NANO
Risk Framework

Environmental Defense – DuPont Nano Partnership

June 2007

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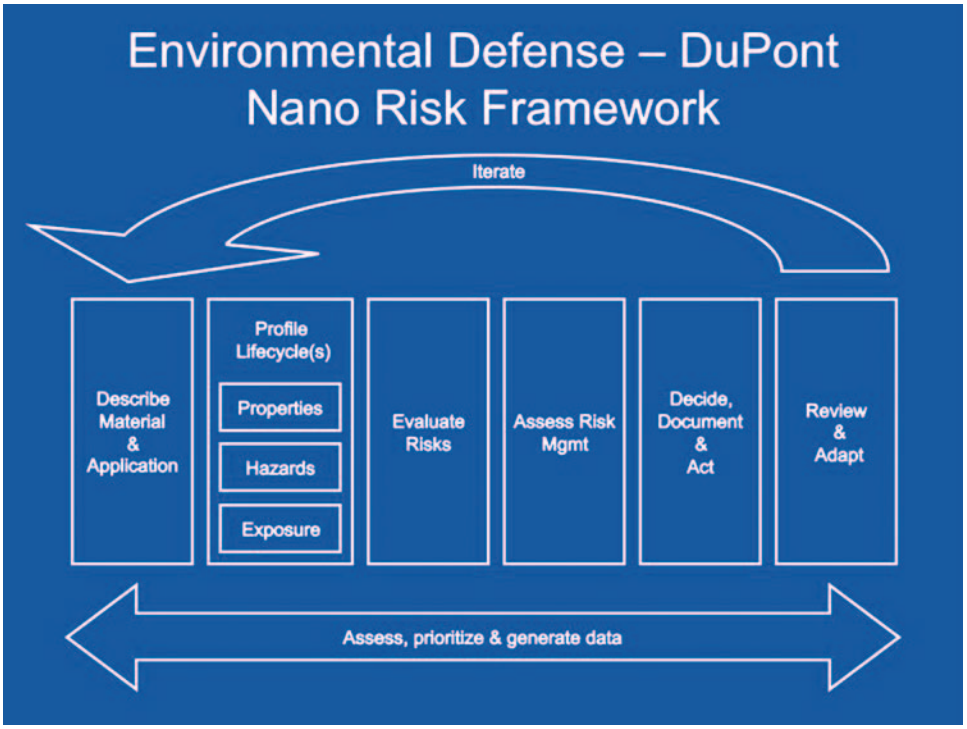

Environmental Defense—DuPont Nano Partnership

June 21, 2007

This document describes a "Framework" — a joint effort by Environmental Defense and DuPont — for ensuring the responsible development of nanoscale materials. It establishes a process that can be widely used by companies and other organizations. Our aim has been to make this Framework as beneficial as possible for a broad audience. In that spirit, reader feedback is welcome.

Environmental Defense—DuPont Nano Partnership

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TABLE OF CONTENTS

Acknowledgements 5
Executive Summary 7
Framework Overview 8
Introduction 11
Developing this Framework 11
Intended Scope and Audience 12
Familiar Elements 14
New and Different Elements 15
Implementing the Framework: Transparency 16
Implementing the Framework: Accountability 16
Implementing the Framework: Roles and Execution 17
Implementing the Framework: Costs 18
Implementing the Framework: Demonstration Projects 20
Continued Evolution of this Framework 21
Step 1: Describe Material and Its Applications 23
Material 24
Applications 25
Step 2: Profile Lifecycle(s) 27
Applying Lifecycle Thinking to Assessing Nanomaterial Risks 27
Stages of the Lifecycle Profile 29
The Use of Base Sets 31
Triggers for Additional Testing 32
Box 1. Potential Triggers for Obtaining Additional Data 33
Sources and References for Base Sets 34
Use of Default Values and Assumptions 34
Use of "Bridging Information" 35
Evaluating Data Quality 36
Step 2A: Develop Lifecycle Properties Profile 37
Base Set of Physical and Chemical Properties 38
Box 2. Physical & Chemical Properties Data 38

Step 2B. Develop Lifecycle Hazard Profile 39
Base Set of Health Hazard Data 43
Box 3. Health Hazard Data 43
Beyond Base Set: Additional Data to Be Developed as Needed 45
Base Set of Environmental Hazard Data 47
Box 4.1. Environmental Hazard Data 47
Beyond Base Set: Additional Data to Be Developed as Needed 49
Base Set of Environmental Fate Data 49
Box 4.2. Environmental Fate Data 50
Box 5. Safety Hazard Data 53
Step 2C. Develop Lifecycle Exposure Profile 55
Box 6. Exposure Data 58
Box 7. Suggested Guidance for Exposure Measurements/Monitoring 60
Step 3. Evaluate Risks 63
Step 4. Assess Risk Management 67
Box 8. Recommended Reading and Guidance 68
Step 5. Decide, Document, and Act 73
Box 9. Potential Review Team Roles 75
Step 6. Review and Adapt 79
Conclusion 83
List of Acronyms 85
OUTPUT WORKSHEET 87

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We released a draft of the Framework to the public on February 26, 2007. We received feedback from stakeholders from various sectors — government, academia, public interest groups, and companies small and large. Their comments helped us further shape and improve the Framework. Except where requested otherwise, we have posted those comments online at www.NanoRiskFramework.com.

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Finally, we note that while this Framework clearly benefited from the input of a great many people, responsibility for it rests with Environmental Defense and DuPont. No assumption should be made regarding the endorsement of any other group or individual.

EXECUTIVE SUMMARY

On June 14, 2005, a column titled "Let's Get Nanotech Right" appeared in the *Wall Street Journal.* Coauthored by Chad Holliday, chairman and CEO of DuPont, and Fred Krupp, President of Environmental Defense, the column outlined several commitments that society should embrace if we are to reap the benefits of nanotechnology's promise. In particular, it called for broad collaboration — interested stakeholders working together — to identify and address potential environmental, health, or safety risks. Less then three months later, Environmental Defense and DuPont entered into a partnership to develop a framework for the responsible development, production, use, and end-of-life disposal or recycling of engineered nanoscale materials — that is, across a product's lifecycle.

What follows is our proposal for a comprehensive, practical, and flexible Nano Risk Framework — a systematic and disciplined process —to evaluate and address the potential risks of nanoscale materials. The Framework offers guidance on the key questions an organization should consider in developing applications of such materials, and on the critical information needed to make sound risk evaluations and risk management decisions. The Framework allows users to address areas of incomplete or uncertain information by using reasonable assumptions and appropriate risk management practices. Further, the Framework describes a system to guide information generation and update assumptions, decisions, and practices with new information as it becomes available. And the Framework offers guidance on how to communicate information and decisions to stakeholders.

We believe that the adoption of this Framework can promote responsible development of nanotechnology products, facilitate public acceptance, and support the development of a practical model for reasonable government policy on nanotechnology safety. We have solicited and incorporated feedback on our overall approach from a wide range of international stakeholders. We have also pilot-tested the Framework on several materials and applications, at various stages of development.

Users acquainted with other risk management tools will recognize some familiar elements within this Framework. In addition, it incorporates several new or atypical elements. For example, it recommends developing informational profiles (or "base sets") — regarding the properties, hazards, and exposures associated with a given nanomaterial and its application — for evaluating risks and guiding decisions. In particular, the Framework recommends developing lifecycle profiles that provide more information on physical-chemical properties, ecotoxicity, and environmental fate than has typically been the case in traditional risk management profiles.

The Framework is information-driven; it does not implicitly assume the risk or safety of any material. Where there is little or no information to guide decisions on the potential for a particular hazard or exposure, the Framework suggests using "reasonable worst-case assumptions" — or, alternatively, using comparisons to other materials or processes that have been better characterized — along with management practices appropriate to those options. The Framework is also designed to encourage replacing assumptions with real information, especially as a product nears commercial launch, and refining management practices accordingly.

The Framework was designed to be flexible, but that flexibility comes with an obligation for users to be transparent and accountable in its implementation. Toward that end, the Framework serves as a tool to organize, document, and communicate what information the user has about the material; to acknowledge where information is incomplete; to explain how information gaps were addressed; and to justify the rationale behind the user's risk management decisions and actions.

The Framework includes an Output Worksheet, which is meant to facilitate evaluation, management, and communication. The worksheet provides a template for organizing all the information requested by the Framework, capturing overall evaluations of that information, and recording consequent decisions.

Framework Overview

The framework consists of six distinct steps. It is designed for iterative use as development advances and new information becomes available.

Step 1. Describe Material and Application.

This first step is to develop a general description of the nanomaterial and its intended uses, based on information in the possession of the developer or in the literature. These general descriptions set up the more thorough reviews, in Step 2, of the material's properties, hazards, and exposures. The user also identifies analogous materials and applications that may help fill data gaps in this and other steps.

Step 2. Profile Lifecycle(s).

The second step defines a process to develop three sets of profiles — of the nanomaterial's properties, inherent hazards, and associated exposures throughout the material's lifecycle. The properties profile identifies and characterizes a nanomaterial's physical and chemical properties. The hazard profile identifies and characterizes the nanomaterial's potential safety, health, and environmental hazards. And the exposure profile identifies and characterizes the opportunities for human or environmental exposure to the nanomaterial — including exposure both through intended use and by accidental release.

