Federal Agencies and Emerging Technology

Examining the Federal Nanotechnology Research Strategy

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Preface

About the Author
Connor Slone is a rising senior at The Ohio State University where he is studying Materials Science and Engineering with minors in Business and Statistics. He worked two summers at the Air Force Research Laboratory in Dayton, Ohio and serves as an undergraduate researcher at school. In addition to his academic pursuits, Connor is involved with Habitat for Humanity, Material Advantage, Ohio State’s Undergraduate Research Office, and his department’s Undergraduate Studies Committee. Outside of these pursuits, Connor enjoys playing his trumpet, writing, and mountain biking.

About the WISE Program
Founded in 1980 through the collaborative efforts of several professional engineering societies, the Washington Internships for Students of Engineering (WISE) has become one of the premier Washington internship programs. The WISE goal is to prepare future leaders of the engineering profession in the United States who are aware of, and who can contribute to, the increasingly important issues at the intersection of science, technology, and public policy. (Description courtesy of the WISE Program website; for more information, please visit http://www.wise-intern.org/.)

About ASTM International
ASTM International, formerly known as the American Society for Testing and Materials (ASTM), is a globally recognized leader in the development and delivery of international voluntary consensus standards. Today, some 12,000 ASTM standards are used around the world to improve product quality, enhance safety, facilitate market access and trade, and build consumer confidence. (Description courtesy of the ASTM International website; for more information, please visit http://www.astm.org/.)

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Executive Summary

Nanotechnology is a broad term used to encompass a multidisciplinary field of study. Although the subjects of nanotechnology research share a characteristic small size, they display a remarkable range of other properties like shape and surface modification that can profoundly affect their interaction with living organisms. This presents a challenge for Federal regulators seeking to promote public safety as an increasing number of nano-enabled consumer products reach the market. The role of government as an arbiter of public safety is an important one, but it must be supported by robust scientific evidence. Nanotechnology is difficult in this regard due to a dearth of reliable health and safety data and particularly the scope of the tests necessary to produce it. Solutions can be expedited with improved coordination, which presents a significant challenge for the bottom-up structure of the government’s National Nanotechnology Initiative. Several policy options are available to facilitate knowledge-sharing and encourage reliable health and safety research.

Foremost among these are policies promoting enhanced inter-agency coordination and the ability to parse large quantities of data quickly. This objective aligns with one of the Federal government’s Nanotechnology Strategic Initiatives and could be implemented with one of two potential nanomaterial database systems. The first is an expansion of the under-developed Nanotechnology Knowledge Initiative’s Nanomaterial Registry, a centralized database which nominally curates nanomaterial data from a variety of sources. The second alternative is to create a new system of federated databases in which each participating agency maintains a separate registry capable of communicating with all the others. In addition to improving data coordination, funding and regulatory organizations can promote the adoption of nanotechnology standards by encouraging their use. As with any emerging technology, widespread adoption of standards facilitates consistent testing and data interpretation. These are all critical elements of developing reliable knowledge on which to base future policies.
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Introduction

Applied nanotechnology is no longer the theoretical dream of researchers and futurists. Developments based on nanoscale research are being used to enhance an enormous variety of products and have the potential to fundamentally alter the materials available to scientists and engineers. The number of nano-enabled products available to consumers has grown by over 500% since 2005\(^1\); perhaps even more promising are the biomedical and drug-delivery systems under development, including three cancer drugs now on the market\(^2\). These applications have already incrementally improved consumer products and showed promise for more effective treatment of diseases.

Interest in the potential of nanotechnology has translated to sustained funding in the United States and abroad. The 2013 Federal Budget provides nearly $1.8 billion in funds for nanotechnology research and development across 15 agencies; since 2001, the US government has cumulatively invested nearly $18 billion\(^3\). Research and manufacturing are also a major source of domestic job creation: there were approximately 150,000 American workers in the field of nanotechnology in 2008 with optimistic estimates predicting the need for 2 million by 2020\(^4\).

Although nanotechnology offers many benefits to the public, responsible development of any emerging technology should include a thorough assessment of its potential as a hazard (a possible source of harm) and the associated risk (the chance of harm when exposed to a hazard). Like their traditional material counterparts, some nanomaterials are demonstrably harmful to living organisms. Nanomaterials can also be more difficult to consistently characterize than traditional ‘bulk’ materials, and the underlying mechanisms by which they can prove toxic are poorly understood. These issues are directly relevant to government regulators charged with protecting consumer safety. Although Federal regulatory bodies assess nano-enabled merchandise with traditional methods, these may be inadequate for evaluating the effects of chronic exposure or other novel interactions. The additional methodological impediments to consistent characterization pose a further challenge to researchers and
regulators alike. Until these difficulties are resolved, statements about product safety will inevitably be viewed with some degree of skepticism. It is therefore in the interest of private industries and government regulators to continue emphasizing not only fundamental research, but also tools supporting the development of scientific consensus around terminology and measurement practices. This document does not endeavor to make recommendations about the future of nanomaterial regulation in the United States; rather, it aspires to concisely identify the impediments that all potential nanotechnology regulators must confront, and to present policy solutions promoting the requisite consensus that will ultimately address those issues.
**Background**

