command-and-control regulation to suggest "new governance" approaches for nano (see, e.g., Mandel 2009), we integrate the range of oversight approaches to propose what we call "dynamic oversight." This approach is depicted in Fig. 1. Dynamic oversight acknowledges that oversight strategies exist along a continuum from "soft" to "hard" approaches. The former include advisory guidelines and requests for voluntary information; the latter include enforced prohibitions and stated standards with penalties for deviation. Our dynamic approach recognizes that governance of emerging technology as complex and varied as nanobio calls for development of oversight over time, with the full spectrum of approaches available, as well as the opportunity to mix "soft" and "hard" oversight tools. Determining the oversight approach at any one time should involve stakeholders, agencies, and a

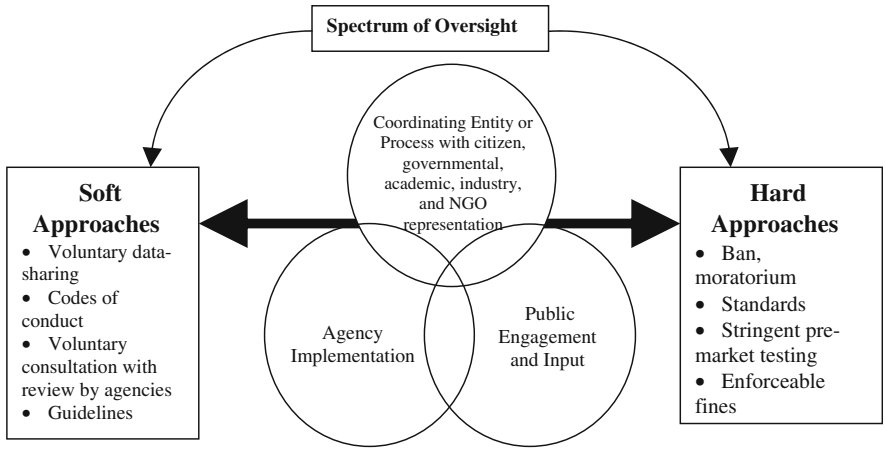

Fig. 1 Key elements of proposed dynamic oversight for nanobiotechnology. The authors offer examples of "soft" and "hard" approaches to oversight, to indicate the spectrum of oversight approaches. Interactions among three entities or processes determine the mix of "soft" and "hard approaches over time. Those three entities or processes are the government agency (or agencies), public engagement and input, and a coordinating entity or process with citizen, governmental, academic, industry, and NGO representation

coordinating entity in an interactive and negotiated process. The development of oversight approaches through time should rest on analysis of success and failure to date, with negotiated readjustment.

E. We develop the U.S. oversight recommendations with an eye on transnational and international approaches. Our research indicates that the U.S. oversight authorities are paying careful attention to what other key countries and organizations such as the Organisation for Economic Co-operation and Development (OECD) are doing. Efforts to coordinate development of data and standards for nanomaterials promise more efficiency and global harmonization of standards.

Lessons from case studies of oversight

From our prior evaluation of oversight in five areas of technology, which are both related and analogous to nanotechnology—GEOs in the food supply, pharmaceuticals, medical devices, chemicals in the workplace, and gene therapy—several key themes or lessons emerged, which are described in this section. In the next section, these lessons are used to develop a framework for oversight of nanobiotechnology.

In the design of oversight systems for nanobiotechnology, it is not enough to focus on "sound science" or narrowly empirically based approaches. It was found in the qualitative and quantitative analyses of the studied oversight systems that oversight process recommendations are also empirically grounded in consideration of less tangible social variables such as transparency, public input, financial resources, and how uncertainty is treated (Paradise et al. 2009b). Designing a successful oversight system requires attention to all these features.

Common weaknesses in the oversight systems that were studied were low transparency, little public input, prominent conflicts of interest, and limited financial resources to regulatory systems. Published studies of how the public perceive emerging technologies suggest that citizens care about these elements of oversight and that these elements affect attitudes, trust, and, ultimately, willingness to accept emerging technology products (Hamlett et al. 2008; ICTA 2008; Macoubrie 2005, 2006; Siegrist 2000; Siegrist et al. 2007; Slovic 1987). For biologically active nanoproducts, there is likely to be substantial public discomfort unless these concerns are taken seriously and addressed. Thus, lessons emerge from our prior study comparing oversight systems:

- Public engagement and transparency are particularly important for products that can easily raise public concern, such as biologically active products. Basing oversight systems on sound science and cost–benefit analysis without considering

public attitudes and transparency is likely to lead to less willingness to accept products. The goal of public engagement is not necessarily to convince people to accept any product or even an oversight process, but rather to have the public as a key player in the decision-making process. It is increasingly recognized that a "best-practices" approach to introducing new technologies to the public involves some form of public consultation "upstream" of widespread deployment. Public engagement is important for normative, objective, and instrumental reasons. Normatively, especially in democratic systems, citizens should have a right to participate in decision-making about things that are of interest to them or that affect them. Objectively, they have important knowledge and insights that can improve decision-making. Finally, engagement may increase trust and understanding, while reducing conflict (Fiorino 1990; NRC 1996). However, this is especially challenging for nanotechnology because it is a broad class of technologies about which most members of the public still know very little.

- There has been a serious deficit in the capacity of regulatory systems. Regulation is not well funded, especially for new, convergent products that require intra- and inter-agency coordination and development of new expertise, as well as mechanisms for public engagement. In addition to investing in nanobio research and development, the federal government should invest in development of competent and effective oversight systems.
- There is a need for oversight through all phases of the product or technology, that is, throughout the life-cycle of the product. For convergent nanobio products (such as DNA-based nanoparticles in agricultural landscapes and biosensors at the nanoscale), monitoring throughout the life-cycle will involve innovation in risk analysis and coordination among agencies focusing on health, safety, and the environment.
- Nanobio technologies are evolving quickly. Any oversight approach will have to be flexible, with the resources and expertise to anticipate, understand, and respond to change in the science and technology.

In sum, "[o]ur five case studies…suggest that nanobio oversight should strive for life-cycle oversight, public input, adequate oversight resources, coordination, preparedness for technological change over time, and clear goals" (Paradise et al. 2009b).

Dynamic oversight

Oversight itself has an arc, moving from problem detection to data gathering to problem formulation to negotiation over evaluation and limits, eventually leading to regulations, guidance, or some other kind of agency action. These approaches to oversight are either "soft" (e.g., voluntary sharing of data, codes of conduct, or consultation with agencies) or "hard" (e.g., enforceable fines/citations, stringent premarket testing, or moratoria). Typically, this arc is unidirectional, that is, the oversight moves from "soft" to "hard" with little chance for movement in the other direction and periodic course corrections.

The history and evolution of nanobio to date call out for a dynamic oversight approach. Because our case studies were historical, we could examine successes and failures in dealing with biologically active and complex technologies in the past. For example, GEOs in the food supply, some drugs and devices, and some gene therapy involve processes and products that can best be considered "active." Oversight of GEOs has addressed the potential for environmental spread, active integration of new or modified genes into other organisms, and dynamic effects on ecosystems. Similarly, nano therapies for cancer are increasingly integrating diagnostic, drug delivery, and continued-release treatment features into a single product. Also, a core concern for gene therapy protocols has been the potential for a vector to affect non-target cells (including germ-line cells) and even to affect non-target organisms. These are "active" material concerns. A key insight from our analysis of the five case studies is that while passive nanomaterials pose unique challenges for oversight, nanobiotechnology with active nanomaterials takes that challenge to a new level. The complexity, combination of multiple technologies, uncertainties, and sheer breadth of applications force us to reinvent static or reactive oversight systems. A technology such as nanobio that is dynamic requires an oversight framework that is also dynamic. There are three key features of the dynamic framework we propose (shown in Fig. 1):

- It integrates soft and hard approaches to oversight, moving between these two poles dynamically as data become available and attitudes and analyses evolve. The oversight system can mix soft and hard approaches at any one time.
- The system provides for strong coordination among regulatory agencies, stakeholders, and the public. It also provides for an overall coordinating entity to capture the dimensions of risk and societal issues posed by active nanobiomaterials, as well as provide oversight throughout the life-cycle of the technology or product.
- The general public has a central decision-making role in the oversight framework. Engagement and inputs from other stakeholders are also an important feature of the oversight framework. Discussions and robust debate between the stakeholders and the public will address the appropriate balance between innovation and oversight.

Our model of dynamic oversight is part of a trend toward flexible and adaptive regulation and governance. The last several decades have seen the emergence of approaches to oversight and governance that reject traditional bureaucratic, top-down, inflexible decision-making and conventional regulatory tools in favor of new approaches that emphasize greater public involvement, democratized decision-making, feedback loops, and flexible regulatory approaches. These models are often referred to as "dynamic," "flexible," "adaptive," "reflexive," "iterative," "engaged," "inclusive," and "upstream" and are being used across regulated sectors ranging from finance to the environment. Some approaches are conceived to apply broadly to regulatory decision-making in general, while others are more narrowly targeted to environmental issues or specific emerging technologies.

For example, Neo and Chen (2007) describe three key functions that make governance dynamic. The first is "thinking ahead," recognizing signs of emerging developments, anticipating how new developments will affect societal goals, evaluating the effectiveness of existing policies for governing new developments, and engaging decision-makers and stakeholders in dialogue about how to respond to new developments. The second function is "thinking again," reevaluating and reformulating existing policies to improve outcomes using real performance data and public feedback. The third function is "thinking across," learning from practices implemented by other institutions in similar situations. These three functions are all part of adaptive policies.