The user takes into account the nanomaterial's full lifecycle from material sourcing, through production and use, to end-of-life disposal or recycling. In so doing, the user considers how the material's properties, hazards, and exposures may change during the material's lifecycle (for example, because of physical interactions during manufacturing or use, or from chemical changes that may occur as it breaks down after disposal). The step suggests base sets of information to guide the development of these profiles. Various conditions (e.g., stage of development, type of use) will influence how fully a user may complete the base sets, or whether a user may incorporate additional information into the profiles. All three profiles work together — for example, exposure information may suggest which hazards are most important to investigate, or vice versa. Similarly, the material's properties may suggest which hazards or exposure scenarios are most likely.

Step 3. Evaluate Risks.
In this step, all the information generated in the profiles is reviewed in order to identify and characterize the nature, magnitude, and probability of risks presented by this particular nanomaterial and its anticipated application. In so doing, the user considers gaps in the lifecycle profiles, prioritizes those gaps, and determines how to address them — either by generating data or by using, in place of such data, "reasonable worst case" assumptions or values.

Step 4. Assess Risk Management.
Here the user evaluates the available options for managing the risks identified in Step 3 and recommends a course of action. Options include engineering controls, protective equipment, risk communication, and product or process modifications.

Step 5. Decide, Document, and Act.
In this step, appropriate to the product's stage of development, the user consults with the appropriate review team and decides whether or in what capacity to continue development and production. Consistent with a transparent decision-making process, the user documents those decisions and their rationale and shares appropriate information with the relevant stakeholders, both internal and external. The user may also decide that further information is needed and initiate action to gather it. And the user determines the timing and conditions that will trigger future updates and reviews of the risk evaluation and risk-management decisions for the nanomaterial or nanomaterial-containing product. A worksheet is provided in the appendix for documenting information, assumptions, and decisions.

Step 6. Review and Adapt

Through regularly scheduled reviews as well as triggered reviews, the user updates and re-executes the risk evaluation, ensures that risk management systems are working as expected, and adapts those systems in the face of new information (e.g., regarding hazard data) or new conditions (such as new or altered exposure patterns). Reviews may be triggered by a number of situations (development milestones, changes in production or use, or new data on hazard or exposure, for example). As in Step 5, the user not only documents changes, decisions, and actions but also shares appropriate information with relevant stakeholders.

Through these six steps, the framework seeks to guide a process for risk evaluation and management that is practical, comprehensive, transparent, and flexible.

The Framework, an editable version of the Output Worksheet and case studies demonstrating the Framework's implementation on a variety of nanomaterials and application are available at www.NanoRiskFramework.com.

INTRODUCTION

We believe that the adoption of the Framework can promote responsible development of nanotechnology products, facilitate public acceptance, and support the formulation of a practical model for reasonable government policy on nanotechnology safety.

Nanotechnology is the design and manipulation of materials at the nanometer scale such that novel or enhanced properties emerge. It is a new area of knowledge that promises a dazzling array of opportunities in areas as diverse as manufacturing, energy, health care, and waste treatment. But while the ability to develop nanomaterials and incorporate them into products is advancing rapidly, our understanding of the potential environmental, health, and safety effects of nanomaterials — and of the most effective ways to manage such effects — has proceeded at a much slower pace. Because of the novel properties that emerge at the nano scale, nanomaterials may require more and different information than called for under traditional risk management systems. And given the enormous commercial and societal benefits that may potentially come from this technology, it is likely that nanomaterials, and the products and other applications containing them, will be widely produced and used. Therefore it is especially important to understand and minimize the potential risks.

Environmental Defense and DuPont worked to develop a comprehensive, practical, and flexible system, or "Framework," for evaluating and addressing the potential environmental, health, and safety risks of nanoscale materials. Further, the Framework is designed to be a tool for documenting and communicating the actions a user has taken — along with the basis for them — to address those risks. We believe that the adoption of the Framework can promote responsible development of nanotechnology products, facilitate public acceptance, and support the formulation of a practical model for reasonable government policy on nanotechnology safety.

Developing the Framework

We began our partnership to develop this Framework on September 1, 2005, [1] and we soon assembled a multidisciplinary team, drawn from both organizations, with expertise in biochemistry, toxicology, environmental sciences and engineering, medicine, occupational safety and health, environmental law and regulations, product development, and business development. We have worked for nearly two years to develop the present Framework.

[1] "Environmental Defense and DuPont: Global Nanotechnology Standards of Care Partnership," October 11, 2005, http://www.environmentaldefense.org/article.cfm?contentID=4821

During that time, Environmental Defense and DuPont took a number of measures in order to be inclusive of all interested parties and improve the Framework based on their input. These measures involved discussing project goals and the overall outline of the Framework, as well as sharing early drafts, with stakeholders from various sectors — government, academia, public interest groups, and companies small and large. We gave presentations on the Framework to numerous organizations and conferences. Prior to releasing its first public draft, Environmental Defense and DuPont shared an earlier version of the Framework with diverse experts in the field. We released a draft of the Framework to the public on February 26, 2007. Since then, the draft document has been downloaded over 1,500 times in nearly 50 countries. Except where requested otherwise, comments we received on the draft have been posted online at www.NanoRiskFramework.com.

We have also pilot-tested the Framework, on several materials and applications and at various stages of development, to ensure that our approach is flexible, practical, affordable, and effective.

Intended Scope and Audience

The purpose of this Framework is to define a systematic and disciplined process for identifying, managing, and reducing potential environmental, health, and safety risks of engineered nanomaterials across all stages of a product's "lifecycle" — its full life from initial sourcing through manufacture, use, disposal or recycling, and ultimate fate. The Framework offers guidance on the key questions an organization should consider in developing applications of nanomaterials, and on the information needed to make sound risk evaluations and risk-management decisions. The Framework allows users flexibility in making such decisions in the presence of knowledge gaps — through the application of reasonable assumptions and appropriate risk-management practices. Further, the Framework describes a system for guiding information generation and updating assumptions, decisions, and practices with new information as it becomes available. And the Framework offers guidance on how to communicate information and decisions to key stakeholders.

The primary audiences for this document, therefore, are organizations (such as companies and public and private research institutions) that are actively working with nanomaterials and developing associated products and other applications. The Framework is designed to help those organizations evaluate the risks of the materials and applications they are considering, determine how to manage those risks, and communicate their decisions to stakeholders such as workers, customers, suppliers, and the public. The Framework can also be useful to other stakeholders, such as government officials, academia, financial institutions, and nongovernmental public-interest organizations (NGOs). Thus we have worked to engage a wide range of stakeholders at various stages throughout the project to draw on their expertise and solicit input. We hope the Framework can make a valuable contribution to the growing public discourse on nanotechnology, and both DuPont and Environmental Defense look forward to participating in such future discussions.

Given the team members' areas of expertise, the Framework concentrates on environmental, health, and safety risks. As a result, a number of other issues that some observers have raised about nanotechnology — social equity, national security, economic development, and personal privacy, for example — are not addressed. While we recognize these omissions as well as their

importance in the broader nanotechnology dialogue, we also note that it might be possible for some users to incorporate such elements into their own adaptations of the Framework.
Given the newness and uniqueness of nanoscale materials, there is a clear need to develop standards for describing them. [2, 3] Government authorities and others have identified property characterization and measurement, including standardization, as essential areas in which further research is needed in order to develop risk-management frameworks. [4, 5] A number of committees and workgroups within standard-setting organizations are also addressing terminology and nomenclature for nanoscale materials. [6, 7, 8] These high-priority efforts are important for ultimately ensuring accurate characterization. [9] But until they have produced results, we expect that different users may define nanomaterials differently. Nevertheless, the Framework is intended to be useful even in advance of clear answers on such terminology questions.

As a working guide, our team has focused on engineered nanoscale materials that exhibit novel properties and consist of particles or physically discrete entities that, in their primary, non-aggregated form, are typically at or below 100 nanometers (nm) in one dimension (e.g., nanoplates or nanoflakes), two dimensions (e.g., nanofibers or nanotubes), or three dimensions (e.g., nanospheres or nanoparticles). The term "nanomaterial," as used in this document, applies to such components, either in their original form or as ingredients in products from which they could be released at some point during their lifecycles — including as a result of downstream activities such as disposal or recycling.

Our Framework is focused primarily on such nanomaterials as they are used in industrial, chemical, manufacturing, and consumer applications, and on the potential risks associated with any releases of nanoscale components from such materials at some point in their lifecycles. We recognize that nanotechnology is being employed in ways that extend beyond this scope. First, nanomaterial applications are emerging in a wide variety of other areas, including pharmaceuticals, medical devices, and pesticides that typically receive greater scrutiny under existing regulatory programs. Second, there are other forms or applications of engineered nanomaterials that have novel or specific properties linked to the nanoscale — for example, materials with nanoscale coatings or nanoscale surfaces or structural features. [10, 11]

[2] Kulinowski, Kristen M. and Colvin, Vicki L., "Environmental Implications of Engineered Nanomaterials," *Nanotechnology Law & Business,* Volume 1.1 (2004)

[3] Maynard, A. Nanotechnology: A Research Strategy for Addressing Risk (July 2006) p.23

[4] UK Department for Environment, Food and Rural Affairs, Characterising the potential risks posed by engineered nanoparticles — A first UK Government research report (2005) p.6

[5] The Royal Society and Royal Academy of Engineering, Nanoscience and Nanotechnologies: Opportunities and Uncertainties 48 (2004), available at http://www.nanotec.org.uk/finalReport.htm (last visited Mar. 6, 2006)

[6] British Standards Institute, PAS 71:2005 Vocabulary — Nanoparticles, May 25, 2005

[7] International Standards Organization, "ISO launches work on nanotechnology standards", November 16, 2005, http://www.iso.org/iso/en/commcentre/pressreleases/archives/2005/Ref980.html

[8] ASTM International, E 2456-06: Terminology for Nanotechnology, December 4, 2006

[9] U.S. Environmental Protection Agency, Nanotechnology White Paper, February 2007, http://www.epa.gov/OSA/nanotech.htm

[10] The Royal Society and Royal Academy of Engineering, Nanoscience and Nanotechnologies: Opportunities and Uncertainties 48 (2004), available at http://www.nanotec.org.uk/finalReport.htm (last visited Mar. 6, 2006)

[11] SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), 29 March 2007, The appropriateness of the risk assessment methodology in accordance with the Technical Guidance Documents for new and existing substances for assessing the risks of Nanomaterials. pp. 12-13. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_004c.pdf

Even where such nanoscale features remain permanently intact, such materials and applications may still present risks — for example, through direct contact of biological tissues or biota with such surfaces. Given the different nature or complexity of such applications, we have not designed the Framework to fully apply to them. While the Framework may be useful in looking at some of the environmental, health, and safety issues associated with these other applications, it doesn't cover all such issues and may well require significant modification to account for the distinct issues raised by such applications and materials.