**Unique Phenomena on the Nanoscale**

The policy options for improving the nanotechnology research infrastructure require a basic technical understanding of the topic. Nanotechnology describes a broad field of research, development, and application taking place in the realm of the nanometer (one billionth of a meter). It specifically refers to products or processes that have unique properties because of their minute size; this typically occurs when at least one dimension of the material is between approximately 1 and 100 nanometers. A typical human hair is about 100,000 nanometers in diameter, so most nanomaterials are too small to be seen with a conventional microscope.

It is critical to understand the terms ‘nanotechnology’ and ‘nanomaterial’ as expressions used to classify an almost infinite variety of materials based on a common characteristic of size. The range of potential applications for nanomaterials is so broad that no single analogy can adequately capture the scope of their use; however, a comparison to automobiles can be enlightening. Automobiles are constructed for a wide variety of purposes by a multitude of manufacturers. Vehicles may have different sizes, colors, and interior designs, but they are all recognizable as automobiles because of certain shared characteristics. Nanomaterials are also produced for a wide range of applications as diverse as structural material enhancement and cancer therapy. These materials exhibit differences in chemical composition, size, and other important properties, but they are unified as nanomaterials because their behavior at such a small scale is different from what it would be at a larger one.

The difference in properties between the large scale of traditional materials and the small scale of nanomaterials is amply illustrated by gold nanoparticles. The simplest example is that of average particle size, which affects color and reactivity in gold. Particles are simply an aggregation of gold atoms; when many atoms aggregate, a particle is large and the particles collectively exhibit their familiar yellow luster. Gold nanoparticles are created when fewer atoms are allowed to aggregate, resulting in
the formation of smaller particles (typically less than about 100 nanometers in diameter). Below this size threshold, the gold particles appear blue-green or, at sufficiently small sizes, ruby red. Traditional, large-scale gold is also resistant to corrosion and tarnish, but gold nanoparticles smaller than about 5 nanometers are chemically reactive. As explained elsewhere, the changes to color and reactivity result directly from the small scale of the nanoparticles; more significantly, other properties can also be affected.

**Difficulties in Defining Nano-Enabled Products**

Nanotechnology is significant because of its promise to translate these property changes into tangible, useful benefits for our society. Researchers and businesses are interested in exploiting the unique properties of nanomaterials that result from their small size. Among many other applications, nanomaterials have been used to strengthen and prolong the life of concrete, imbue common paint with antibacterial properties, improve the efficiency of solar cells, and develop earlier cancer detection techniques. Broader applications include potential uses in electronics, clothing, medical devices, cosmetics, fuel cells, biosensors, and environmental remediation.

Significant dispute surrounds the definition of nano-enabled products: while these are presumably products whose function relies on incorporated phenomena at the nanoscale, efforts to strictly define the quantity of nanomaterial that makes a nano-enabled product have been stymied in the United States. For example, many sunscreens now incorporate zinc oxide or titanium dioxide nanoparticles to block harmful ultraviolet rays. These sunscreens, unlike traditional sunscreens that do not contain nanoparticles, might be considered nano-enabled. The difficulty arises from the measurement of nanoparticles in the sunscreen or any other product: what should be measured? Average particle size, fraction of the particles in a product below a certain size threshold, and average particle surface area have all been considered as potential regulatory metrics. The second measurement based on the fraction of nanoparticles in a product can be further divided as a percentage.
of total volume or a percentage of total mass\textsuperscript{14}. The next hurdle is one of measurement: given that different measurement techniques produce different results, which technique should be used to evaluate the chosen metric? Size, count fraction, and surface area can be characterized by a variety of methods that produce different measurements. For example, the Nanotechnology Characterization Laboratory lists five distinct methods for measuring average particle size. No single method is necessarily superior to another, but each measures size based on different fundamental principles. For example, the dynamic light scattering technique measures a property known as the hydrodynamic radius of a nanoparticle (the equivalent radius of a hypothetical perfect sphere travelling through a liquid) whereas transmission electron microscopy measures a projection of a nanoparticle (conceptually similar to a shadow). These are both accepted methods for measuring the size of a nanoparticle, but the difference in the measuring technique is significant. In addition to choice of metric and the technique for assessing that metric, a final consideration is required to complete a definition of nano-enabled products: what is the threshold of the chosen metric for a product to be considered nano-enabled? Considering size as an example again, the generally accepted definition for a nanomaterial is one with at least one dimension measuring less than 100 nanometers. Material properties do not fundamentally change at the 100 nanometer limit; the number represents an arbitrary distinction of convenience rather than a scientific one\textsuperscript{11}. As with count fraction and surface area, any broad definition based strictly on a size measurement might include some materials which still retain their bulk properties and exclude larger materials that exhibit novel properties at larger sizes.