"New governance" is one broad approach that emphasizes public–private partnerships to enhance the participation of traditionally excluded stakeholders in regulatory decision-making (Alexander 2009). New governance schemes for environmental management often involve the creation of networks to link individuals, institutions, agencies, and other stakeholders to collaborate on flexible management incorporating both centralized and decentralized controls (see, e.g., Scholz and Stiftel 2005).

Reflexive governance is a dynamic concept developed by Voss and Kemp (2005) to manage interconnected problems associated with sustainable development. This approach uses constructive technology assessment, interdisciplinary research, participatory decision-making, and collaborative policy-making, as well as integrating stakeholder viewpoints, engaging in scenario analysis and forecasting, and adopting strategies that are responsive to change. Hendriks and Grin (2006) offer a vision of reflexive governance in which "citizens, government officials and parliamentarians come together to consider issues for collective decision making." The authors see this system of deliberation as a series of "interconnected and overlapping spheres of public discourse" taking place in state-sponsored and non-state-sponsored arenas.

The literature about engaged governance, much of which focuses on international development, is concerned with ensuring that decision-making processes incorporate the inputs from different citizen groups and those who may be affected or marginalized by government decisions. It strives to promote government activity that is more responsive, transparent, and durable (Guthrie 2003). Outside of the international development literature, engaged governance has come to refer to decision-making and public policy processes that involve collaboration between state and non-state actors. Tikhomorov (2005) has applied this concept in the context of technology.

Dynamic approaches developed in the environmental sector address issues directly relevant to nanobiotechnology. In this sector, scholars have proposed oversight frameworks to respond to changing knowledge about risk, toxicity, and societal implications, as well as other uncertainties of science

and technological advancement. In 1978, Holling developed the concept of Adaptive Environmental Assessment and Management (AEAM) as an incremental approach to managing environmental problems as new information becomes available (Holling 1978). Since the 1990s, several environmental fields, most notably natural resources management, have developed and used adaptive management processes that attempt to optimize oversight outcomes in the face of uncertainty by creating a continuous feedback loop between new scientific information and decision-making. In 2002, Gunderson and Holling developed a concept of "panarchy," described as repeating cycles of adaptive management characterized by "forward-loop" stages of innovation, growth, exploitation, consolidation, predictability, and conservation, followed by "back-loop" phases of instability, release, collapse, experimentation, novel recombination, and reorganization" (Karkkainen 2005).

Some scholars have also begun proposing dynamic approaches to regulation and governance for nanotechnology and other emerging technologies. Mandel (2009) has proposed a new governance approach for nanotechnology, biotechnology, and synthetic biology that emphasizes improved data-gathering and sharing, creating incentives for voluntary corporate stewardship, improving agency coordination, developing and using adaptive and flexible regulatory tools, and providing for significant, diverse stakeholder participation. Marchant et al. (2008) have recommended an incremental regulatory approach for nanotechnology that emphasizes the use of decentralized measures, such as self-regulation in the near-term; as the public becomes more familiar with nanotechnology, government can begin to implement some regulations through a transparent and participatory process. Guston and Sarewitz (2002) have proposed Real-Time Technology Assessment (RTTA) for nanotechnology. This approach builds on Constructive Technology Assessment (CTA), a Scandinavian effort from the 1980–1990s to drive technology decision-making by conducting controlled experiments to identify risks, enhancing dialogue among stakeholders, and assessing social aspects of new technology (Schot and Rip 1996). While some of these proposals have garnered attention in the policy literature, their impact on federal policy-makers has been limited to date. There is some indication that the results of the National Citizen's Technology Forum (NCTF), the first nation-wide citizen consensus conference in the United States, led to policy-relevant conclusions that are now being considered through legislation by the U.S. Senate and House (Philbrick and Barandiaran 2009) (see also discussion below on Senate Bill 1482). However, this legislation has yet to be adopted, and the NCTF was not designed to feed into decision-making. The lack of connection between public engagement and decision-making remains a problem. Important reasons for this might be resource limitations faced by agencies, as well as uncertainties about nanomaterial properties that may impact health risks. While some of these proposals incorporate dynamic aspects, operationalizing such a framework for a dynamic and evolving technology is a serious challenge. Figure 1 below lists key proposals for nanotechnology oversight.

Our dynamic oversight proposal captures the most important aspects of these other dynamic models, namely greater public involvement, democratized decision-making, feedback loops, and flexible regulatory tools. However, our approach goes further. First, the complexity and dynamic evolution of the technology demands that the oversight also be dynamic, iterative, and responsive to changes. Second, it addresses the unique multidisciplinary, cross-sector, and cross-agency oversight challenges posed by nanobiotechnology and the need for a life-cycle approach to oversight that will require optimizing and enhancing resources and coordination among various agencies. Third, our proposal sets forth specific, detailed agency-by-agency recommendations for change that we urge at this juncture in the development of nanobiotechnology oversight. The authors present recommendations to improve EPA, OSHA and NIOSH, FDA, NIH, and USDA oversight. Finally, our proposal is grounded in historical and comparative analysis of past oversight efforts for related science and technology, as reported in detail in our prior Symposium (Wolf et al. 2009b). Consequently, in developing our dynamic oversight model, the authors have tried to learn from the successes and failures of past oversight efforts.

Integrating "soft" and "hard" approaches to oversight

Early in the development and oversight of any emerging technology, the greatest challenges may

be in conceptualizing the problem, eliciting data for health and safety evaluation, developing a framework and methods for assessing risk, and identifying populations at risk. Given the context, oversight can be approached from the soft or the hard end of the regulatory spectrum. With the development of more data and analysis, the oversight authority may adjust the oversight approach in either direction, toward harder approaches or softer ones.

Oversight can take many forms ranging from temporary bans, to mandatory and specific regulations, to guidelines or something intermediate such as incentives or disincentives (see Fig. 1). Regulations can mandate the outcome or mandate the processes by which the outcomes are achieved. Oversight mechanisms can operate by motivating industry to share information, innovate, or change to meet articulated targets voluntarily (without specific regulations), or, at the other end of the spectrum, they can manage industry more directly through what is often called "command and control" (Wiener 2004). Regulatory and oversight tools along this spectrum include performance standards, tradable allowances, consultation between government and industry, and premarket safety and efficacy reviews (Paradise et al. 2008). A debate continues about the relative merits of various regulatory approaches along the spectrum from mandatory to voluntary approaches. Some believe that promotion of voluntary best practices may be preferable to regulation (e.g., Kuzma et al. 2009; Macoubrie 2005). Voluntary approaches have risks, though. They may fail to generate enough information to signal and characterize a serious problem. They may lead to a lack of public confidence. "Bad actors" may take advantage of the lack of close monitoring and hard regulation. The U.S. experience with voluntary approaches (described below) has been mixed.

In the case of GEOs, FDA has taken a voluntary approach to oversight, encouraging but not requiring consultation about foods derived from products of biotechnology (including GEOs). Arguably, this voluntary system has led to a lack of trust in the oversight system for GE foods, as supported by the GEOs case study from our project (Kuzma et al. 2009). Voluntary systems generally do not inspire as much public confidence as a mandatory system with requirements for premarket safety review (Macoubrie 2005; ICTA 2008; Kuzma et al. 2009).

In June 2010, FDA commenced collecting data on new submissions of drugs less than 1000 nm in a dimension. This 1000-nm scale also reflects uncertainty as to how to define nano for FDA purposes, as some other definitions adhere to a less than 100-nm range (e.g., EPA 2009b). As data accumulate and greater certainty emerges about how to define and evaluate nano, harder oversight approaches may follow.

Experiences at EPA indicate that voluntary approaches to nano oversight have not worked well. EPA developed the Nanoscale Materials Stewardship Program (NMSP) (http://www.epa.gov/oppt/nano/stewardship.html) to encourage industry and other organizations researching and developing nanoscale materials to generate and submit characterization, risk, and other data that will subsequently be used to inform regulatory decisions, including treatment of nanomaterials under the Toxic Substances Control Act (TSCA) (see http://www.epa.gov/lawsregs/laws/tsca.html). Participants have the option of two NMSP subprograms: the Basic Program, and the In-Depth Program. However, this initiative has met with poor response from industry to date. Indeed, the EPA's 2009 Interim Report on the program noted that "nearly two-thirds of the chemical substances from which commercially available nanoscale materials are based were not reported under the Basic Program" and "[t]he low rate of engagement in the In-Depth Program suggests that most companies are not inclined to voluntarily test their nanoscale materials." (EPA 2009b, p. 27)

Voluntary mechanisms can be used as an interim measure to fill gaps in current regulations. Recently, Howard and Murashov (2009a) have proposed a voluntary approach using partnerships between NIOSH and industry to develop information on occupational risks from exposure to nanomaterials. Once a body of knowledge can be developed on these risks and ways to control them, this can be used as the basis for applying the "General Duty Clause" of the OSHAct of 1970 as an enforcement tool (see http://www.osha.gov/pls/oshaweb/owasrch.search_form?p_doc_type=oshact, creating a "general duty" to provide employees with a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm"). Thus, it may be possible to leverage a voluntary approach into legally binding standards. This would be an example

of a "soft" to "hard" approach. Such an approach can sometimes address regulatory concerns with a minimum of cost and can address potential information asymmetries between industry and government agencies, particularly in the early stages of the development of nanotechnologies.