Finally, this Framework, intended for application in its entirety by users who choose to adopt it, is a stand-alone process; it is not tied to any existing regulatory or voluntary assessment process. Nonetheless, while some elements of the Framework are consistent with certain aspects of governmental guidance and requirements, its utilization will not in any way change the user's obligation to comply with all applicable statutes, laws, or regulations of the country where the user is based.

Familiar Elements

Users acquainted with other risk-management frameworks will recognize some familiar elements here. Although we began this partnership without any preconceived opinions on whether nanoscale materials might require entirely new methods for evaluating and managing risks, we were pleased to find that the basic principles of many existing frameworks could be applied to our work. For example, this Framework follows a traditional risk-assessment paradigm similar to those used by regulatory agencies to evaluate chemicals. [12] A similar approach is also used in many health and environmental management systems and product stewardship systems already employed by numerous companies and organizations. Our hope is that this similarity makes the Framework easy to incorporate into existing systems.

Another familiar element is evident in the Framework's reflection of the typical product-development process that many companies use. This process [13] sets up several milestones as a product moves through basic R&D, prototyping, pilot testing, test marketing, and finally to full-scale commercial launch. Before a product passes from one stage to the next, companies generally hold a product-review meeting to determine whether it is promising enough for continued investment and whether any changes need to be made. It is anticipated that such milestones will be natural points at which to conduct another iteration of the Framework: the information thus produced can help inform product-development decisions by identifying opportunities to "design out" potential risks.

This Framework also draws on principles from lifecycle assessment — that is, the process of systematically and comprehensively evaluating the full environmental, health, and safety impacts of a product over the course of its life. [14] As described further in Step 2, the Framework is not intended to be a full-scale lifecycle analysis, in which one pays prominent attention to resource inputs. Here, we confine the assessment to potential environment, health, and safety risks.

[12] For example, see EPA's New Chemicals Program homepage: http://www.epa.gov/oppt/newchems/index.htm

[13] As described, for example, in McGrath, Michael E. (ed) (1996) Setting the PACE in Product Development. Butterworth-Heinemann, Boston

[14] Fava, J.A., Denison, R.A., Jones, B., Curran, M.A., Vigon, B., Selke, S., and Barnum, J. (eds.), 1991, A Technical Framework for Life-Cycle Assessment, Society for Environmental Toxicology and Chemistry and SETAC Foundation for Environmental Education, Washington, D.C.

While the Framework outlines a prudent or precautionary approach, we do not explicitly invoke the "precautionary principle" in this document. Though the term is used by many organizations and in many contexts, there is no widespread agreement on its meaning. An Internet search to define "precautionary principle" yielded 19 different definitions, [15] while another study notes 14 variations of the principle in "treaties and nontreaty declarations." [16] The European Commission, noting the controversy over the definition of the term, avoids defining it altogether in its 29-page directive on how to apply the principle. [17] We do not intend to enter into the debate over what is meant by the term, and therefore do not use it in this document. However, we believe that the Framework incorporates principles similar to those espoused by some of the organizations that invoke the precautionary principle. [18]

New and Different Elements

In addition to conserving some tried-and-true elements, we also hope with our Framework to improve upon typical risk-management frameworks by incorporating several new or atypical elements. For example, it recommends developing informational profiles ("base sets") — sets of measures relevant to the properties, hazards, and exposures associated with a given nanomaterial and its application — for evaluating risks and guiding decisions. In particular, we recommend lifecycle profiles that provide more information on physical-chemical properties, ecotoxicity, and environmental fate than has typically been the case. These additions are needed because of: a) the limited information and experience with nanomaterials for guiding decisions; b) the inability to predict or extrapolate risk evaluations based on limited information; and c) the importance of properties beyond chemical structure in defining nanomaterials' behavior.

The Framework is thus information-driven. It does not implicitly assume the risk or safety of any material. Where there is little or no information to guide decisions on the potential for a particular hazard or exposure, the Framework suggests using "reasonable worst-case assumptions" — or, alternatively, using comparisons to other materials or processes that have been better characterized — along with management practices appropriate to those options. The Framework is also designed to encourage replacing assumptions with real information, especially as a product nears commercial launch, and refining management practices accordingly.

The Framework establishes a recurrent process that drives a continuous enhancement of understanding and an addressing of information gaps. Unlike some frameworks, this process extends beyond product launch; it includes triggers to reexamine data, gather additional information, update risk evaluations, and adapt controls as the user's understanding of and experience with a material and its application become more advanced over time. In other words, the iterative nature of the Framework allows the user to move forward at early stages of development, without full information.

[15] Google search: "define: precautionary principle", accessed 5/7/07. http://www.google.com/search?hl=en&q=define%3A+precautionary+principle

[16] Kenneth R. Foster, Paolo Vecchia, Michael H. Repacholi, "Science and the Precautionary Principle," Science p. 979-981, May 12 2000. http://www.biotech-info.net/science_and_PP.html

[17] European Commission. *Communication from the Commission on the Precautionary Principle.* February 2000. http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf

[18] See, for example, the European Commission's five general principles of proportionality, non-discrimination, consistency, examination of the benefits and costs of action or lack of action, and examination of scientific developments. European Commission. *Communication from the Commission on the Precautionary Principle.* February 2000. pp. 18-21. http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf

Similarly, the Framework recognizes that different applications may have different safety, health, and environmental implications, and that pre-launch information requirements should be tailored accordingly. Thus a nanomaterial that will find low-volume use in an application in which it is entirely bound within a durable matrix can be treated differently from the same material intended for use in a high-volume and dispersive application.

The elements of this Framework, and particularly the recommendations regarding data requirements, are designed to be useful to practitioners working with nanoscale materials that are entering, or have entered, broad commercial use. However, we recognize that many nanoscale materials are in an early stage of R&D, that there is still considerable uncertainty regarding the nature and extent of their future commercial use, and that full commercialization will typically be preceded by several developmental stages. It is clearly unrealistic, therefore, to take a "one size fits all" approach that ignores these different stages, or to expect that companies will invest heavily in the accumulation of a full set of health, safety, and environmental data for materials whose commercial prospects are still unclear. Nevertheless, it is important to establish a level of understanding appropriate to each stage and to establish corresponding controls over exposure and release.

Our Framework is a flexible tool to organize, document, and communicate what information the user has about the material; to acknowledge where information is incomplete; to explain how information gaps were addressed, including what assumptions were made; and to justify the user's risk-management decisions and actions. But in order for such a Framework to offer assurances to stakeholders, it requires transparency and accountability. The Output Worksheet included in the Appendix, or a variation thereof, may be used as a means of summarizing the relevant information and sharing it with key stakeholders. Again, the iterative nature of the Framework suggests that the amount of information a user shares with stakeholders may vary by stage of development. Though it is likely that less information will be shared at the early stages of development (when little is to be had), users should share enough information by the time of a product's commercial launch that stakeholders have a reasonable understanding of its potential risks and how they are to be safely managed.

Implementing the Framework: Transparency

The flexibility inherent in the design of this Framework should be counterbalanced by the maximum amount of transparency still protective of confidential business information CBI. There are many different ways to insure transparency, such as having key stakeholders (e.g., NGOs) on the review team and making risk information and decisions public. Throughout the process of risk evaluation it is particularly important to clearly identify what assumptions are made and where professional judgment is used in the absence of data, and the basis of the expert assessment should be clearly documented and justified.

Implementing the Framework: Accountability

Framework users must each take primary responsibility for its implementation. Because there may be practical limits to how much the manufacturer of a nanomaterial knows about how it is used, such responsibility for nanomaterial evaluation may need to be shared throughout the value chain. In that way, the evaluation of environmental, health, and safety considerations are promot-

ed throughout the material lifecycle. This sharing of responsibility could require the development of novel collaborations to assure that all the information called for by the Framework will be collected and assessed. Examples of such collaborations could include the creation of supply-chain consortia to address environmental, health, and safety questions that have impacts at different points along the value chain. These kinds of consortia could also provide mechanisms for equitably sharing or allocating costs, thereby addressing concerns regarding cost burdens —especially important for small/medium enterprises (SMEs).

Implementing the Framework: Roles and Execution

Different organizations, depending on their size and structure, will have differing ways of implementing this Framework for maximum effectiveness. In some cases, users will be able to incorporate it into their existing product-development and -stewardship processes. In other cases, users may employ models such as supply-chain consortia.

A critical element of any such system is that a specific person is assigned the responsibility for ensuring the Framework's implementation. In most cases, that person will be a product steward. He or she champions the effort, pulling in knowledgeable individuals from other parts of the organization, or from consultants, supply-chain consortia, or industry consortia, to help generate and compile the necessary information.