The difficulty of creating a broad definition for regulatory purposes is further compounded by the difference in “bound” and “unbound” nanoparticles: some nano-enabled products contain nanoscale materials and structures which are immobilized in a larger surrounding structure (a “matrix”) that precludes easy exposure\textsuperscript{15,16}. For example, regulators must determine whether tennis rackets with composite bodies containing bound nanomaterials\textsuperscript{17} warrant the same consideration as cleaning sprays
containing unbound nanomaterials. The previous examples also presuppose the use of nanoparticles, but the classification challenge becomes yet more difficult with the consideration of other emerging nanoscale structures. The distinction is exemplified by some computers and smartphones: although they do not contain nanoparticles, these products include embedded flash memory and processing chips less than 100 nm across. Regulators must decide if these types of developing technologies should also be encompassed by their definitions.

Regulators in the European Union have attempted to create a generic definition for nano-enabled products with a combination of count fraction (≥ 50% of particles in a material), size (diameter between 1 and 100 nanometers), and surface area to volume ratio (≥ \(60\text{m}^2/\text{cm}^3\)). Several industry groups criticized the definitions for their breadth and suggested some well-established products would be subject to increased scrutiny and regulation using those rules. The definitions were also criticized as being inadequate for addressing particles slightly larger than the threshold (for example, particles with an average size of 105 nanometers). The definitions also fail to address which method should be used to obtain size and surface area measurements. The difficulties in defining nano-enabled products have compelled regulatory agencies in the United States to examine them on a case-by-case basis without creating a broader regulatory framework.

The Significance of Contemporary Nanotechnology

Despite growing research and commercialization efforts, there is substantial dispute regarding the significance of current nano-enabled products. Study at the nanoscale has yet to lead to a truly high-impact, ubiquitous technology; there is even debate as to whether nanotechnology represents something new from a regulatory or commercial perspective. These are critical issues worthy of examination because of the resources being expended under the assumption of an affirmative answer.

Nanoparticles are decidedly not new to the environment. They are present in natural sources such as volcanic ash and clay and have also been produced commercially for many years as carbon black.
in automobile tires. Carbon black was first produced industrially in the late 19th century and was quickly adopted as a strengthening additive for rubber, but particle sizes and surface features could not be accurately measured and were not controlled. Precise manipulation of nanoparticle size and composition developed in the early 1980s with the advent of advanced microscopy techniques that enabled imaging and manipulation of single atoms. Commercialization began in earnest during the early 2000s, after which the number of nano-enabled products increased dramatically: one widely touted estimate projects nanotechnology research and production will provide 6 million jobs worldwide by 2020 as the number of available products and services increases. Numerous specific products utilizing nanotechnology are available to consumers; several databases of these products are publicly available. As critics contend, the nanotechnology in these products does not make them disruptive and the products themselves are not ubiquitous; however, they are present across a wide variety of market sectors and have already created tangible improvements for some industries like electronics. The long-term adoption of nanotechnology might resemble that of synthetic plastics, which were limited for many years to products like billiard balls, shirt buttons, and combs. As basic knowledge and production techniques advanced, plastics became widely adopted and now represent one of the world’s largest industries. This transformation occurred largely over the seventy years between the 1860s and 1930s and is still ongoing; nanotechnology has existed barely thirty years and is vastly more complicated. While complexity may slow development, it also gives nanotechnology the potential to have an even greater impact than a simple set of materials like plastics, which are used primarily for static manufactured components. The absence of transformational nanotechnology does not indicate a lack of potential but rather its relative youth as an industry and field of study.

**Regulatory Challenges for Nanotechnology**

With regard to nanotechnology’s novelty from a regulatory standpoint, it is crucial to bear in mind that regulations typically apply to products and not broad technologies. Many products
incorporating nanotechnology can be reasonably assessed with traditional methods. However, the primary concern surrounding the growing number of nano-enabled products and processes lies in the incomplete understanding of the mechanisms by which nanomaterials can prove toxic. Characterization and testing at the Nanotechnology Characterization Laboratory (NCL) have shown that toxicity for some nanoparticle systems is effectively impossible to predict based on simple, standard tests that have traditionally been employed; where biological interactions are concerned, some nanomaterials require development of their own tests. The challenge is greatly compounded by the number of variables that apparently influence toxicity, which include nanoparticle size, shape, surface electric charge, chemical composition, purity, propensity for aggregation, and dispersing medium. Changes to any of these factors can profoundly alter the manner of interaction between the nanomaterial and a biological organism, leading to an almost infinite number of potential interactions and therefore tests. If a particular nanomaterial or nanoparticle is toxic via previously unobserved mechanisms, regulatory tests created for traditional materials are unlikely to capture the potentially dangerous result. Even if most basic mechanisms were well-understood, nanomaterials can be difficult to characterize because of their extremely small size. Different measurement techniques for size alone produce distinct results: the size measurements from one technique will not be the same as the size measurements from another, and the problem is further complicated by disparities in sample preparation, which can also affect measurements. Reporting one of the simplest characteristics of a batch of nanoparticles—their average size—is essentially meaningless without the context of a detailed procedure, which might still differ from that used at other institutions.