However, one can envision an equally viable hard-to-soft approach as well (perhaps prompted by a precautionary approach in the face of uncertainty) in which the oversight starts off with a command-and-control approach, stringent premarket approval requirements, heightened review or moratoria on some products and/or processes, and information-forcing approaches such as those implemented in California through Proposition 65 (Karkkainen 2006). As more data become available, regulations can be relaxed and tiered toxicity assessment strategies adopted (e.g., as in the regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) in the European Union (http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm)). In other words, there need not be rigidity in the use of the spectrum of oversight approaches, and, with a flexible scheme, the overseers can mix and match as appropriate. An example of movement from hard-to-soft oversight is the Recombinant DNA Advisory Committee (RAC) oversight of human gene therapy at NIH, which evolved from mandatory RAC review of each proposed protocol and required RAC approval to selective use of detailed review and an advisory role for the RAC.

Thus, the oversight development process is intended to unfold over a period of time in either direction. Oversight may indeed involve a mix of hard and soft approaches. New information (risk data, analyses, or experienced success or failure of the oversight system) will guide the next steps taken in the oversight trajectory by relevant agencies. Stakeholders will have much to say about each step in the development of an oversight approach.

Public empowerment and engagement

Nanotechnology has the potential to transform many key industries and have broad social impact. With the rapid introduction of nanoproducts into the market and the limited data on environmental, health, and safety effects, the potential exists for public controversy. Oversight systems generally benefit from the inclusion of the perspective of the public (e.g., consumers, users, human participants in research, and patients). Public education and dialogue about the science and technology issues will allow the exploration and integration of concerns related to values and ethics. In the past few decades, there have been increasing calls for public engagement in decision-making about science, risk, and technologies (NRC 1996, 2008). There is growing consensus that public engagement increases public trust and legitimacy and produces better decisions by incorporating local and "non-expert" knowledge (Kysar 2004). In the re-authorization of the U.S. National Nanotechnology Initiative (NNI), there is a specific call for the federal government to engage the public (NNI Amendments 2009), and the new U.S. *Federal Register* notice of proposed changes in federal regulatory review explicitly seeks comments on public engagement, the role of values, and the place of social and behavioral sciences in regulation (OMB 2009). Nanotechnology has been a major locus of public engagement activity including the European Commission's Nanodialogue, the U.S. Nanoscale Informal Science Education (NISE) Network activities conducted through science museums across the country, the U.S. National Citizen's Technology Forum, and the Madison Citizens' Consensus Conference (Philbrick and Barandiaran 2009; Powell and Kleinman 2008), the UK Citizen Juries on Nanotechnology (Rogers-Hayden and Pidgeon 2008), and Danish consensus conferences (Dryzek and Tucker 2008). In our studies, it was found that public input was correlated with other elements of oversight such as capacity, transparency, and empirical bases in oversight systems (Kuzma et al. 2009; Paradise et al. 2009a, b; Choi and Ramachandran 2009; Wolf et al. 2009a). Public engagement, debate, and transparency leading to mutual learning, dialogue, and communication between expert and non-expert publics (CAISE 2009) will be critical factors in the successful and appropriate oversight of nanotechnology processes and products. It is important to recognize that such open debates are not without challenges. For example, disruptions by protestors have led to the public being banned from debates on nanotechnology in France (http://www.rsc.org/chemistryworld/News/2010/January/22011001.asp).

Convergent, active nano—especially biologically active materials beset with uncertainties and lacking relevant risk assessment—requires innovative

engagement of a large range of public stakeholders. The authors propose that the oversight system includes the public not only as members of a coordinating entity (described in the next section), but also in the process of negotiation over important issues, such as who will bear the burden of generating data, formulation of standards and limits, and the balance between promoting innovation and oversight at any point in the oversight trajectory. Thus, the oversight system is grounded in an attempt to understand the perspectives of the various non-expert publics (e.g., the consumer, user, human participant in research, patient, and so on), rather than expert publics alone. The authors suggest an active and ongoing role for public and stakeholder engagement that is specifically tied to the design and change of oversight for nanobio. At the outset, the oversight coordination groups should include multiple stakeholders (industry, nongovernmental organizations, social scientists and other academics, trade organizations, civic society groups) who can help set the initial agenda for information-seeking, research, and exploration of regulatory approaches. Wider public dialogue should then occur throughout the initial phase of goal-setting and information-generation. The public dialogue should then feed directly as input into the next round of goal-setting, research agendas, and regulatory approaches for the coordination group. Thus, there would be two mechanisms of public engagement: membership on the coordinating entity, and participation in public dialogue.

Whether an independent dialogue is created, or stakeholders participate in private and public initiatives as they arise, it is important to ensure the representation of a wide range of interests. If key players are missing from the development of oversight discussions, then it can lead to a distortion of policy. Stakeholder involvement can also provide credibility and stature to any outputs. A long-range action plan should identify the wide range of non-traditional stakeholders to be included in any processes associated with government or private sector initiatives on nanotechnology environmental health, and safety. Many of the key nanotechnology players, such as start-ups and non-U.S. manufacturers, are not typically at the table in generating the U.S. agency policy and action. Public involvement in decision-making should not follow the usual format (i.e., public meetings with 1-min comments from the audience), but rather should constitute shared deliberation through a consensus conference or other deliberative approach, which is a way to overcome the general lack of familiarity with nanotechnology and yet incorporate non-expert voices. The NRC has suggested an analytical–deliberative approach (NRC 1996), where multiple perspectives from "interested and affected" parties contribute to shaping oversight scope, issues, and efforts. The hope is that decision-makers will learn from these engagement events and be more likely to consider in an anticipatory way possible scenarios of harm, risk issues, limitations of oversight, and socioeconomic impacts. However, it is important that the goal be not only mutual learning by the various publics and the regulatory bodies, but the public's active incorporation into the decision-making process.

What has become known as "upstream" public engagement—that is, public engagement activities that take place when technologies are being imagined and developed, not after they are deployed—is one possible framework, involving the inclusion of public and stakeholder perspectives in technological decision-making even before product deployment (Wilsdon and Willis 2004). Nanotechnology has already prompted public engagement activity such as the European Commission's Nanodialogue, in the U.S. NISE Network activities conducted through science museums, and the U.S. National Citizen's Technology Forum (Philbrick and Barandiaran 2009; Powell and Kleinman 2008). The 2003 re-authorization of the NNI also calls for the federal government to engage the public (21st Century Nanotechnology Research and Development Act 2003).

There is growing consensus that public engagement is important for democratic, normative, and utilitarian reasons such as increased public legitimacy and better decisions from the incorporation of non-expert knowledge. The NRC has published two prominent reports on the need for deliberative dialogue with stakeholders in risk-based and environmental decision-making to improve decisions in the face of uncertainty (NRC 1996, 2008). A purely scientific risk-assessment paradigm for decision-making ignores legitimate political and moral concerns and mistakenly consults only the scientists generating technical information and the decision-makers with power (Kysar 2004). Indeed, in our own interviews and case studies (Choi and Ramachandran

2009; Kuzma et al. 2009; Paradise et al. 2009a; Wolf et al. 2009a), the need for public input in the design and operation of oversight systems was supported by a range of experts. The authors also found that public input in the design and operation of an oversight system was correlated with positive features such as transparency and use of an empirical basis for decisions (Choi and Ramachandran 2009; Kuzma et al. 2009; Paradise et al. 2009a, b).

Despite the need for public engagement in technological decision-making, problems can arise. Published critiques of how public participation efforts have been conceptualized and implemented have cited lack of influence on programs or policies, the inability of citizens to contribute effectively without in-depth knowledge of the issues, and the dominance of vocal, activist groups (Olsen 2004; Sunstein 2005; Tait 2009). While some of the practical challenges can be overcome with well-planned efforts (Philbrick and Barandiaran 2009), the most pressing barriers to engagement are lack of political will and the need for resources.

Because decisions for evolving and highly convergent technologies such as nanobio should not be set in stone, public engagement should be ongoing. Thus, to match our dynamic oversight proposal, a continuing role for public and stakeholder engagement in the design and evolution of oversight for nanobiotechnology is suggested. At the outset, the oversight coordination groups should include multiple stakeholder and citizen representatives (such as industry, NGOs, social scientists, trade organizations, civic society groups, etc.), which set the initial agenda for information seeking, research, and regulatory approaches. Wider public dialogue involving citizens should then occur throughout the initial phase of goal-setting and generating information. The public dialogue should then feed directly as input into the next round of goal-setting, research agendas, and regulatory approaches for the coordination group. In each loop of the diagram in Fig. 1, there would be two points of public engagement: on the coordinating committee (through representation), and through public dialogue.

Life-cycle approach and coordination among regulatory agencies

Nanobiotechnology oversight spans a wide range of fields from drugs and medical devices to gene therapy to occupational and environmental agents to genetically engineered organisms. No one mechanism can suffice for effective oversight of all these fields. There is a need for an entity to coordinate oversight by the agencies involved, as the breadth, interdisciplinary nature, and convergent character of nanobio makes involvement by multiple agencies likely. A number of scholars and practitioners have suggested that an overarching federal coordination structure or process is needed to ensure that there is appropriate oversight of nanobio applications (Davies 2009; Kuzma and VerHage 2006). Davies (2009) has recommended the development of an entirely new organization for the oversight of nanotechnology, with new legal authority and new regulatory tools. This proposed organization, hypothetically named the Department of Environmental and Consumer Protection, would go so much far as to provide integrated oversight on products, pollution, and the workplace, as well as risk research, technology assessment and forecasting, and monitoring of environmental and health impacts.