Typically, their roles include:

- **Product steward or project leader.** A person who shepherds information from the early stages of the development and is responsible for collecting the environmental, health, and safety data as the Framework is executed.
- **Product or process development team.** The group charged with the technical development of the new nanomaterial and the processes for producing it.
- **Business development or venture team.** The individuals charged with marketing a product and eventually making it available for sale. They are knowledgeable in likely uses of the material and how it is distributed.
- **Manufacturing.** The people involved in commercial production of the nanomaterial (e.g., line workers or managers). They are knowledgeable in how the material is handled and the potential exposures that result from its manufacture.
- **Product stewardship manager.** A person, knowledgeable about the product stewardship protocols of the organization, who acts as a resource.
- **Cross-functional decision-making review team.** A group of key stakeholders, experts, and decision makers charged with critically examining compiled Framework information. They analyze the options, document the resulting analysis, make decisions, and take appropriate actions that are appropriate to the product's stage of development.

Ideally, the team will include professionals with expertise in risk assessment, toxicology, environmental fate, and industrial hygiene. It is recognized, however, that some SMEs may not have the resources to include such staff. One option is to engage appropriate outside experts (e.g., hiring consultants or partnering with university researchers). Additionally, the creation of consortia could leverage resources and furnish the needed areas of expertise.

It is also important to note that implementation of the Framework depends on the user's position in a nanomaterial's lifecycle. For example, companies that manufacture nanomaterials for sale as primary products in diverse applications may have different responsibilities — relating to safe preparation, handling, use, further distribution, and disposal or recycling of these materials, and to the development of relevant data — from companies that purchase the nanomaterials for particular applications. We thus anticipate that cooperation and timely information exchange between nanomaterials' suppliers and their customers will be important, perhaps essential, to the Framework's successful utilization.

Implementing the Framework: Costs

Because many organizations already have a system in place for evaluating material risks and ensuring workplace safety, the most significant factor affecting the incremental costs of implementing this Framework in such cases is the thoroughness of the existing management program. For large companies with well-established systems in place, much if not all of the information gathering is likely already being conducted and thus incremental costs will be lower. Smaller companies that may not have established risk-management systems or in-house expertise may face higher increment costs.

The potential for higher incremental costs also goes up with wider risk or with rising expectations of return on investment. For example, completing the Framework for products in the early-development stage — where only a small research staff subject to potential exposure and product viability is unproven — may not require any new data generation, thus minimizing testing costs. By contrast, products that are ready to be launched commercially — with potential for broader exposure but also greater certainty of financial return — could require a higher level of care and the generation of new test data, thus incurring greater costs.

When it is necessary to generate new data, testing costs will vary widely with the type of material and the type of test. For example, the estimated costs for assessing short-term toxicity — some of the most expensive tests in the Framework's base sets — range from $50,000 to $280,000, depending on the source of the estimate.[19] This is an extreme example, however. Other tests in the base set are not nearly as expensive and their costs are not expected to vary as widely; estimates for the cost of skin sensitization testing, for example, range from $2,800 to $3,000. The point is that the costs of implementing this Framework will vary from user to user and product to product.

Will SMEs have the financial and technical resources to independently implement every facet of the Framework for the products they develop? In many cases, they may not have to. For one thing, we encourage Framework users to share information and costs — for instance, the several companies that may make up a product supply chain may do so. We also allow for other ways to control costs, especially at early stages of product development. Such ways may include:

[19] Sources for estimates included the following:
1) Risk & Policy Analysts Ltd., Revised Business Impact Assessment for the Consultation Document, Working Paper 4, Prepared for the European Commission Enterprise Directorate-General, October 2003, Annex 1, available online at www.rpaltd.co.uk/tools/downloads/reports/reachrevisedbia.pdf
2) Internal cost estimates from DuPont Haskell Labs
3) Cost estimate from international chemical company executive.

- **Compensating assumptions.** The Framework allows for the use of "reasonable worst-case assumptions" in lieu of newly generated information. We expect that users may choose to base management decisions on such options — e.g., assume that a material is toxic and institute standard worker-protection protocols — especially at the early stages of product development. In that way, the incremental costs of generating new information may be avoided. (This alternative is discussed further in Step 2.)
- **Compensating risk management and engineering controls.** A company may wish, in the absence of sufficient information that would fully characterize its material, to utilize practices or technologies that can be shown to eliminate release and exposure — that is, to manage a material as if it were extremely hazardous. Such practices would need to be in place to mitigate any potential risk at all stages of the material's lifecycle.
- **Available information.** Hazard information may already be available in the literature for some nanoparticles or applications, or it may possibly be developed by "bridging" to another, better-characterized material.
- **Intended use.** The amount of information required in the Framework is directly related to the potential extent and degree of exposure of the specified application. Where a user can show a sound basis for ruling out a particular route of exposure or exposed population, the user need not develop corresponding hazard elements.
- **Available methods.** The science of nanoparticle risk assessment is still new, and in some cases new methods for generating hazard information are required. As these methods become standardized, the incremental cost will decrease.
- **Breadth of application.** Materials intended for single or few applications will likely engender a smaller set of exposure scenarios and thus require less hazard information for making risk management decisions.
- **Timing.** It may take years for materials or applications to get from bench scale to commercialization. The Framework envisions a process by which hazard and exposure information is built up during this period, thus spreading potential incremental costs over time.
- **External support.** Organizations may be able to acquire direct financial support, through government grants, for developing hazard or exposure information. Or they may form strategic partnerships with universities or other research institutions that already have funding to develop risk information.
- **Cost-sharing.** It may be possible for several companies within a supply chain to share information and incremental costs over the course of the product-development process.

[20] See, for example, the databases on existing and current research on nanomaterials provided by the U.S. National Institute for Occupational Safety and Health (http://www2a.cdc.gov/niosh-nil/index.asp); the International Council on Nanotechnologies (http://icon.rice.edu/research.cfm); and the Woodrow Wilson International Center for Scholars and the Pew Charitable Trusts Project on Emerging Nanotechnologies (http://www.nanotechproject.com/index.php?id=18). Users may also wish to consult the U.S. National Library of Medicine's TOXNET®, a collection of toxicology and environmental health databases (http://toxnet.nlm.nih.gov/index.html).

Implementing the Framework: Demonstration Projects

DuPont conducted three demonstration projects in order to evaluate the comprehensiveness, practicality, and flexibility of the Framework. The three nanomaterials under consideration differed in terms of composition, structure, intended application, stage of development, and DuPont's role in the development, evaluation, or potential use of the material. Full documentation on these projects is available at www.NanoRiskFramework.com.

The first material, DuPont™ Light Stabilizer 210, is a surface-treated high-rutile phase titanium dioxide. Now nearing commercial availability, it has been optimized to absorb and scatter ultraviolet light so that it is effective as a UV stabilizer and UV screener for polymers. When used in polymer films and coatings, this product can protect substrates from the sun's damaging rays.

DuPont generated a complete Output Worksheet for this product, addressed all of the base sets, completed a risk evaluation, and selected risk management measures. Using the Framework process concurrently with product development, DuPont decided to proceed with making the product commercially available, determined what workplace handling procedures would be necessary, and documented this information. The estimated incremental cost of implementing the Framework in this case was approximately 125 hours of work from product managers and research scientists and $170,000 in direct costs to generate risk data. [21] This demonstration project had the highest cost among the three because the material was closest to commercialization. Also, as DuPont was the sole developer, it had to bear the full cost independently.

The second material, carbon nanotubes (CNTs), consists of cylindrical carbon molecules whose novel properties make them potentially useful in a wide variety of applications (e.g., electronics optics, and materials). CNTs exhibit extraordinary strength, possess unique electrical properties, and are efficient conductors of heat. DuPont is testing the impacts of these properties when blended into a wide range of polymers for diverse applications. Both single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) are being tested.

DuPont developed an Output Worksheet, but it did not address all of the base sets with data because the company's use of CNTs at this point are in the research and development phase, with potential exposures limited to lab workers. However, using available data and conservative assumptions — i.e., that CNTs should be treated as if they were highly hazardous — DuPont considered potential risks and implemented appropriate risk management engineering controls. DuPont identified additional information that would need to be generated — such as relevant toxicology and environmental data appropriate to the specific exposure scenarios envisioned — if any specific applications were to advance closer to the market. Toward that end, DuPont is studying ways to obtain hazard and exposure data from other manufacturers, given that CNTs are already commercially available from them. DuPont is also considering generating its own data. In any case, the Framework analysis would need to be updated with relevant toxicology

[21] There are at least three factors that influence this estimate. First, because DuPont uses a well-established product-stewardship protocol for all new-product development, the estimates above applied only to the incremental effort necessitated by nanomaterials. Second, all tests were performed internally, rather than being contracted out to an external laboratory. Third, DuPont's studies were more extensive than those strictly called for under the Framework. Thus the costs may be different for other companies where these factors do not apply.

and environmental data appropriate to the specific exposure scenarios envisioned at that time. The estimated cost for completing the Framework assessment for CNTs, up through a decision to continue laboratory work, was 80 hours of engineering analysis work and $5,000 in direct costs for a toxicology literature review. [22]

The third material, nano-sized zero-valent iron (nano-Fe^0), is being developed and evaluated for potential use as a reagent to destroy contaminants in groundwater. Developers include a variety of vendors (though not DuPont), and the material and some of its intended applications have been pilot-tested at roughly 15 field sites. At present, DuPont is monitoring the continuing development of nano-Fe^0, as well as competing technologies, specifically for treatment of contaminated aquifers.