**Potential Nanomaterial Toxicity**

These challenges might be of less concern if not for the demonstrated toxicity of some nanomaterials. It should be reiterated that many nanomaterials have been tested with minimal or no harm to living organisms, and human beings are constantly exposed to a variety of nanoparticles in the
air from other sources such as volcanic eruptions, dust storms, and diesel emissions. However, exposure to these substances in high concentrations is demonstrably harmful to human health, and other nanomaterials have proven toxic or otherwise harmful to a variety of fish, small mammals, and humans\textsuperscript{11,16}. In fish and small mammals, nanoparticles have instigated reactions ranging from irritation of the skin to severe lung lesions. Humans and animals exposed to natural nanoparticles in volcanic dust have also developed respiratory complications related to the small size of the particulates. In addition to the negative effects attributed directly to the nanomaterials, some nanoparticles have an affinity for foreign substances like metal ions or endotoxin\textsuperscript{27}, which is a chemical excreted by bacteria that causes many of the adverse symptoms associated with bacterial infections in humans. Endotoxin is present in every environment containing bacteria and can become attached to certain nanoparticles at nearly any stage of the production or distribution process. Although those nanoparticles might not be inherently toxic, any endotoxin they bring into the body will prompt an unpleasant or dangerous inflammatory response.

The results of previous research demonstrate that certain specific nanomaterials can be considered hazardous, but predictive capacity for the hazard posed by an arbitrary formulation is low. Tests performed with cellular components outside living organisms (\textit{in vitro} experiments) cannot yet be applied generically to assess whether a nanomaterial will have inimical results inside living organisms (\textit{in vivo} experiments)\textsuperscript{28}. Although this challenge is not unique to nanomaterials, nanoparticles tend to aggregate or change in other possibly unpredictable ways when introduced into living organisms\textsuperscript{11,27}. Other known hazards, like the presence of endotoxin, can be difficult to detect: the NCL reports nanoparticles can interfere with traditional tests for the presence of endotoxins\textsuperscript{27}. The sum of these concerns is that insufficient characterization, or misinterpretation of the results, could eventually enable an unsafe product or process to reach the marketplace as the use of nanotechnology increases.
Federal Nanotechnology Research and the NNI

American regulatory bodies are aware of these issues, and several government agencies are at the forefront of research to characterize basic nanomaterial properties. The National Nanotechnology Initiative (NNI) was created in 2001 to coordinate nanotechnology research across different Federal departments and agencies. A full list of the fifteen bodies with dedicated nanotechnology budgets is reproduced in the Appendix as Figure 1. The NNI budget is not a top-down, coordinated distribution of funds for nanotechnology research; rather, each agency performs nanotechnology research relevant to its mission and reports back the estimated funding used therein. The overall NNI budget is compiled from these estimates and can fluctuate with shifting priorities at each agency.