In the case studies of oversight that the authors have analyzed, involving multiple agencies (Kuzma et al. 2009; Paradise et al. 2009a, b; Choi and Ramachandran 2009; Wolf et al. 2009a), agency coordination was identified as a major challenge and hypothesized to have impacts on oversight effectiveness. Such a coordination structure could help ensure intra-agency (and cross-disciplinary) information exchange, inter-agency coordination, and avoidance of gaps in oversight.

An approach providing attention to inputs or outputs from initial synthesis of nanomaterials and manufacture of nano-enabled products in workplaces, to consumer use in the general population, to the products' eventual disposal in the environment has been called a life-cycle approach (PEN 2007). A life-cycle approach has also been proposed for risk assessment (Shatkin 2008) and regulatory coverage (Davies 2007). Taking a life-cycle approach to regulation will require a much greater degree of coordination and communication among agencies. For example, oversight of occupational exposures to nanomaterial hazards requires coordination among EPA, OSHA, and NIOSH regarding TSCA (Toxic Substances Control Act), and the OSHAct, as well as research coordination. The challenges become different, but no less complex, when dealing with multi-media pollution problems, the wide range of industries, sectors, and agencies that may

be involved, and multiple applications of a technology. Coordination is needed not only among agencies at the federal level (e.g., FDA, OSHA, NIOSH, EPA, and CPSC), but also among federal, state, and local levels. This requires adequate resources for coordination.

Nanotechnology products that are convergent will face many of the problems that GEOs oversight has faced with regard to coordination among EPA, FDA, and USDA. One major problem that inhibits coordination and sharing of information is protection of confidential business information (CBI) during regulatory review. Another is that no overarching national entity has authority for assuring coordination. Clear and routine mechanisms for coordination should be established. Our case studies clearly identified a need to create and regularize mechanisms for enhanced coordination in oversight systems. Plans for facilitating inter-agency and stakeholder interactions and for information sharing should be incorporated into oversight systems.

A variety of mechanisms could be utilized to provide inter-agency coordination. Potential models include, but are not limited to, the following:

- The Office of Science and Technology Policy (OSTP) took on a key role in the development of the Coordinated Framework for the Regulation of Biotechnology (CFRB) in 1986 (OSTP 1986). It also published case studies in 2000 to highlight gaps and redundancies in the CFRB for new, convergent GEOs (OSTP/CEQ 2008). However, it did not sustain an active role in ensuring coordination throughout the development and regulation of GEOs. Empowering OSTP to take the lead in coordinating nanotechnology oversight should be considered, especially for convergent products. An overarching coordinating entity would be helpful, perhaps modeled on or under the OSTP, with legal authority to act as an oversight entity and to mandate inter-agency interactions. There are several bodies that could be considered as candidates for this role, albeit with modifications, such as the National Science and Technology Council's (NSTC) Nanoscale Science, Engineering, and Technology (NSET) subcommittee that operates within OSTP, or the NNI's Nanotech Environmental and Health Implications (NEHI) Working Group. The key modification that would be needed is the added membership of relevant stakeholders, including representatives from the public, industry, non-governmental organizations, and academia.
- Mandatory subject and issue consideration systems—the National Environmental Policy Act (NEPA) is an existing example of a statutory mandate for non-environmental agencies to consider environmental issues posed by any significant federal action, including nanobio-related actions.
- Memoranda of Understanding (MOUs) between agencies defining agency roles, interactions, and coordination.
- A cross-agency coordination advisory committee that includes external stakeholders and experts. This could be housed under OSTP or another entity.
- Inter-agency information exchanges and voluntary cooperation systems. In many ways, NNI is an example of such a cooperative initiative. NNI could create a subgroup for work on federal oversight.

As these examples demonstrate, potential coordination mechanisms cover a broad range of authority, flexibility, ease of use, and role. Aspects of various models can be combined, if desired, to create a tailored coordination or oversight system for nanobio applications. Additional research and analysis are needed to fully understand the advantages and disadvantages of these approaches.

Proposed legislation has moved in this direction. Senate bill S. 1482 (National Nanotechnology Initiative Amendments of 2009) proposes that multiple subgroups under OSTP focus on coordination of research on environmental, health, and safety as well as on public engagement. However, the bill does not include a coordinating oversight body, which is essential for dynamic oversight. The body should have authority to require the regulatory agencies to participate, and should have broad membership, including not only industry and government, but also citizen groups, social scientists, and policy experts in non-governmental organizations (NGOs) ("interested and affected parties," in the language of NRC 1996).

Improving oversight

Federal agencies have thus far responded to the oversight challenge largely by using existing institutional structures, laws, regulations, and guidance to

govern nanobio products. The panoply of administrative tools available to federal administrative agencies is complicated and a function of the authority delegated to the agency by Congress in statute. Federal agencies promulgate regulations under the authority vested in them by the relevant statute. Agencies then clarify and interpret those regulations through a variety of mechanisms including guidance documents and internal procedural publications. Any discussion of federal agency oversight necessarily implicates this complicated spectrum of administrative tools. For the purposes of these studies, the authors will mainly be touching on the formulation and application of agency-promulgated regulations, the development of agency guidance, and methods of information-gathering that agencies have initiated in the nanotechnology realm. The authors refer to this spectrum collectively as "oversight."

Current oversight of existing passive nanomaterials, processes, and products has been a continuation of existing oversight mechanisms that are reactive, static, and generally unable to handle new challenges because of emerging technologies. While passive nanomaterials pose less of a challenge than active nanomaterials, current oversight mechanisms have nevertheless been largely ineffective. In this section, the authors recommend improvements in oversight of passive nanobio materials. This is the dominant category now facing EPA, OSHA, FDA, NIH, and CPSC. A dynamic approach to oversight of these passive nanomaterials is the best way forward.

Issues relating to health and safety data

Oversight decisions should have an empirical basis. The availability of such data is a key component deciding the trajectory of oversight over time. Obtaining basic data on nanomaterials, including health effects and safety, is critical. It is important to develop information that is available to regulatory agencies on toxicity and human health effects from exposures to nanomaterials. This will lead to more effective oversight by providing foundational risk and benefit information to the relevant federal oversight agencies. Risk assessment and management depend on the availability of such information. Such data need to be obtained using standardized procedures and protocols, including standards for physical and chemical data, dose metrics, testing regimens from screening assays to long-term tests, human exposure data, and procedures for deriving safe levels (Engel-Cox et al. 2008).

Industry should shoulder significant responsibility for generating data

The current regulatory system for OSHA has placed the burden of proving risk and assessing it on a regulatory agency without the budgetary means to do this, while private firms have little incentive to reveal toxicity or exposure information. Similarly, EPA's approach to nano oversight through its Voluntary Stewardship Program has left the agency in the position of waiting for materials information and assessments from industry, which have largely failed to appear. The FDA does not shoulder the same burden as OSHA to prove risk and assess it and can demand that the applicant for approval provide sufficient data on risks for drug and device products. However, even with this authority, the FDA has on many occasions not obtained such detailed information, and the companies submitting documents have not done studies for generating the right information. This paradigm should change so that the burden of developing risk-relevant data and evaluating those data are shared between the private sector and the regulatory agencies. Sharing the burden of generating health and safety data and evaluating those data will increase the stakeholder investment in the oversight process and outcome. It will also catalyze continuing dialogue between the stakeholders and the agency, leading to more dynamic oversight based on the data, evaluation, and dialogue. The idea of having manufacturers generate some of the health risk data to ease the resource burden on regulatory agencies, however, raises questions of conflict of interest. How can data on the health and ecological risks of a product that are generated by the product manufacturer be trustworthy? This is an important concern that needs to be allayed. Our proposed framework addresses this issue from two angles: (a) standardized procedures and protocols that are agreed on by the various parties would be used for testing that is done by both the manufacturers and agencies, and (b) the data obtained would be validated/vetted by the overall coordinating agency (or a subset of it) that includes members from the agencies, various stakeholder groups, and the public. Such an approach strikes a balance between

sharing the costs of data generation and maintaining public trust in the data.

Oversight authorities should use tiered strategies to test nanobio materials and products, based on hazard characteristics

Tiered toxicity testing strategies offer a cost-effective way to reduce hazard-evaluation costs. Using tiers means sorting materials and products by hazard characteristics, so that resources can be concentrated on the most hazardous. This approach is similar to the approach being used by the EU under REACH (European Commission 2006). Testing tiers should be based on hazard characterization that captures both potential exposures and toxicity. For active and convergent nanobio products, tiers should also be based on uncertainty associated with the active nature of the nanomaterials under different physiological or environmental conditions. Recent efforts in this direction by the National Institute of Environmental Health Sciences (NIEHS), EPA, and the NIH Chemical Genomics Center (Collins et al. 2008) and others (e.g., Shaw et al. 2008) suggest that it may be feasible to do rapid in vitro profiling of nanoparticles that will help in prioritizing substances for further investigation according to toxicity. Choi et al. (2009) show the plausibility of tiered testing for risk assessment of nanoparticles. Their study indicates that tiered testing for risk assessment of nanoparticles may reduce total cost by about 35–40%, compared to conventional full testing, which costs about $5 million per chemical.