DuPont did not generate a full Output Worksheet for nano-Fe0. Rather, the company used the Framework to identify key uncertainties that must be addressed before DuPont would proceed further with evaluating the application. In particular, using the Framework process helped DuPont pinpoint some key physical-safety concerns — specifically, potential fire hazards — that DuPont had not previously identified. The total cost of implementing the Framework for nano-Fe0 was approximately 40 hours of labor by experienced research scientists. The costs were limited to collecting existing information from the supplier or the literature, analyzing that information, and writing up the decision document. No out-of-pocket expenses were incurred, as no tests were conducted or new data generated. While additional data would be called for if the application were to be pursued, some may be available through deeper inquiries with potential suppliers. Also, given the level of interest in the technology among manufacturers, users, and government, there is potential for cost-sharing.

Continued Evolution of this Framework

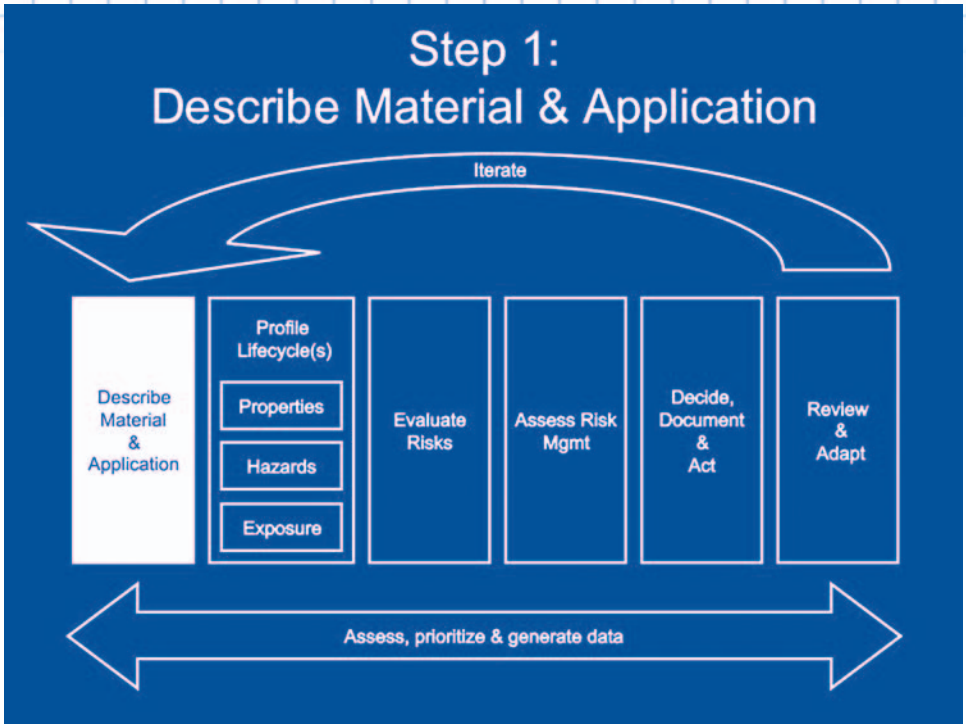
We believe that an "open architecture" approach to the application and continued evolution of the Framework will be the most effective way of ensuring that it remains current as the understanding of nanomaterials evolves. The Framework was developed in an inclusive and transparent manner and we hope it will thereby serve as input for the development of government policy, industry standards, and best practices. We also hope that other organizations and individuals will carry it forward by contributing their own experiences and insights. While the Framework is not intended to be a substitute for government regulation or continuing public discourse, we believe it can make a valuable contribution to the growing global dialogue on nanotechnology.

From the outset of this project, we have recognized that nanotechnology is a complicated and evolving field, and that any risk management framework we develop will be imperfect from the start. This reality further emphasizes the importance of the Framework's iterative and transparent nature. Our hope is that, by applying the Framework through multiple cycles, users will be able to identify and address any potential risks that may not have been apparent at earlier stages. Moreover, by being transparent about what information has been evaluated and what assumptions have been made in applying the Framework, it will be clear what risks have been considered and what gaps remain.

[22] This does not included the costs incurred over the last 50+ years to develop the ability to run a laboratory on a zero exposure basis or the recent cost to develop the ability to monitor laboratory work areas for materials in the nanoscale range.

Ultimately, once fully adopted, this Framework should help the user to assess, manage, and report on the environmental, health, and safety risks associated with a particular material and application. The Framework should prove invaluable in guiding the user to make decisions and take actions that ensure the safety of its materials and products, as well as in communicating the bases for those decisions and actions.

STEP 1
Describe Material and Its Applications



The Framework's first step is to develop basic descriptions — general overviews — of the nanoscale material and its intended uses. These descriptions should be sufficient to later guide development of more detailed profiles of the material's properties, and its hazard and exposure potential, at various lifecycle stages — such as manufacture, use, and end-of-life. For instance, specific details about the material's physical and chemical properties, and how they may change over time, are more fully developed in Step 2A.

The basic descriptions of Step 1 entail chemical composition (including impurities), physical structure, physical form, concentration, size (or surface area) distribution, solubility, and aggregation and agglomeration state. They also identify the material's sources and manufacturing processes, review the literature on its known uses, and identify relevant reference materials [23], incumbent materials (that is, existing materials that would be replaced by the nanomaterial), and bulk counterparts (that is, larger-scale materials with the same chemical composition as the nanomaterial).

A basic description should be generated that covers each of the material's intended uses — existing or new — including any expected consumer uses as well as post-use management or

[23] The International Organization for Standardization (ISO) defines reference materials as follows: "A material or substance, one or more of whose properties are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials." See http://www.vam.org.uk/referencematerials/reference_definition.asp

end-of-life disposal or recycling. Essentially, the basic description should allow all interested stakeholders to become familiar with the material and its reasonably foreseeable applications.

Given its broad and general nature, the information necessary for Step 1 should already be in the possession of the developer or be available in the literature. It should not require additional data, except where there is a need to fill gaps in fundamental information about material characteristics.[24] In such cases, it is reasonable to expect that user will generate the information.

The following questions and suggestions should help to derive the basic descriptions of the material and its applications:

Material

- *What is the stage of development — lab scale, pilot, demonstration, or commercial — of this material?*
- *What is the chemical composition and physical structure of the material?*
- *Are the particles coated? If so, with what?*
- *Are the particles dry powders or in suspension?*
- *What are the approximate sizes and distributions of the primary particle and of agglomerates/aggregates?*
- *What is the general particle shape?*
- *What are the general physical and mechanical properties of this material?*
- *What are the relevant properties of this material in relation to bulk powder handling?*
- *Is the material soluble in water?*
- *Briefly describe the source of the material. Is it manufactured in-house or purchased?*
- *If purchased, describe who produces the material, where it is produced, and how and in what form is it transported to your facility(ies).*
- *What manufacturing process is used to produce the material?*
- *Is there a larger-sized version of this material in commerce?*
- *What other materials exist that are similar to this one?*
- *How long has this material, or a similar material, been in commerce?*
- *What are sources of additional information on this material?*

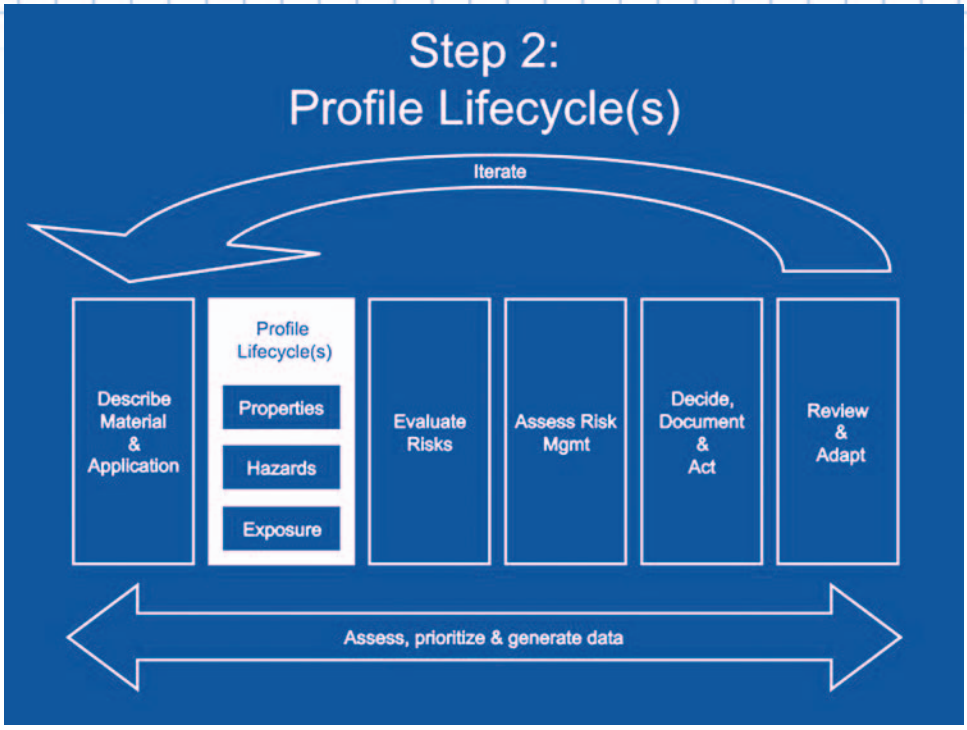
[24] Our expectation that this basic information will generally already be in the possession of the developers is shared by US and UK regulatory agencies. See:
National Pollution Prevention and Toxics Advisory Committee [NPPTAC], A Federal Advisory Committee to the U.S. Environmental Protection Agency. Overview Document on Nanoscale Materials, November 22, 2005
Consultation on a Proposed Voluntary Reporting Scheme for Engineered Nanoscale Materials, United Kingdom Department for Environment Food and Rural Affairs [DEFRA], March 2006.