Interagency coordination is effected through the Nanoscale Science, Engineering, and Technology (NSET) subcommittee in the Executive Branch and the National Nanotechnology Coordination Office (NNCO), which facilitates preparation and publication of NNI documents in addition to meetings of the NSET subcommittee. To reiterate, these organizations do not command an overall nanotechnology research budget or dictate funding allocation within each agency. Coordination has instead been achieved through the creation of five Nanotechnology Signature Initiatives (NSIs), which represent specific areas of research focus and potential interagency collaboration as determined by the NSET subcommittee and the Office of Science and Technology Policy (OSTP). An overview of the Federal nanotechnology research infrastructure and coordinating bodies is available in the Appendix as Figure 2. NSIs are informed by the four overarching objectives of the NNI and eight broad research categories referred to as Program Component Areas (PCAs). The full list of NNI objectives, PCAs, and NSIs is available in the Appendix as Figure 3. Multiple agencies have engaged in research pertaining to each of the five Signature Initiatives, enhancing cross-agency communication and collaboration. Figure 4 contains the full list of NSIs and the agencies participating in each.
Detailed breakdowns of the overall NNI budget by agency and Program Component Area (the NNI’s eight broad research and development investment categories) are available in the Supplement to the President’s 2014 Budget, but several trends are relevant to the issues addressed here. Environment, health, and safety (EHS) research is one of eight Program Component Areas (PCAs) and has received increasing funds for the past several years. Ten agencies have requested a total of over $120 million for nanomaterial EHS research in the 2014 budget, which amounts to approximately 7% of the total NNI budget. Instrumentation Research, Metrology, and Standards for Nanotechnology (PCA 4) make up just over 3% of the requested nanotechnology funds with $56.5 million. This number has remained relatively constant since 2011. Combined funding for NSIs is also available. The most relevant NSI to the issues addressed here is the Nanotechnology Knowledge Infrastructure (NKI), which seeks to improve the structure and organization of nanotechnology research data and facilitate the sharing of that knowledge for collaboration. Ten agencies are nominally participating in this NSI during the 2014 fiscal year and contributing combined funding of $23 million. This is a significant increase over the 2012 and 2013 budgets, during which the NKI received combined funding of $2 million per year. The 2014 request for the NKI represents almost 7% of the total budget dedicated to the five NSIs ($343 million) and just over 1% of the combined NNI budget ($1.7 billion). The most notable feature of the NKI is its work on assembling a database for nanomaterials; although this registry nominally has over a thousand materials from seven sources (three government agencies, two universities, a private business, and the National Nanomanufacturing Network alliance), a majority of entries contain only chemical composition and average size measurements without any further data. A similar database has been compiled by the international Organization for Economic Cooperation and Development (OECD). Most entries in the OECD database do not contain data but rather descriptions and links to external studies. The database is actively maintained as of July 2013 and 472 of the 730 entries were provided by American sources (57% of American projects were funded by the EPA, NIOSH, and NSF with...
the remainder of funding coming from a plurality of government agencies, universities, and private sources).

American regulatory agencies have been particularly active in examining the widespread implications of nanotechnology. The Food and Drug Administration (FDA) assembled a Nanotechnology Task Force in 2006 and has since issued several draft guidance documents, including the FDA’s broad definition for nanotechnology and several voluntary guidelines pertaining to the presence of nanotechnology in food and cosmetics. The agency also issued a 2007 Nanotechnology Task Force Report that echoes many of the characterization concerns expressed in this document. However, the FDA does not categorically regulate nanomaterials; rather, the agency has maintained a regulatory approach that focuses on individual products and keeps the onus of safety on nanomaterial producers in industry. The Environmental Protection Agency (EPA) has also responded to concerns about nanotechnology. Although the agency is primarily interested in the environmental effects of nanomaterials, their work on characterization is also hampered by many of the same difficulties hindering other researchers. The EPA has published a Nanotechnology Research Strategy and three nanomaterial case studies examining the environmental impact of specific commercially utilized nanomaterials but has not made any regulatory measures.

The Consumer Products Safety Commission (CPSC) is the final regulatory agency with a designated nanotechnology research budget. The CPSC actively collaborates with the EPA, the National Institute for Standards and Technology (NIST), and the National Institute for Occupational Health and Safety (NIOSH) for testing of commercially available nanomaterials. CPSC also worked with the National Science Foundation (NSF) to review previous studies of nanomaterial release and exposure. Although CPSC works primarily in conjunction with other agencies to evaluate consumer products for safety, it also allocates some resources to maintaining an internal database of nano-enabled consumer products and contributes to the National Library of Medicine’s Household Products Database (HPD).
Critics have targeted the CPSC’s ability to monitor nanotechnology products, particularly given the agency’s recent difficulties with well-understood substances such as lead and phthalates\textsuperscript{42}. Several key non-regulatory Federal participants also have significant nanotechnology research initiatives. For example, NIOSH has released five guidance documents and four publications relating to nanomaterials\textsuperscript{43} and developed the Nanoparticle Information Library (NIL), an online nanomaterial database\textsuperscript{44}. Although the NIL contains 88 entries submitted by 53 organizations, the website has not been updated since 2009 and the last nanomaterial was entered in 2007. An additional key Federal participant in nanotechnology research is the Nanotechnology Characterization Laboratory (NCL), an agency founded in 2004 by the National Cancer Institute in conjunction with the FDA and NIST. The NCL does not fabricate nanomaterials or perform basic research, but instead thoroughly characterizes nanomaterials being developed as cancer therapeutics. This gives the agency a unique perspective as one of the primary testing facilities for nanotechnology and its interactions with living organisms. The characterization and testing techniques employed by the laboratory have been thoroughly developed (often in conjunction with NIST) and the laboratory has produced several articles and reviews based on the trends it has observed\textsuperscript{27,45,46,47}.