Agencies should develop in-house expertise to participate in characterizing nanobio materials and analyzing data generated by others

The FDA is an example of an oversight agency recognizing the need for in-house expertise to participate in nanobio materials characterization and analysis. In a 2007 report, FDA's Nanotechnology Task Force recommended a variety of mechanisms to facilitate production of information to support oversight. These include increasing the FDA's participation and investment in nanotechnology characterization, risk, and toxicity research; evaluating data on the interactions between biological systems and nanoparticles of specific concern to the FDA; and developing in-house expertise in nanotechnology. The FDA has requested submission of research data on the safety and effectiveness of nanoscale materials, as well as information on whether nanoscale materials should be subject to additional manufacturing safeguards.

Both at FDA and other agencies involved in nanobio oversight, such as EPA, OSHA, NIOSH, and CPSC, oversight authorities need more capacity and resources. Until there is commitment on the part of the federal government to support oversight, providing more resources to agencies and coordination bodies, it will be difficult to improve oversight. Fixing this will require political will and funding (Kuzma 2006). Increasing oversight capacity will require increased investment, and there is growing recognition of this need within the government (e.g., NNI 2010).

Oversight authorities should develop approaches to confidential business information (CBI) that maintain public accountability and avoid compromising public health and safety

There is an inevitable tension between disclosing environmental, health, and safety data and protecting CBI. This tension has been a significant one in gene therapy oversight, for example; FDA protection of proprietary information has, at times, prevented communication of risk and adverse event information to the RAC at NIH, where reviews are public. Oversight of nanobio should involve development of approaches that reconcile protection for CBI and intellectual property with the need to maintain public accountability and trust (Kuzma et al. 2009). Mechanisms for sharing CBI between stakeholders and regulatory agencies need to be established. Agreements for respecting confidentiality among diverse stakeholders could help overcome the current gridlock between protection of intellectual property and transparency.

Agencies should adapt current regulations; Congress should modify certain statutes

There is an immediate need to modify certain statutes and regulations to address the challenges of nanobiotechnology. The changes that are needed by agency will be enumerated shortly. The changes that

are proposed here will lead to an improved dynamic oversight of nanobio.

The authors recognize that some of the recommendations proposed for change have administrative law implications. Congress authorizes federal administrative agency action through enabling statutes that determine the scope of regulatory authority. Restructuring existing agencies, creating new ones, and authorizing new regulatory actions as a result of emerging nanobiotechnologies may require amendments to existing law as well as new or revised Executive Orders. Even working within the current scope of delegated authority and using the current tools of each agency in new ways may require regulatory changes and creative use of formal and informal rulemaking procedures. The authors do not spell out the administrative law challenges here. Instead, the focus will be on articulating a new vision of dynamic oversight for nanobio, a vision that may require legal change at a number of levels.

EPA

The EPA has taken significant steps in the last 2 years to begin regulating nanomaterials under TSCA (http://www.epa.gov/lawsregs/laws/tsca.html) and the Federal Insecticide, Rodenticide, and Fungicide Act (FIFRA) (http://www.epa.gov/oecaerth/civil/fifra/fifraenfstatreq.html). EPA has drafted and published its intent to regulate silver nanomaterials under FIFRA (http://www.epa.gov/fedrgstr/EPA-PEST/2007/September/Day-21/p18591.htm) and carbon nanotubes (CNTs) under TSCA (http://www.epa.gov/oppt/nano/). It has also implemented the Nanoscale Material Voluntary Stewardship Program as discussed above and is planning to "establish reporting requirements for certain nanomaterials" (Inside EPA 2009).

The TSCA applies to new molecular entities (NMEs), but the definition of NMEs is open to interpretation. For example, CNTs are currently treated the same as other carbon-containing molecular entities, but there have been criticisms of this approach given the special properties of CNTs and the demonstrated risk in laboratory studies (Davies 2009; Howard and Murashov 2009a; Maynard 2006). In 2009, the EPA published two proposed Significant New Use Rules (SNURs) under TSCA for multi- and single-walled CNTs so that they could be subject to premarket notification and possible testing (http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480a52a30). However, shortly thereafter, the agency retracted those rules, due to received "notice of intent to submit adverse comments on these rules." (EPA 2009a) The agency is in the process of proposing updated SNURs for CNTs.

The EPA has also published a proposed intent to regulate silver nanomaterials under FIFRA (http://www.epa.gov/fedrgstr/EPA-PEST/2007/September/Day-21/p18591.htm), but has yet to finalize a rule. FIFRA regulation depends on the manufacturer's intent that the chemical serve as a germ-killing agent. Consequently, some companies have removed these claims from their nano-silver products in advance of EPA regulation under FIFRA.

In summary, despite EPA activity, little has been done to assure pre-market testing and the safety of nanomaterials. However, Congress has held hearings on broadly reforming TSCA, and the EPA Administrator Lisa Jackson has already signaled the intention of the Obama Administration to make toxic chemical reform a major priority (Beckstrom 2010; Birnbaum 2010). In addition, the heads of environmental agencies of 13 state agencies have proposed principles for "meaningful TSCA reform" (States' Principles on Reform of the Toxic Substances Control Act 2009). A notable ongoing problem with TSCA is the issue of the burden of proof. The EPA has been required to demonstrate unreasonable risk of harm from chemicals to regulate chemicals under TSCA. Amending the burden of proof requirements so that manufacturers and users share the burden to demonstrate safety would be a step forward. A recent GAO report notes that only a negligible fraction of chemicals out of more than 60,000 have been regulated by EPA under TSCA (GAO 2009). Thus, the challenges that EPA faces in regulating engineered nanomaterial is embedded in the larger context of historical problems with chemical regulation in the United States.

- Reforming TSCA should include a change in the evidentiary standards and shifting the burden of proof from being entirely on EPA to a balance between the agencies and the chemical (in this case, nanomaterial) producers and users. In this context, the European Union's REACH regulation is an appropriate model for revising TSCA.

- Distinguishing between new and existing materials is crucial for nanomaterials, but TSCA needs to be re-interpreted for this to happen. The current definition of a "material" is based on chemical rather than physical structure, so that there is no distinction between the nano and macro forms of the same chemical material even though they may have radically different toxic physical/chemical properties and interactions with biological systems.
- TSCA currently exempts research and development applications, low-volume manufacturing, and low-environmental-mass emissions from any oversight, but these exemptions should be considered inapplicable, as their application could result in many potent nanomaterials not being regulated at all.
- EPA should take adverse action and regulate under FIFRA if a company is producing a product that is intended to kill or remove pests. Silver-coated materials for "fresher" clothing, food, or other consumer products should fall in this category even if the manufacturer does not directly claim "germ-killing" intent.

OSHA

- As in the case of TSCA, a series of court decisions and statutory amendments over the years have made the process of rule-making and setting occupational standards by OSHA so onerous that these activities have come to a virtual standstill (Howard and Murashov 2009b). OSHA currently has to prove that any proposed standard is feasible technically and economically and must demonstrate significant health risks in the workplace (requiring a detailed human health risk assessment that is resource- and time-intensive). This rigid approach does not work. The roadblocks to OSHA oversight will hamper oversight of new engineered nanoparticles. A major effort to reform the Occupational Safety and Health Act (OSHAct) of 1970 (29 U.S.C. §§ 651–678) is required to streamline the oversight process, although the political feasibility of this is unclear. As mentioned in a previous section, tiered toxicity testing strategies would be more cost-effective. Such context-specific assessments may reduce hazard evaluation costs and we recommend such a strategy be adopted in any future revisions to the OSHAct. Resource constraints should also be alleviated by a combination of (a) a major increase in the budget allocation to OSHA and NIOSH for efforts related to standards development and (b) shifting the burden of carrying out human health risk assessments from being completely on the agency to a joint effort by both industry and agency. To maintain public trust in the data, there needs to be a mechanism of validating and vetting the data generated by all parties. These changes to the OSHAct will affect the proper oversight of not only nanomaterials but also other chemicals.
- In the past, OSHA has used the general duty clause (a "general duty" to provide employees with a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm" (29 U.S.C. § 654(a)(1)) as an enforcement tool. To show that the hazard was "recognized," there must be evidence of risk to workers' health from authoritative sources such as NIOSH publications, peer-reviewed articles in the scientific literature, industry guidelines, consensus standards, and voluntary national or international codes (Howard and Murashov 2009a). However, scientific knowledge about the hazards of engineered nanoparticles is still at an early stage, thus preventing the use of the general duty clause by OSHA for enforcement activities. NIOSH has proposed and embarked on a soft-to-hard approach to develop the necessary data on the risks of engineered nanoparticles through a voluntary program of cooperation with industry, while simultaneously promoting guidelines and practices for safe use in workplaces (Howard and Murashov 2009b). It is expected that such data will help our understanding of worker exposures, the proper metrics by which to measure them, and safe levels for occupational exposures, and control methods for achieving safe levels. These data can, in the near future, form the basis of oversight by regulatory agencies such as OSHA through the general duty clause of the OSHAct and, in the more distant future, lead to risk-based exposure limits. The authors support this approach. Indeed, this is an example of dynamic oversight where an initially soft approach based on a voluntary program leads to harder oversight as one learns more about the health risks of nanomaterials.