Applications

- *Review the literature on known uses.*
- *Briefly describe the expected applications of this material, noting especially any differences from the uses of incumbent and bulk materials. Are these uses new relative to any that are already represented in the literature?*
- *Why is the material being manufactured in the nanosize range, as opposed to other sizes?*
- *How will the material be handled when received by downstream processors? by end- users?*
- *Is the material bound in the application? If so, is it a chemical bonding?*
- *Will the material be dispersed in the environment or used by a large number of users?*
- *How much of the material will be present in the various products (wt %)?*
- *Is this a high-volume use?* [25]
- *What new or different application benefits does this material offer relative to existing alternatives for the same application?*
- *List all other potential applications.*
- *Are there applications for this material that intentionally will not be pursued?*
- *How will the materials or products be handled and disposed of, post-use?*

[25] Identifying what constitutes "high volume" for nanomaterials is as yet undefined, and will therefore require professional judgment and will likely vary widely by material and application.

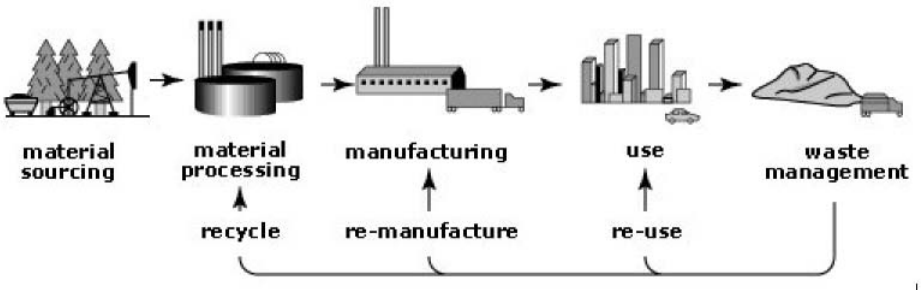
STEP 2
Profile Lifecycle(s)



Step 2 is really three steps, to be discussed in turn in the succeeding sections. It includes examination of the material's properties (Step 2A), its inherent hazards (Step 2B), and the associated exposures (Step 2C) throughout its lifecycle.

Applying Lifecycle Thinking to Assessing Nanomaterial Risks

The lifecycle can be thought of as encompassing all the processes and activities that occur from initial extraction of the material (or its precursors) from the earth to the point at which any of the material's residuals are returned to the environment. [26] A typical diagram of the lifecycle is shown below.



(adapted from www.ami.ac.uk/courses/topics/0109_lct/)

[26] Related concepts or approximate synonyms for the term "lifecycle" used in other contexts include "product trail" and "value chain." Terms such as "industrial ecology," "design for environment," "product stewardship," and "extended producer responsibility" in practice tend to focus more on the end-of-life stage of the lifecycle and hence are more suggestive of specific methodologies.

We propose using lifecycle thinking, appropriately modified to account for the nature of nanomaterials and their applications, to systematically evaluate the safety of a nanomaterial. Assembling such a profile need not entail use of a formalized methodology for lifecycle assessment (LCA), much less the associated consideration of all material and energy inputs and outputs that LCA typically entails. Rather, the lifecycle *concept* is used as a means for organizing all relevant processes and activities to which a nanomaterial (or its predecessor or successor materials) is subjected.

Those processes and activities can then be evaluated to determine whether they carry the potential for the release of, or exposure to, the material or any of its derivatives. That is, the lifecycle profiles developed in Steps 2A, 2B, and 2C will respectively assess the material's physical-chemical properties; hazard; and nature, magnitude, and probability of exposure as a function of any given process or activity.

Three other considerations are important in defining the lifecycle profile of a material. First, it can actually have multiple lifecycles. For example, a material may be handled in several different ways after use — e.g., by recycling, incinerating, or landfilling. Or the raw materials used to make it may be acquired from different sources or processed somewhat differently. Thus the lifecycles can be as envisioned as a many-branched tree, with each branch representing a different application. Because knowledge of each application will reside downstream of the primary nanomaterials producer, that party may need to provide guidance (based on the current state of knowledge) regarding potential limits on the material's uses.

Second, it is important to consider both *established* and *reasonably anticipated* activities or processes to which the material may be subject over its lifecycle, and these may be either intended or unintended.

Third, the lifecycle profile also serves as a useful means of identifying the different actors (typically, commercial entities) that are involved, as the linkages between them are important. While the material manufacturer typically decides on or influences activities (such as workplace-safety practices) "within its four walls," such decisions can profoundly affect the options available to the other actors in the value chain. For instance, a decision to use a toxic heavy metal in a product may ultimately compromise the safety of, or limit the disposal or recycling options for, that product at the end of its service life.

Thus to define and catalog the elements of a material's lifecycle, the following breakdown should generally be followed:

- Describe each known activity by lifecycle stage (e.g., those directly under a company's control).
- Project reasonably anticipated activities by lifecycle stage (e.g., those upstream or downstream of the company).

Each known and projected activity can then be assessed in Step 2C for its potential to result in a material release or direct exposure. If such potential exists, further examination may reveal whether the material is released, or is likely to be released, in nano form, and whether its subsequent fate and behavior may transform it into a non-nano form (or vice versa).

Stages of the Lifecycle Profile [27]

It is important to organize discrete activities according to the stage, or stages, of the lifecycle in which they occur. A general description of the scope and boundaries of the various stages, and their relevance to nanomaterials, is provided below, using the specific example of carbon nanotubes:

Materials Sourcing

This stage of the lifecycle profile encompasses activities for gathering the needed inputs; thus it includes transport from points of acquisition to the point of processing. For a nanomaterial, activities at this stage are relevant if an input is actually acquired in a nano form to which there is potential exposure or if the specific sources of the starting materials influence the composition, properties, or behavior of the resulting nanomaterial — e.g., by affecting the extent of impurities present.

Manufacturing

Three substages — materials manufacture, product fabrication, and filling/packaging — are involved in the transformation of source materials into a product to be delivered to end-users.

> *Materials Manufacture.* This phase entails all the activities involved in converting a source material into a form that can be used to fabricate a finished product. The production of intermediate chemicals or materials is normally included in this category, as is their transport. For example, carbon nanotubes (CNTs) can be produced by several techniques, including arc discharge, laser ablation, chemical vapor deposition (CVD), or high-pressure carbon monoxide (HiPco). In the arc-discharge method, carbon electrodes serve as the raw material; arc discharge between them (either with or without a metal catalyst present) creates a soot-containing mixture of relatively short single- and multi-wall CNTs, as well as many other impurities. In the second method, a pulsed laser beam impinging on a graphite target in the presence of several possible metal catalysts creates relatively pure CNTs. In the CVD method, a carbon-containing process gas (such as ethanol, methane, or ethylene) is passed over a heated surface containing metallic catalyst particles whose composition and size can be varied to alter the characteristics of the resulting carbon nanotubes. In the HiPco process, nanotubes are grown from the interaction between carbon monoxide, flowing at high pressure and high temperature, and catalytic clusters of iron formed "in place" by thermal decomposition of iron pentacarbonyl. Each process thus yields a distinct combination of products — a mixture of materials whose composition varies both with respect to the resulting CNTs and their associated catalysts and impurities. If a user is employing two or more of these techniques, it is important that their associated processes, the differences between them, and the differences between the resulting products be cataloged in this substage of the lifecycle profile.

[27] Adapted from Life Cycle Assessment: Inventory Guidelines and Principles (EPA 600/R-92/245). Cincinnati, Ohio: U.S.EPA, Office of Research and Development, Risk Reduction Engineering Laboratory, February 1993.

Product Fabrication. This phase involves the processing of raw or manufactured materials in order to create a product ready to be filled or packaged. A consumer product, to be distributed for retail sales, is often involved, but the product could also be an intermediate or component of a larger product for use by other industries. Purification of CNTs, their incorporation into matrices (to form a polymer nanocomposite, for example), and their preparation for final or intermediate use (e.g., by means of grinding and smoothing operations) would all be activities in this substage of the lifecycle profile.

Filling/Packaging. This phase includes all manufacturing processes required to fill and package an intermediate or finished product. Although these activities may commonly require a change in the location or physical configuration of a product, they do not involve a transformation of materials. Packaging CNT-containing polymer pellets for distribution to automotive-parts producers, for example, or packaging molded parts for distribution to end-product manufacturers (or to retail or repair facilities), would be included in this substage.

Distribution

This stage includes all transportation required to deliver an intermediate product to industrial users or a final product to manufacturing sites, retail outlets, or directly to the consumer.

Use/Reuse/Maintenance

This stage begins after the distribution of products or materials for their intended use; it includes any process in which the product (such as an automotive part containing CNTs) is reconditioned, maintained, or serviced to extend its useful life. Replacement or repair — for example, of an automotive part containing CNTs —would be among the activities included here. Product storage, consumption, wear, weathering, or other kinds of degradation are also included in this stage.

Recycle/Waste Management

This stage begins after the product or material has served its intended purpose and will enter either a new system (through recycling) or the environment (through the waste-management system). Post-use options such as recycling, composting, and incineration are included. Automobile repair and recycling, which can entail separation and recovery of some nanomaterial-containing components — as well as the shredding and landfill disposal or incineration of others — are types of activities associated with this stage. It would also include the treatment of wastes and the fate and behavior of nanomaterials released to the environment — the down-the-drain release of a nanomaterial used in a personal care product, for example, or the subsequent movement, reaction, and degradation of a nanomaterial injected into groundwater for remediation purposes.