Private standards developers have also reacted to the needs of nanotechnology researchers. ASTM International’s Committee E56 on Nanotechnology was formed in 2005 in response to requests from an academic group. In 2013, Committee E56 had six technical subcommittees with a total of 180 members representing 22 countries. ASTM International has eleven active standards pertaining to nanotechnology: two concerning informatics and terminology, five pertaining to physical and chemical characterization, three regarding relevant tests for environmental, health, and safety concerns, and one pertaining to nanoscale particles in occupational settings\textsuperscript{48}. The European-based International Organization for Standardization (ISO) formed Technical Committee (TC) 229, Nanotechnologies, in
TC 229 also has six subcommittees made up of delegations representing 34 countries. ISO has published thirty-five standards concerning nanotechnology: seventeen pertaining to preparation and characterization, ten regarding terminology and vocabulary, and eight related to the environment, health, and safety. Information about relevant nanotechnology standards from ASTM International, ISO, and other standards developers was compiled by the American National Standards Institute Nanotechnology Standards Panel (ANSI-NSP) and published in their Nanotechnology Standards Database.

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1 In contrast to ASTM International, ISO committees are populated by government standards bodies from each member country; because the United States lacks a central government standards agency, it is represented by the private American National Standards Institute (ANSI), which accredits other American standards developers.
**Issue Definition**

To perform an accurate assessment of the potential hazard and risk from nanomaterials, researchers, businesses, and Federal agencies need consistent and reliable techniques for characterization and toxicity testing. These stakeholders also need to build a research-driven consensus regarding the underlying mechanisms of nanomaterial toxicity; that knowledge will optimally be used to improve the efficacy of *in vitro* testing, which can significantly reduce the overall costs of assessment in dollars and animal lives. Many properties can affect nanomaterial toxicity, including chemical composition, size, shape, surface charge, surface functionalization, purity, and stability. Changes to any of these properties for a single nanomaterial can dramatically alter its interactions with living organisms, and the number of potential combinations is almost infinite. Additionally, consistent characterization of those significant properties can be difficult. Different methods for measuring the same property can produce different results and variations in sample preparation also have a dramatic impact. Although these are technical challenges that must be solved with additional research, there are also two major organizational challenges impeding progress.

**Insufficient Standardization**

The first of these is a lack of standardized methodologies in sample preparation, testing, and reporting. Although there is ongoing deliberation as to which measurements are most relevant, this should not preclude standardization of the methods in use. For example, the NCL lists five methods for measuring the size and size distribution of nanoparticles. The idiosyncrasies of each method produce different results that make comparison between methods difficult, particularly across laboratories. Multiple measurement techniques are likely necessary for accurate characterization, but there must be consensus on the circumstances in which each technique is utilized, and particularly in how the experimental procedure is reported. This knowledge must also be available such that the entire
nanomaterial research community is aware of it. While the NCL is an outstanding resource for well-tested characterization methods, the laboratory works almost exclusively with nanotechnology as a cancer therapeutic. Its knowledge should not, however, be limited to nanotechnology researchers working in that niche. Widespread adoption and standardization are dependent on broad dissemination of that knowledge through conferences, publications, and a presence at standards development organizations.

**Insufficient Knowledge Sharing**

The second significant source of organizational difficulty stems from the lack of coherent data sharing for nanomaterial toxicity results. Changing the properties of a nanomaterial typically necessitates additional testing; however, assessing a plethora of nanomaterials is clearly an unpalatable option because of the obvious time and financial resources such an undertaking would consume. Despite this challenge, there is no widely-used consolidated source of information that can be searched by material or property of interest. This seems to be a significant disadvantage: much of the knowledge gleaned by NIST and the NCL are a result of their experience with a large number of diverse nanomaterials. The NCL has published an entire article on the trends it has observed that would not be obvious to researchers working with a small subset of nanomaterials. The problem is compounded by the multidisciplinary nature of nanotechnology and particularly the study of its potential toxicity (nanotoxicology). These studies sit at the intersection of chemistry, physics, materials science, biology, and pharmacology. Each of these is a distinct field of study, and it is exceedingly difficult to acquire full expertise in all of them. Research on nanomaterials is consequently a multidisciplinary endeavor, particularly for biological applications. The number of journals that contain nanomaterial publications is staggering, and most journal databases do not simultaneously cover journals from each of those fields. Consequently, it can be difficult and time consuming to perform a thorough search of the available
knowledge. This has also contributed to the lack of standardized sample preparation and characterization methods.

Although these challenges are not inherently issues of government policy, they directly affect government researchers and regulators working to promote public safety. They also influence universities and businesses, which in turn impact the economy and job market. Regulators cannot balance the need for safe products and the freedom of private businesses without reliable information; researchers in government, academia, and industry are slowed by the lack of standardization and irreproducibility of results; and industry incurs high risk in developing products and processes in a system without an established and well-known regulatory framework. These issues are all important to the role of the government or its ability to function. The specific policy options available to it can potentially address contemporary challenges in nanotechnology research.
Policy Proposals and Alternatives