- Key mechanisms for exposure processes and toxicity effects of manufactured nanoparticles to humans and ecological receptors remain poorly understood. Uncertainties about mechanisms include those related to (a) how long manufactured nanoparticles may persist in the atmosphere depending on their rates of agglomeration (and some nanoparticles are designed specifically not to agglomerate), thus influencing the probability of exposure; (b) the effect of particle shape on their fate and transport; (c) the routes of exposure and the metrics by which exposure ought to be measured (e.g., particle mass or number or surface area concentration); (d) mechanisms of translocation to different parts of the body after nanoparticles enter the body; (e) mechanisms of toxicity including oxidative stress due to surface reactivity, the presence of transition metals leading to intracellular calcium and gene activation, and intracellular transport of nanoparticles to the mitochondria (Kandlikar et al. 2007). Thus, both the exposure and toxicity aspects of risk are poorly understood. These scientific uncertainties should be addressed through the voluntary program. NIOSH has been engaged in cutting-edge intramural research on nanomaterial toxicity evaluations, exposure assessments, and evaluation of control technologies. However, testing the plethora of nanomaterials will clearly be beyond the capacity of one agency. While the voluntary program has focused on exposure assessment and control technology evaluation to date, it is recommended that the program be extended to toxicity evaluation in cooperation with industry.

FDA

The FDA regulates a broad scope of products ranging from highly complex drugs, biologics, and medical devices to much less complex (and generally lower risk) foods, cosmetics, and dietary supplements. While nanotechnology can impact all product types, the scope of our project is limited to drugs, biologics, and medical devices, and any conclusions are only applicable to those products (issues involving GEOs and food are discussed in "Coordinated framework for GEOs (EPA, FDA, USDA, NIH)" section).

- The existing statutory and regulatory scheme provides FDA with sufficient authority over nano drugs, biologics, and medical devices (should they choose to exercise it to develop nano-specific rules and regulations according to established administrative procedures allowing for public comment and consideration). However, as detailed in the subsequent sections, there are various modifications that would enhance FDA's regulatory oversight. The critical concern regarding emerging drug and medical device nanoproducts in the health and medical realm is whether FDA has the expertise to assess much-needed data regarding safety and efficacy, risks and benefits, and long-term effects attributable to nanotechnology. This section exclusively addresses FDA oversight of drugs and medical devices, the focal point of our project investigations. Other product areas regulated by the FDA, including foods, cosmetics, and dietary supplements, clearly raise additional concerns based on the limited pre-market and post-market authority of the FDA although these areas were not addressed by this project. While FDA has broad statutory authority to require pre-market and post-market data submission, FDA may currently lack the expertise to identify the appropriate information to request initially, subsequently to assess the data provided, and to respond, because of the nascent state of understanding of properties and characterization of nanotechnology. The FDA needs to focus on gathering relevant pre- and post-market information in an effort to acquire nano-specific data to guide future regulatory action. As described in an earlier section, this needs to be accomplished through a joint process involving the agency as well as the manufacturers, other stakeholders, and the public, with processes in place for vetting the health and safety data. FDA routinely engages with the scientific community on questions of scientific expertise in the drug and medical device realms through a variety of mechanisms including advisory boards, targeted requests for information from the scientific community, and requests to expert organizations to analyze a particular issue. These mechanisms are in place and should be utilized to develop this type of collaboration for emerging nanoproducts. Such an approach might be more efficient and cost-effective than having

agency experts on the broad array of questions that may arise. However, it is also important the agency have the experts intramurally who can identify the relevant issues and the experts who need to be accessed to address any particular issue.

- The authors see no current need for a special nanobio center or nano-unique regulatory process within FDA for nano drugs, biologics, or medical devices. Creating a separate, nano-specific center within FDA would create silos of information, restrict cooperation and information exchanges, limit cross-functional and cross-disciplinary coordination, trigger multiple "forum shopping" risks, and limit the agency's ability to review products, risks, and policy in a holistic fashion. In addition, within the drug and medical device arenas, FDA already has substantial pre-market and post-market authority.
- FDA should develop a specific definition of a nanobio product for FDA regulatory purposes. Existing definitions such as the current NNI-based definition (http://www.nano.gov/html/facts/whatIsNano.html) are not adequate from a regulatory standpoint, as they do not define nanobio products with sufficient specificity. They also do not describe how the size, novel features, and interactions with the human body are to be evaluated when reviewing the safety and efficacy (or bioequivalence) of drugs, biologics, or medical devices.
- FDA should periodically reexamine existing statutory definitions, regulatory requirements, and guidance documents to determine whether current and future nanoproducts stretch those definitions and categorizations in a way that poses problems for proper oversight. The FDA Nanotechnology Task Force examined a limited set of questions with regard to nanoproducts and concluded in 2007 that the current oversight framework was appropriate. In 2010, FDA has acknowledged the limitations of defining nano as less than 100 nm for drugs and devices by starting to collect data on new submissions of drugs less than 1000 nm in a dimension. However, with evolving information, the FDA will need to routinely reexamine these issues, feeding information acquired from collaboration with experts and industry into that process. The FDA specifically needs to reassess the boundaries separating biologics, drugs, and medical devices and to consider whether "combination products" that use nanotechnology will be sufficiently categorized based on their "primary mode of action" (PMOA) (http://www.fda.gov/CombinationProducts/RFDProcess/default.htm) when mechanical, chemical, and biologic properties are intertwined. In order to aid in this process, FDA should increase institutional collaborations among the Office of Combination Products, Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Center for Biologics Evaluation and Research (CBER) regarding nanotechnology.
- FDA should use the amendments made in 2007 to FDCA that provide a mechanism to request additional information from industry and develop effective ways to mine that information and ensure that similar requirements can be applied to biologics and high-risk medical devices (see http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm). Specifically, the amendments bolster post-market obligations (21 U.S.C. § 355-1) and "new safety information" procedures to revise labeling (21 U.S.C. § 355(o)). For example, FDA could require the manufacturer of a specific product or product classification to report and describe nano-features of their medical device or drug product in the submission process, require the manufacturer to periodically update nano-information, and require elevated reporting and post-market monitoring for nanoproducts. This enhanced reporting and post-market monitoring is an important component of the life-cycle approach to oversight described earlier.
- FDA should begin to develop guidance and, where appropriate, promulgate regulations on any distinct requirements or divergence from current review and approval pathways. For example, FDA should require that a generic nano-version of a "non-nano" pioneer drug go through the full new drug approval process rather than the abbreviated approval process because the nano-version could pose safety and efficacy issues not addressed by the abbreviated process. Likewise, FDA should not

determine that a product incorporating nanomaterials is "substantially equivalent" to a predicate medical device unless the predicate device had substantially equivalent nanomaterials. Otherwise, the agency should specifically assess the technical, scientific, and medical issues and, as appropriate, utilize the de novo process to determine regulatory classification or classify the product up to a higher risk class. The key theme of these recommendations is that nanoproducts should require the full complement of safety and efficacy data rather than piggy-back on earlier non-nanoproducts using a flawed definition of substantial equivalence that does not account for the unique properties of nanomaterials and nano-products.

NIH and FDA for gene transfer research

- Gene transfer research or "gene therapy" in human beings remains an experimental procedure. Gene transfer has already begun to use nanotechnology, specifically nano-vectors for gene transfer, yet it is not clear that FDA or the RAC have adequate expertise to assess these protocols, especially given the uncertainty surrounding long-term effects on human research participants. The FDA and NIH share oversight authority over gene transfer research. CBER at FDA evaluates the safety and efficacy of proposed gene therapy research in human beings, while the RAC under the Office of Biotechnology Activity (OBA) at NIH reviews proposed protocols to identify those posing new ethical issues warranting further review. These federal oversight entities build on local institutional oversight conducted by Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs). Increased capacity and expertise are needed to deal with the challenges of analyzing protocols using nanobio and protecting human subjects.
- The current regulations governing human subjects' research at both NIH (the Common Rule, 45 C.F.R. Part 46) and FDA (21 C.F.R. Part 50) were developed with no consideration of nanobio. By their terms, applying these rules to the proposed human subjects research requires assessment of risk to the human participant, potential benefits if any, and the relationship between the two. This is likely to be challenging for protocols involving nanobio, given current levels of uncertainty. Both the NIH and FDA oversight authorities should address this explicitly, considering what levels and types of uncertainty currently render protocols unapprovable, and giving guidance on this to local authorities such as IRBs.
- The Common Rule and its FDA equivalent focus on the human participant in research trials. They say nothing about risks to lab workers or close contacts of the participant and also fail to address environmental effects from materials used in trials. Both oversight authorities need to address this gap, ideally in coordination with each other as well as OSHA and EPA.
- The RAC specializes in ethical analysis of proposed human trials. Yet the RAC has thus far been silent on the ethical challenges of human trials using nanotechnology, though they have reviewed some individual protocols involving nano. The RAC should undertake thorough ethical analysis of this challenging topic to provide adequate guidance and recommend protections going forward. The FDA should collaborate on this ethical analysis, to coordinate oversight approaches. Because gene therapy protocols require FDA approval, the FDA is positioned to put into effect protections that the RAC recommends.

Coordinated framework for GEOs (EPA, FDA, USDA, NIH)

- The history of oversight for GEOs illustrates one way to oversee converging products based on biological organisms or molecules: the Coordinated Framework for the Regulation of Biotechnology (OSTP 1986). Although this particular framework has been criticized and has some weaknesses (see Kuzma et al. 2009), a similar one could be developed for nanobio products. One criticism is that FDA's treatment of GE foods was predicated on the doctrine of substantial equivalence, treating GE foods as generally substantially equivalent to their conventionally bred counterparts unless shown otherwise to pose increased risk. Given the special properties of nanomaterials, a substantial equivalence approach for food products may not be appropriate. Regardless, a

Coordinated Framework approach for convergent and active nanobio products should be explored for its ability to bring the agencies together to deal with oversight for convergent products. This exploration could occur under the coordinating body for nanobio oversight within OSTP.