The Use of Base Sets

For each of the three main categories of information (physical/chemical properties, hazard, and exposure potential) in Steps 2A, 2B, and 2C that form the basis for the risk evaluation in Step 3, "base sets" of information have been defined (see boxes 2 through 7 on the following pages). Base sets, which have been applied in other programs that promote or require hazard-data development for chemicals, [28] represent those test results and other types of data that are deemed by experts to be the minimum needed to prioritize chemicals for more detailed risk assessment or risk management. For the purposes of this Framework, which is meant to apply to a wide variety of nanomaterials and nanomaterial-containing products at different stages of product development, the base sets serve as a reference point for the type and amount of information that should be addressed by the time of a product's commercial launch.

The generation of base sets of information is especially important for nanomaterials because, at the time of development of this Framework, insufficient data are available for many nanomaterials. Empirical data are needed, therefore, to sufficiently characterize a material and its potential risks.

We support the development of validated *in vitro* methods for application to nanomaterials, both as complements to — and, where appropriate, replacements for — *in vivo* testing. Our base sets already incorporate such tests where they exist. Both approaches have a role to play in developing a robust understanding of the biological behavior and potential effects of nanomaterials. *In vitro* tests can help to elucidate modes and mechanisms of action at the molecular and cellular level, while *in vivo* methods are needed to understand the biological relevance of these modes and mechanisms of action in the whole animal, where there are critical interactions between different cell types and within and between organ systems. In particular, critical tasks such as determining dose-response relationships and identifying relevant target organs and cells require *in vivo* testing. [29]

With respect to the potential to use *in vitro* tests as screening tests or replacements for in vivo tests, we believe that the most expeditious way to move toward further development and validation of such methods is through parallel testing with in vivo and in vitro methods. In that way, the extent of correlation between results for the same or similar endpoints can be determined, and the *in vitro* methods can be modified as needed to strengthen their ability to mirror results found *in vivo*. The extent to which *in vitro* cellular systems can elucidate the relative toxicity of nanomaterials remains to be determined. Some studies suggest they will need to be further developed, standardized, and validated relative to *in vivo* effects prior to such use, [30] while others suggest they can provide useful early screening data. [31]

[28] For example, the screening information data set (SIDS) program of the Organization for Economic Co-operation and Development (OECD)

[29] SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), 29 March 2007, The appropriateness of the risk assessment methodology in accordance with the Technical Guidance Documents for new and existing substances for assessing the risks of nanomaterials. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_004c.pdf

[30] Sayes et al., 2007 (in press), *Toxicological Sciences.*

[31] Stone, Vicki and Donaldson, Ken. Signs of stress. *Nature Nanotechnology,* Vol 1, Oct 2006.

The base sets are designed to characterize the inherent hazards associated with exposures to nanomaterials, both in mammalian species as well as in ecological environments. Information gained from the hazard-assessment tests provides a basis for making reasonable and responsible decisions and for taking action — including the triggering of more substantive and longer-term toxicity tests.

The base sets of hazard tests are not meant to provide a comprehensive assessment or full toxicological profile of a given nanomaterial. Rather, they are designed to provide a reasonable balance between an adequate characterization of properties, hazards, and exposure and a practical strategy for the development of new nanomaterials. Thus the goal is to make the base sets sufficiently robust in order to guide adequate risk-evaluation processes, concomitant with applicable regulatory and voluntary standards. The strategy outlined in Boxes 2 through 7 represents one approach for achieving those goals.

The base sets are not meant to be overly prescriptive, as circumstances may well arise in which it may not be necessary to generate certain data that they call for. For example, where data are sufficient to rule out a particular route of exposure, the user will not likely pursue base-set hazard elements specific to that route. Similarly, as described in the introduction, the user may elect not to pursue certain elements of the base set, or may need to develop more information than is called for in the base set, depending on the expected uses of a nanomaterial or its stage of development. Thus the lists of tests and other types of information comprising the base sets are neither exhaustive nor set in stone. Rather, they provide a benchmark for the level and types of information needed to make informed risk decisions.

Triggers for Additional Testing

As a general rule, it is strongly recommended that these base sets of information be addressed (either through data, "reasonable worst case" values or assumptions, or controls) by the time of product launch so that the user can make reasonably sound conclusions about potential risks. Any decision to forgo developing a complete base set should be justified by providing a clear and transparent rationale. On the other hand, information *beyond* the base set may be required in order to make informed risk decisions, and the Framework provides guidance for dealing with such circumstances. In some cases, the need for additional data is driven by information that indicates cause for greater concern about potential risk; in other cases, the additional data in one category is needed to compensate for greater uncertainty or lack of data in another area (for example, more detailed information to demonstrate the lack of inhalation hazards could be used to compensate for lack of data on the possibility of inhalation exposure). A summary of potential triggers can be found in Box 1.

Box 1. Potential Triggers for Obtaining Additional Data

High exposure potential

- High exposure potential related to manufacture and production:
    - Number of workers handling nanomaterials or general population living around nanomanufacturing facilities
    - Magnitude of environmental release during production
    - High production volume [32] (in the absence of the preceding elements)
- High potential for chronic human or environmental exposure related to use, disposal, or recycling
    - Uses resulting in repeated or continuous release
    - High volume [32] of material used in application
    - Detection in environment or biota (e.g., based on monitoring)
    - Diversity of uses (i.e., multiple applications may provide cumulative exposure to a given nanomaterial)
    - Broad scale of uses (e.g., based on market penetration, commonness of use)
    - Directness of contact or proximity to exposure sources

Significant change in production, processing, or use pattern

Uncertain or high inherent hazard potential

- Similarity to analogous material that was evaluated to be hazardous
- Stability/transformability of the material or modifications to material (e.g., how stable are coatings or derivatives of a nanomaterial?)

Results of base set

- High persistence and bioavailability
- Physical-chemical properties indicate potential for widespread dissemination in environment
- Evidence of toxicity at the lowest dose tested
- Uncertainty
    - Conflicting results for same endpoint
    - Disparity of results across various base set tests

Compensating for incomplete base set of either hazard or exposure data

[32] Identifying what constitutes "high volume" for nanomaterials is as yet undefined. Assessing it will therefore require professional judgment, which will likely vary widely by material and application.

Sources and References for Base Sets

For each of the base sets of Steps 2A, 2B, and 2C, existing and proposed test batteries and information sets were reviewed and adapted for nanotechnology applications. In each case, every effort was made to make the base set comprehensive enough — capable of guiding adequate risk-evaluation and risk-management processes, consistent with existing regulatory and voluntary standards and programs — and reasonable in terms of cost and effort. Step 2A's base set for product characterization was derived from the principles of the International Life Sciences Institute (ILSI) [33] and the ongoing characterization work of the National Cancer Institute's Nanotechnology Characterization Laboratory (NCI-NCL).[34] Sources for Step 2B's base set for hazard characterization included the OECD's Screening Information Data Set (SIDS) program [35] and the ILSI Health and Environmental Sciences Institute review of available toxicology tests for nanomaterials.[36] Lastly, sources for Step 2C's exposure base set included reporting requirements for industrial chemicals regulated under the Toxic Substances Control Act [37] and guidance on nanomaterials provided by the National Institute for Occupational Safety and Health. [38]

A variety of methods and protocols for conducting the kinds of tests included in the base sets, plus additional elements developed for the testing of conventional chemicals, are available (most notably through the OECD). [39]

These base sets are expected to be dynamic; that is, they may need to be revised as more information is published on nanomaterials' risks and as other efforts to refine appropriate risk-assessment and risk-management approaches are developed and made public.

Use of Default Values and Assumptions

It may not be feasible or appropriate, especially at the early stages of product development, to perform new tests on nanomaterials in order to complete the base sets. The Framework accounts for this contingency by providing for the use of "reasonable worst-case" default values or assumptions.

"Reasonable worst-case" default *values* can be derived from several sources, such as data available on analogous bulk materials or non-engineered nanoparticles. For example, one could manage a material as if it were as toxic as a material for which the toxicity is well understood (e.g., quartz dust). Alternatively, reasonable worst-case values could come from assignment to the highest-level tier in an existing classification system. For example, one could manage a material

[33] Oberdorster et al, "Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy," *Particle and Fibre Toxicology,* October 2005, http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1260029

[34] See Assay Cascade of the Nanomaterial Characterization Laboratory of the National Cancer Institute (http://ncl.cancer.gov/working_assay-cascade.asp)

[35] See OECD, "Manual for the Investigation of HPV Chemicals," chapter 2, available at http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html

[36] Oberdorster et al, "Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy," *Particle and Fibre Toxicology,* October 2005

[37] See EPA's guidance document "Instructions for Reporting for the 2006 Partial Updating of the TSCA Chemical Inventory Database," available online at www.epa.gov/oppt/iur/pubs/tsca_cheminv_database.pdf (especially Section 1 and Table 1-1).

[38] See NIOSH's "Approaches to Safe Nanotechnology," available online at www.cdc.gov/niosh/topics/nanotech/safenano/.