The most immediately useful solution policymakers can implement is one that begins to address the lacking informatics structure in nanotechnology health and safety research. The benefits of accessible data for trend analysis are clear based on the experiences of the NCL and NIST, and a more centralized repository for information could expedite future literature searches and research. An improved informatics structure could potentially take several forms. The first is an expanded configuration of the NKI’s current database in which more Federal agencies participate and do so more thoroughly. Only the National Institute for Occupational Safety and Health (NIOSH), the National Cancer Institute (NCI), and NIST currently participate, and to varying degrees. Increased involvement by regulatory agencies like the FDA, EPA, and CPSC would significantly boost the utility of the database. Increased data submission from participants is also essential to database efficacy: for example, of the 1033 materials counted by the registry, only 37% report nanomaterial shape and only 12% report size distribution (as opposed to an average size)\textsuperscript{31}. These types of data will be essential to examining trends in biological and environmental interactions, and any database without them will likely be of minimal use. The NKI’s database has several advantages as a platform for expansion, the greatest of which is its current availability. The underlying structure already exists and simply needs additional participants and more data. The database is also accessible to the public (i.e, academic and private researchers), enabling widespread collaboration and enhanced communication across traditional boundaries. Finally, the concept of the single database fits within the framework of the government’s current NSIs, which already receive some degree of funding. The greatest disadvantage of the single database results from the bottom-up nature of Federal nanotechnology research and has impeded its expansion thus far. The challenge is a product of differing missions among Federal agencies, each of which has a separate priority. The particular nanomaterial qualities important to the FDA (for example, the ability of nanoparticles to penetrate the skin) are unlikely to be the same qualities of importance to the EPA.
(which might have more interest in examining how nanoparticles disperse or aggregate in bodies of water). The problems are not fundamentally unrelated: taking the previous example, aggregation of certain nanoparticles could conceivably affect the extent to which those nanoparticles were able to penetrate the skin. However, this effect might not be immediately obvious and the questions of interest at each agency have remained seemingly disparate. Disagreements over the structure and necessary content for a central database have consequently stymied full implementation. Database maintenance and curation have also impeded progress: if many agencies are to use the database, which will devote resources to sustaining it? The NKI database is presently sponsored by the NIH and managed by RTI International, which addresses that particular question for the moment. However, as the database expands, conflict might arise from increased funding demands.

Structural and funding challenges based on the separated nature of Federal agencies could be addressed with a second, alternative database option: use of a federated database system. Under this plan, each participating Federal agency would maintain its own in-house database. Although separated, each database would be capable of communication with the others and could make its contents available to every other database in the system. Federated databases are employed in other industries such as business and finance, which regularly experience corporate mergers that require data integration from separate systems. A federated database system has several important advantages in the context of Federal nanotechnology research, notably that it confers the same benefits as a single database but with added flexibility. Researchers could take advantage of insight gleaned in other agencies and easily analyze broad trends, while each agency would only be responsible for maintaining a database relevant to its mission. This directly addresses challenges of maintenance and funding inherent to the single database system and gives participating agencies the opportunity to examine their own qualities of interest. Like the single database, the federated database could be made accessible to academic and private researchers in addition to participating agencies. Like the single database, the
federated database also has the advantage of being potentially covered by an existing, funded NSI. The largest disadvantage of the federated system comes from the same NSI in the form of the pre-existing NKI database. Funding and resources have already been devoted to the other system that would be rendered redundant with the creation of an additional database system. Nor can a federated database escape the need for some coordination across agencies, at least in the creation and establishment of the technical infrastructure. As the coordinating body for budgets and inter-agency endeavors, the NNCO might be a logical choice as a mediating organization. However, this would require significant technical expansion for that office and the addition of designated staff with experience in information management. Implementing a single or federated database would be invaluable to the research community, but either system presents unique additional challenges.

Federal agencies are also in a position to promote the use of standards in nanotechnology characterization and testing. Inconsistencies and incomplete reporting hamper the research community’s ability to rely on older publications which consequently hinders analysis of any overarching trends. Standardized methods for data acquisition and reporting offer considerable insulation against irreproducibility; reference materials, such as those produced at NIST, also promote consistency across laboratories. The utility of standards is widely accepted and many are implemented by government agencies; however, increasing the use of nanotechnology characterization and testing standards outside government labs would be beneficial to both public and private researchers. Several avenues exist for increasing the implementation of nanotechnology standards, the most expeditious of which is to bring them to private standards developers like ASTM and ISO. For example, the NCL maintains an extensive online list of the characterization and toxicity tests it performs, many of which are broadly applicable procedures refined in conjunction with NIST. Although some toxicity tests will not be applicable to every nanomaterial, the characterization techniques in particular could be codified as standards at ASTM and ISO. Creating international consensus standards from the methods would increase industry and
academic awareness of their existence through the very process by which standards are created and approved. Their official nature and widespread recognition also encourages use in future research. Even without the authority of a private standards developer, a method can be considered “good practice” and widely adopted. Ubiquitous implementation requires awareness of the methods by the nanotechnology research community, but, continuing with the previous example, the techniques on the NCL website have not been promoted elsewhere and are unlikely to be seen except by researchers already interested in the NCL.