- The FDA does not have strong pre- or post-market testing requirements for GEOs and seems to be taking a similar path for foods derived from nanomaterials (as well as dietary supplements and cosmetics, although our case studies did not address these). In the case of GEOs, FDA's voluntary approach did not inspire public confidence nor did it lead to rigorous pre- or post-market testing (Kuzma et al. 2009). FDA has stated a general policy not to treat nanomaterials in foods as any different from non-nanomaterials (FDA 2007). As a result, some nano-food additives or packaging are likely not subject to pre-market testing. Currently, it is difficult to determine which nanomaterials in food or packaging materials have gone through more rigorous pre-market testing, because data submissions to FDA are not marked as nanoproducts. FDA should reconsider its approach to nanomaterials in foods and packaging materials, in light of historical experience with GE foods. At the very least, data submissions to FDA should clearly mark whether a food product is derived from nanomaterials so that the public can discern how FDA is treating these products.
- From the GEOs' case study and analysis of emerging agrifood nanotechnology products (Kuzma and VerHage 2006; Kuzma et al. 2008), it is clear that USDA will need to take a greater role in nanotechnology oversight (under the Federal Plant Pest Act (1994), Federal Meat Inspection Act (1906), and Virus-Serium-Toxic Act (VSTA) (1985)). USDA has paid little attention to nanotechnology oversight to date, and this is a troubling gap. However, USDA has significant expertise and capacity for risk assessment, as evidenced by its farm-to-fork risk assessments for biological hazards such as bacteria in meat and poultry (Crutchfield et al. 1997). USDA could play a much more important role in nanobio risk assessment. USDA should convene a task force including inter-agency and external advisers to explore how to apply its laws and regulations to emerging nanobio products for which the department will likely have authority. In particular, the Office of Risk Assessment and Cost Benefit Analysis should help to design risk assessment protocols and identify data gaps.
- For nanobio, which will involve materials that can act, respond, react, and perhaps translocate in biological systems, risk-assessment paradigms need to be reconsidered. For active nanobio products and applications there will need to be a blend of Ecological Risk Assessment (ERA) with multiple endpoints and iterative monitoring and adaptation (EPA 1998), traditional chemical risk assessment for human health (with more of a linear approach) (NRC 1983), and microbial risk assessment paradigms (USDA-FSIS 1998). Methods for risk assessment may need revision. For example, even for genetically modified organisms (GMOs) in agriculture, there are still no comprehensive risk assessments with multiple endpoints and quantification of overall risk to human health, the environment, and multiple ecological species. Professional organizations such as the Society for Risk Analysis, National Academies of Science (NAS), National Research Council (NRC), and Institute of Medicine (IOM), and Society of Environmental Chemistry and Toxicity (SETAC) should take an active role in developing nanobio risk-assessment paradigms. We may need a focused summit on risk analysis for nanobio, which could be modeled on the basis of the 1997 Presidential Risk Commission to develop risk assessment paradigms (see http://www.riskworld.com/riskcommission/default.html).

Conclusions

The responses of many federal oversight agencies to nanobio have been to use existing laws and other oversight mechanisms. This will ultimately prove to be inadequate for such a complex and convergent technology. The technology demands a new, more dynamic approach to oversight. The authors are proposing a new oversight framework with three essential features: (a) the oversight trajectory needs to develop over time dynamically; (b) it needs to integrate inputs from all stakeholders, with strong public engagement in decision-making; and (c) it should include an overarching

coordinating entity to assure strong inter-agency coordination and communication.

The proposed recommendations in this article of dynamic oversight and specific regulatory and statutory changes are based not only in the historical analysis of oversight experiences in related realms but also based in the analysis of the oversight experience with nanobio materials and products to date. Close analysis of that experience suggests that agencies are themselves beginning to discover that what we are calling dynamic oversight is needed. Both NIOSH and EPA are showing evolution in their approaches to nanobio oversight, based on feedback and experience. At the Congressional level, the initiative to reform TSCA is largely a response to the REACH initiative in Europe. If a tiered approach to risk assessment is indeed adopted as a part of TSCA reform, then this too would represent a move toward a more dynamic oversight model in which risks are evaluated with increasing rigor when data show the need for it.

Early indications of a shift toward more dynamic processes are telling. They suggest that one can learn from the frustrations of earlier experience with science and technology oversight at EPA, FDA, OSHA and NIOSH, NIH, and USDA and from the difficulties on nanobio oversight to date. Successful oversight of this complex, fast-moving, and highly convergent technology will require a dynamic process, multi-stakeholder collaboration, cross-agency coordination, and the capacity to adapt over time. The stakeholder base needs to be expanded to consider and incorporate the views of ordinary citizens who are not members of organizations or professions with specific stakes as these are usually defined; they are, nevertheless, the future consumers, current taxpayers, and the potential patients, who will inevitably encounter nanobiotechnology issues. A vision for a new type of public consultation, which will consider a broader range of voices is needed.

The authors have modeled such a framework that suggests how each of these features can be practically achieved. Rising to the oversight challenge for this complex, convergent, and widely applicable technology requires a major leap forward in the development of oversight for emerging science and technology. The proposed approach is the next step toward an oversight approach that is dynamic and flexible enough to address the challenges of nanobiotechnology.

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References

21st Century Nanotechnology Research and Development Act. 15 U.S.C. § 7501 (2003)

Abbott KW, Marchant GE, Sylvester DJ (2006) A framework convention for nanotechnology? Environ Law Reporter 36:10931–10942

Alexander LT (2009) Stakeholder participation in new governance: lessons from Chicago's public housing reform experiment. Georgetown J Poverty Law Policy 16:117–185

Beckstrom M (2010) The chemical revolt. Pioneer Press. Feb. 7, 2010

Birnbaum LS (2010) TSCA reform under way in congress. Environ Health Perspect 118:a106–a107. doi:10.1289/ehp.1001917

Bowman DM, Hodge GA (2006) Nanotechnology: mapping the wild regulatory frontier. Futures 38(9):1060–1073

Breggin LK, Carothers L (2006) Governing uncertainty: the nanotechnology environmental, health, and safety challenge. Columbia J Environ Law 31:286–329

Center for Advancement of Informal Science Education (CAISE) (2009) Many experts, many audiences: public engagement with science and informal science education. A CAISE Inquiry Group Report. http://caise.insci.org/uploads/docs/public_engagement_with_science.pdf. Accessed 29 November 2010

Choi J, Ramachandran G (2009) Review of the OSHA framework for oversight of occupational environments. J Law Med Ethics 37:633–650

Choi J, Ramachandran G, Kandlikar M (2009) The impact of toxicity testing costs on nanomaterial regulation. Environ Sci Technol 43:3030–3034

Collins FS, Gray GM, Bucher JR (2008) Transforming environmental health protection. Science 319:906–907

Crutchfield SR, Buzby JC, Roberts T, Ollinger M, Lin CTJ (1997) An economic assessment of food safety regulations: the new approach to meat and poultry inspection. Economic Research Service/USDA

Davies JC (2007) EPA and nanotechnology: oversight for the 21st century. Project on Emerging Nanotechnologies, Washington DC

Davies JC (2009) Oversight of next generation nanotechnology. Project on Emerging Nanotechnologies, Washington DC

Dryzek JS, Tucker A (2008) Deliberative innovation to different effect: consensus conferences in Denmark, France, and the United States. Public Admin Rev 68:864–876

DuPont, Environmental Defense (2007) Nano-risk framework. DuPont/Environmental Defense, Washington, DC

Engel-Cox JA, Van Houten B, Phelps J, Rose SW (2008) Conceptual model of comprehensive research metrics for improved human health and environment. Environ Health Perspect 116:583–592

Environmental Protection Agency (EPA) (1998) Guidelines for ecological risk assessment. Federal Register 63:26846–26924

Environmental Protection Agency (EPA) (2009a) Certain chemical substances; withdrawal of significant new use rules. Federal Register 40:42177–42178

Environmental Protection Agency (EPA) (2009b) Proposed new rules on certain chemical substances. Federal Register 40:6160–6161

ETC Group (2003) No small matter II: the case for a global moratorium. Occasional Paper Series 7(1). ETC Group, Ottawa

European Commission (2006) EC 1907/2006 REACH: what is reach? http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm. Accessed 29 November 2010

FDA Nanotechnology Task Force (2007) Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force. Food and Drug Administration, Washington, DC

Federal Meat Inspection Act of 1906. Pub. L. 3913, 34 Stat. 674

Federal Plant Pest Act. 7 U.S.C §§ 150aa-150jj (1957) as amended 1968, 1981, 1983, 1988, and 1994

Fiorino DJ (1990) Citizen participation and environmental risk: a survey of institutional mechanisms. Sci Technol Human Values 15:226–243

Government Accountability Office (GAO) (2009) Chemical regulation: observations on improving the toxic substances control act. GAO-10-292T, Dec. 2, 2009

Greenwood M (2007) Thinking big about things small: creating and effective oversight system for nanotechnology. Project on Emerging Nanotechnologies, Washington, DC

Gunderson LH, Holling CS (2002) Panarchy: understanding transformations in human and natural systems. Island Press, Washington, DC

Guston DH, Sarewitz D (2002) Real-time technology assessment. Technol Soc 24:93–109

Guthrie DM (2003) Engaged governance: an institutional approach to government-civil society engagement. http://unpan1.un.org/intradoc/groups/public/documents/un/unpan013171.pdf. Accessed 29 November 2010

Hamlett P, Cobb MD, Guston DH (2008) National citizens' technology forum: nanotechnologies and human enhancement. CNS-ASU Report #R08-0003

Hendriks CM, Grin J (2006) Ground reflexive governance in practice and context: some democratic considerations. http://www.sozial-oekologische-forschung.org/_media/Hendriks_Grin.pdf. Accessed 29 November 2010

Holling CS (ed) (1978) Adaptive environmental assessment and management. John Wiley and Sons, London

Howard J, Murashov V (2009a) Essential features for proactive risk management. Nat Nanotechnol 4:467–470

Howard J, Murashov V (2009b) National nanotechnology partnership to protect workers. J Nanoparticle Res 11:1673–1683

Inside EPA (2009) EPA poised to propose new reporting rules for nanomaterials. Dec. 25, 2009

International Center for Technology Assessment (ICTA) (2008) Citizen petition for rulemaking to the United States environmental protection agency. International Center for Technology Assessment, Washington, DC

International Center for Technology Assessment (ICTA), Friends of the Earth (FOE) (2007) Principles for the oversight of nanotechnologies and nanomaterials. International Center for Technology Assessment, Washington, DC

Kandlikar M, Ramachandran G, Maynard AD, Murdock B, Toscano WA (2007) Health risk assessment for nanoparticles: a case for using expert judgment. J Nanoparticle Res 9:137–156

Karkkainen BC (2005) Panarchy and adaptive change: around the loop and back again. Minnesota J Law Sci Technol 7:59–77

Karkkainen BC (2006) Information-forcing environmental regulation. Fla State Univ Law Rev 33:861–902

Keiner S (2008) Room at the bottom? Potential state and local strategies for managing the risks and benefits of nanotechnology. Project on Emerging Nanotechonologies, Washington, DC

Kuzma J (2006) Nanotechnology oversight: just do it. Environ Law Reporter 36:10913–10923

Kuzma J, VerHage P (2006) Nanotechnology in agriculture and food protection. Project on Emerging Nanotechnologies, Washington, DC

Kuzma J, Romanchek J, Kokotovich A (2008) Upstream oversight assessment for agrifood nanotechnology. Risk Anal 28:1081–1098

Kuzma J, Larson J, Najmaie P (2009) Evaluating oversight systems for emerging technologies: a case study for genetically engineered organisms. J Law Med Ethics 37:546–586

Kysar DA (2004) Preferences for processes: the process/product distinction and the regulation of consumer choice. Harvard Law Rev 118:525–642

Linkov I, Satterstrom FK, Steevens J, Ferguson E, Pleus RC (2007) Multi-criteria decision analysis and environmental risk assessment for nanomaterials. J Nanoparticle Res 9:543–554

Lux Research (2007) The nanotech report, 5th edn. Lux Research Inc., New York

Macoubrie J (2005) Informed public perception of nanotechnology and trust in government. Project on Emerging Nanotechnologies, Washington, DC

Macoubrie J (2006) Nanotechnology: public concerns, reasoning, and trust in government. Public Understanding Sci 15:221–241

Mandel GN (2009) Regulating emerging technologies. Law Innovation Technol 1:75–92

Marchant GE, Sylvester D (2006) Transnational models for regulation of nanotechnology. J Law Med Ethics 34:714–725

Marchant GE, Sylvester DJ, Abbott KW (2008) Risk management principles for nanotechnology. Nanoethics 2:43–60

Maynard AD (2006) Nanotechnology: the next big thing, or much ado about nothing? Ann Occup Hyg 51:1–12
Meaney ME (2006) Lessons from the sustainability movement: toward an integrative decision-making framework for nanotechnology. J Law Med Ethics 34(4):682–688
National Nanotechnology Initiative (NNI) (2010) Supplement to the President's 2011 Budget, Report prepared by National Science and Technology Council Committee of Technology, Subcommittee on Nanoscale Science, Engineering, and Technology, February 2010
National Nanotechnology Initiative Amendments Act of 2009. S.1482 §§ 6, 8, 11
National Research Council (NRC) (1983) Risk assessment in the federal government. National Academy Press, Washington, DC
National Research Council (NRC) (1996) Understanding risk. National Academy Press, Washington, DC
National Research Council (NRC) (2008) Evaluating research efficiency in the U.S. Environmental Protection Agency, National Academies Press, Washington, DC
Neo BS, Chen G (2007) Dynamic governance: embedding culture, capabilities and change in Singapore. World Scientific, New Jersey
Office of Management, Budget (OMB) (2009) Federal Register 74:8819
Office of Science and Technology Policy (OSTP) (1986) Coordinated framework for the regulation of biotechnology. Federal Register 51:23302–23393
Office of Science, Technology Policy (OSTP), Council on Environmental Quality (CEQ) (2001) CEQ and OSTP assessment: case studies of environmental regulations for biotechnology. Office of Science and Technology Policy, Washington, DC
Office of Science, Technology Policy (OSTP), Council on Environmental Quality (CEQ) (2008) OSTP 2.0 critical upgrade enhanced capacity for White House science and technology policymaking: recommendations for the next president. Office of Science and Technology Policy, Washington, DC
Olsen JP (2004) Citizens, public administration and the search for theoretical foundations. Polit Sci Polit 37:69–79
Paradise J, Wolf SM, Ramachandran G, Kokkoli E, Hall R, Kuzma J (2008) Developing oversight frameworks for nanobiotechnology. Minnesota J Law Sci Technol 9:399–416
Paradise J, Tisdale AW, Hall R, Kokkoli E (2009a) Evaluating oversight of human drugs and medical devices: a case study of the FDA and implications for nanobiotechnology. J Law Med Ethics 37:598–624
Paradise J, Wolf SM, Kuzma J, Kuzhabekova A, Tisdale AW, Kokkoli E, Ramachandran G (2009b) Developing U.S. oversight strategies for nanobiotechnology: learning from past oversight experiences. J Law Med Ethics 37:688–705
Philbrick M, Barandiaran J (2009) The national citizens' technology forum: lessons for the future. Sci Public Policy 36:335–347
Powell MC, Kleinman DL (2008) Building citizen capacities for participation in nanotechnology decision-making: the democratic virtues of the consensus conference model. Public Underst Sci 17:329–348
Project on Emerging Nanotechnologies (PEN) (2007) Nanotechnology and life cycle assessment: A systems approach to nanotechnology and the environment. Project on Emerging Nanotechnologies, Washington DC
Roco MC (2008) Possibilities for global governance of converging technologies. J Nanoparticle Res 10:11–29
Rogers-Hayden T, Pidgeon N (2008) Developments in public participation in nanotechnology: towards sustainability. J Cleaner Prod 16:1010–1013
Scholz JT, Stiftel B (eds) (2005) Adaptive governance and water conflict. Resources for the Future Press, London
Schot J, Rip A (1996) The past and future of constructive technology assessment. Technol Forecast Soc Change 54:251–268
Shatkin J (2008) Nanotechnology health and environmental risks. Taylor and Francis Group, LLC, Boca Raton, FL
Shaw SY, Westly EC, Pittet MJ, Subramanian A, Schreiber SL, Weissleder R (2008) Perturbational profiling of nanomaterial biologic activity. Proc Natl Acad Sci 105:7387–7392
Siegrist M (2000) The influence of trust and perceptions of risks and benefits on acceptance of gene technology. Risk Anal 20:195–203
Siegrist M, Keller C, Kastenholz H, Frey S, Wiek A (2007) Laypeople's and experts' perception of nanotechnology hazards. Risk Anal 27:59–69
Slovic P (1987) Perceptions of risk. Science 236:280–285
States' Principles on Reform of the Toxic Substances Control Act, December 2, 2009, at http://www.saferchemicals.org/PDF/States%27_TSCA_Principles_TSCA_Reform_Principles_Signatures_FInal.pdf
Subramanian V, Youtie J, Porter AL, Shapira P (2010) Is there a shift to "Active" nanostructures? J Nanoparticle Res 12:1–10
Sunstein CR (2005) Group judgments: statistical means, deliberation, and information markets. New York University Law Rev 80:962–1049
Tait J (2009) Upstream engagement and the governance of science: the shadow of the genetically modified crops experience in Europe. EMBO Reports 10:S18–S22
Tikhomorov A (2005) Engage governance and public policy during transition to a market economy. http://www.engagingcommunities2005.org/abstracts/Tikhomirov-Alexei-final.pdf. Accessed 29 November 2010
USDA-FSIS (1998) Preliminary pathways and data for a risk assessment of *E. coli* O157:H7 in beef. USDA-FSIS, Washington, DC
Virus-Serum-Toxic Act 1985. 21 U.S.C. §§ 151-159
Voss JP, Kemp R (2005) Reflexive governance for sustainable development: incorporating feedback in social problem solving. Paper for ESEE Conference, June 14–17, 2005 in Lisbon
Wardak A, Gorman ME, Swami N, Deshpande S (2008) Identification of risks in the life cycle of nanotechnology-based products. J Ind Ecol 12:435–448
Wiener JB (2004) The regulation of technology, and the technology of regulation. Technol Soc 26:483–500
Wilsdon J, Willis R (2004) See through science: why public engagement needs to move upstream. Demos, London
Wolf SM, Gupta R, Kohlhepp P (2009a) Gene therapy oversight: lessons for nanobiotechnology. J Law Med Ethics 37:659–684
Wolf SM, Ramachandran G, Kuzma J, Paradise J (eds) (2009b) Symposium on "Developing Oversight Approaches to Nanobiotechnology: The lessons of history. J Law Med Ethics 37:543–789