This might be addressed through grant-giving organizations like the NSF, which communicates with a wide variety of researchers. All funding from the NSF is conditional upon agreement to a set of fixed terms and additional potential stipulations which vary with award type. For projects involving nanotoxicology or similar research, the NSF could include relevant references to vetted methodologies developed at Federal labs like NIST and the NCL. Researchers would maintain their independence to design and implement their studies, but increased awareness of extensively developed procedures could increase their use. The NSF could also formally encourage the use of methods and standards from specific sources like NIST and the NCL or ASTM and ISO. Although this would not constitute an enforced requirement, it would exert additional pressure on private and academic researchers to use the specified procedures and standards. Formal promotion of specific practices is not unprecedented: for example, the NSF officially encourages use of the metric system and the use of American-produced equipment in any research performed with its grants. Utilization of the NSF as a disseminator of information is potentially complicated by the need to define which projects would receive information or formal encouragement. Fortunately, grant applications to the NSF are specific and self-defined, and the lack of mandates would enable a liberal classification system (i.e., promotion of specific test procedures to an irrelevant research group would be an inconsequential mistake). It should be noted
that characterization methods and test procedures, whether formalized as standards or simply treated as accepted practices, could also be widely disseminated through either database system.

The greatest nanotechnology concern preoccupying regulators and businesses is the question of whether specific nanomaterials will require regulation, and what form that regulation would take. The difficulties with generic regulation are clear, not least of which is defining a nano-enabled product for regulatory purposes. The case-by-case examinations practiced by organizations like the FDA have not been proven inadequate, but they also rely on data submitted by the business sponsoring the product. To ensure thorough and accurate characterization, regulatory agencies could consider utilizing more standards and official NIST/NCL practices in their requested information. This is an ongoing process at the FDA, EPA, and CPSC, but it is included here for emphasis.
Recommendations

Inter-agency research coordination and communication could be improved with a nanotechnology database, but the optimal structure for that database remains an issue best left to participating researchers. The federated database system would likely be a better, more flexible system for agencies and their researchers in the long run, but it would be difficult and potentially expensive to establish. The current database produced to advance the NKI Strategic Initiative has the benefit of immediate convenience and some current participation, but is less attuned to the needs of different agencies and could pose funding and maintenance issues with increased use. Although either option could be feasible, the best route for researchers and policymakers is to pursue one system or the other rather than attempting to hedge their choices. Considering the present availability of the NKI database and the technical and organizational difficulties associated with creating federated databases, developing the former with input from multiple agencies is likely the more viable option.

Federal agencies should also emphasize widespread implementation of accepted practices or standards in nanomaterial characterization and testing. Of the options presented, a continued presence with private standards developers is likely the most easily achieved, followed by promotion of methods through grant-giving agencies like the NSF. Interaction with standards developers is crucial to the long-term success of the nanotechnology research enterprise. Although this is already widely recognized, other test methods developed by the NCL and NIST might be sufficiently developed to warrant standardization. Standardization would encourage widespread acceptance over the long term. In the short term, highly visible promotion of those methods as accepted practices would likely bring them to the attention of researchers who wouldn’t otherwise have discovered them. Although the NSF could implement the policy informally, the detriments of formal encouragement are negligible and the practice would be more likely to reach researchers.
Conclusion

The Federal government has a variety of available policy options to continue improving its nanotechnology research strategy. The single most essential element for success in the present and future is to maintain support for the National Nanotechnology Initiative and funding for each of its participating agencies. Although the optimal extent of government research and funding for nanotechnology is beyond the scope of this document, Federal commitment to promoting the general welfare and providing some degree of protection for consumers is a widely accepted endeavor. This requires strategic thinking for nanotechnology, which challenges regulators with a lack of reliable information and a difficult path to obtaining it. Although an improved research structure will not directly alter the regulatory paradigm, it will provide the tools required to ground decisions in scientific knowledge.
### 15 Federal departments and agencies with budgets dedicated to nanotechnology research and development

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<td>Consumer Product Safety Commission (CPSC)</td>
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**Figure 1:** Federal departments and agencies participating in the National Nanotechnology Initiative with designated nanotechnology research budgets[^29] ([return to the text](#))
Figure 2: Overview of the Federal nanotechnology research infrastructure (return to the text)
Figure 3: Relationships between the NNI goals, broad research categories (PCAs), and specific areas of potential interagency collaboration (NSIs)²⁹ (return to the text)
**Figure 4:** Complete list of Nanotechnology Signature Initiatives (NSIs) and their participating agencies

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Works Cited


[34] “FDA Issues Two Draft Guidances Related to nanotechnology Applications in Cosmetics and Food Substances.” U.S. Food and Drug Administration http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301093.htm