[39] OECD. Current through January 2007. OECD Guidelines for the Testing of Chemicals, http://titania.sourceoecd.org/vl=1355287/cl=17/nw=1/rpsv/periodical/p15_about.htm?jnlissn=1607310x.

as if it possessed characteristics of reproductive toxicity sufficient to classify it as a Category 1 substance (known or presumed human reproductive or developmental toxicant) under the OECD's Globally Harmonized System for Classification and Labeling. [40]

"Reasonable worst-case" default *assumptions* are especially useful in the absence of exposure-related data, as they allow a risk characterization or assessment to be conducted for determining whether, in a reasonable worst case, a material is or is not a concern. For example, if no data exist on the fate of a material in a sewage treatment plant, one could assume that none of the material is degraded and all of it is discharged in effluent — that is, the environment gets the full dose. Such assumptions are routinely used by regulatory agencies as inputs to exposure models when measured data are unavailable. A case in point is EPA's New Chemicals Program to assess potential risk. [41]

It is not intended that default values and assumptions be taken as characterizations of the actual toxicity or exposure to a material or even to indicate any presumption of toxicity or exposure potential (or lack thereof). Rather, they are meant to allow a reasonable worst-case risk assessment to be conducted even in the absence of data and experience, a not-uncommon situation when analyzing the potential hazards of nanomaterials. As new data and experience with nanomaterials accumulate, these values or assumptions can be updated or supplanted with more specific information.

While it is expected that, in general, new data will be used to complete the base sets by the time of commercial launch, some users of the Framework may by choice or necessity not generate the necessary data. In this case, the default values and assumptions are intended to provide a margin of safety to workers and other potentially exposed populations and environments. As additional data are generated, risk-management decisions more specific to the materials being commercialized will be possible.

It is important, however, that in cases in which a user has relied on assumptions rather than data to develop risk evaluations and to drive risk management decisions and practices, the user should share with other key stakeholders what assumptions were made, why they were made, and why the user believes them to be reasonable guides.

Use of "Bridging Information"

When a material has few specific hazard data, one way to inform decisions about it is to extrapolate or "bridge" to a material that has robust hazard data for a specific type of endpoint of interest (e.g., pulmonary toxicity). The two materials may be entered into a toxicological study, with the well-characterized material serving as an additional "control" for the material of interest. In most cases, the test being conducted is a shorter, simpler test than what would be needed for a more thorough understanding of the specific type of toxicity endpoint under consideration for the material of interest. [42]

[40] United Nations, Globally Harmonized System of Classification and Labelling of Chemicals (GHS), 2005, http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

[41] See EPA's New Chemicals Program homepage, http://www.epa.gov/oppt/newchems/index.htm

[42] An example would be bridging from markers of pulmonary inflammation in a short-term test to pulmonary fibrosis on a chronic assay.

The strength of the bridging strategy is dependent on: robust data on the control material from more thorough toxicity tests; and evidence that supports the relevance of the reference material to the new material, particularly with respect to its potential mechanisms of toxicity. Where such relevance can be established, bridging studies may provide useful insights into the new material's relative ability to cause a particular type of toxicity through mechanisms shared with the well-characterized material. [43]

The results of bridging are not as reliable as actually performing thorough toxicity studies on the material of interest, and it is not possible to bridge across endpoints and different mechanisms. Nevertheless, appropriate bridging studies can provide a preliminary screen when evaluating the same or closely related toxicological effects for a newly developed nanoscale compound or when making small modifications to an existing nanomaterial product.

As used here, bridging has a narrower meaning than the term connotes in certain settings involving conventional chemicals; in those cases, similarity of two materials' chemical structures alone is considered by some to be a sufficient basis for bridging – even when there are no test data on the substance being bridged *to.* Bridging in those contexts is also often applied to multiple, unrelated endpoints. But the properties and potential toxicity of nanomaterials are related to other factors besides chemical structure. Hence, a more conservative approach to bridging for nanomaterials should be taken. First, bridging should be limited to identical or closely related endpoints. Second, it should only be applied when there are data available for the nanomaterial of concern from a short-term or mechanistic test for a given endpoint, and those data indicate that it responds similarly to a well-characterized substance subject to the same test. In these cases, bridging may appropriately be used to predict that the nanomaterial would also respond similarly to the way the well-characterized substance performed in a related, but more robust test (e.g., longer duration, more relevant route of exposure, etc.).

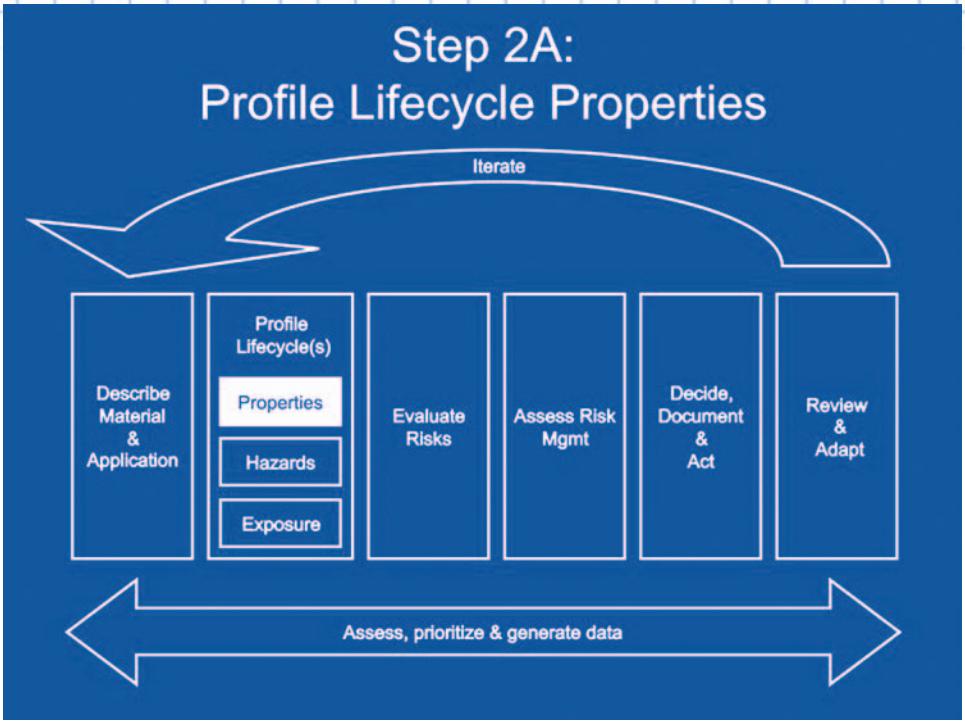
Evaluating Data Quality

Evaluating, documenting, and communicating the quality, sufficiency, and uncertainty of data are integral parts of the decision-making process of this Framework. Basing decisions on scientifically sound and defensible information, identifying uncertainty, and maximizing transparency in communicating the basis for decisions to stakeholders and the general public — to the maximum practicable extent — increase the integrity and credibility of the process. An assessment of the degree of confidence in the data should be made and carried along with the data themselves. Where additional data will likely be needed to conduct a complete risk assessment, that fact should be noted. So too should the intention that as additional data become available, the assessment will be updated. The EPA has developed guidelines and provides training to facilitate the evaluation of data quality. [44]

[43] This strategy has been used in a recent publication, wherein toxicity assessments for a new ultrafine TiO2 particle were conducted and compared to toxicity assessments for two other types of TiO2 and a control. See Warheit DB, Webb TR, Reed KL, Frerichs S, and Sayes CM. "Pulmonary toxicity study in rats with three forms of ultrafine-TiO2 particles: Differential responses related to surface properties." *Toxicology* 230: 90-104, 2007, Nov 10, 2006 [Epub ahead of print].

[44] EPA 2006. Quality Management Tools — Data Quality Assessment, http://www.epa.gov/quality/dqa.html

STEP 2A
Develop Lifecycle Properties Profile



This part of the Framework's second step identifies and characterizes the nanoscale material's physical and chemical properties, including property *changes,* throughout the full product lifecycle. This knowledge is critical to the correct handling of the material, to anticipating its behavior when interacting with its surroundings, and to assessing the ultimate fate and behavior of the material in the environment.

Thus the nature of the material must be understood not only in the free form (in which it is usually generated) but also — appropriate to the stage of development — after subsequent processing, incorporation with or into other materials, ultimate fate, potential reuse/recycling, or release (during or after its service life) in the form of waste. The extent of variations in the properties, including those resulting from differences in manufacturing, processing, and specific applications, should also be noted. Similarly, the properties of the nanomaterial should be compared to those of the corresponding bulk materials, where appropriate.

Any physical and chemical properties from the base-set list that remain unknown, as well as any additional physical and chemical properties that the user deems important, should be highlighted for investigation. The order of collection of the missing data should then be prioritized, test methods defined, and testing completed as needed. Note that data on physical and chemical

properties beyond the base set need only be gathered if they are deemed relevant to determining the fate, behavior, hazard, or exposure potential — and subsequently to determining the risks — associated with the nanomaterial or nanomaterial-containing product.

Any anticipated changes in relevant physical and chemical properties across the lifecycle of the material should be noted. For example, if the material is heated, milled, dispersed into liquids, or surface-treated with other chemicals, how do its properties change? How does the material change as it is produced in larger volumes and moves toward commercialization? How does variability in how the material is produced or handled change its physical and chemical properties? And what are the impacts of impurities?

For these reasons, it may be necessary to characterize the material at multiple points — unless there is good reason to expect that the material will remain unchanged.

Base Set of Physical and Chemical Properties

The base set shown in Box 2 is not only desirable for helping those who work with the material to better understand its nature. [45] These physical and chemical properties also have implications for hazards (Step 2B) and exposure (Step 2C).

Box 2. Physical & Chemical Properties Data

Technical Name
Commercial Name
Common Form
Chemical Composition (including surface coating)
Molecular Structure
Crystal Structure
Physical Form/Shape (at room temperature and pressure)
Particle Size, Size Distribution and Surface-Area
Particle Density
Solubility (in water and biologically relevant fluids)
Dispersability
Bulk Density
Agglomeration State
Porosity
Surface Charge
Surface Reactivity

45 See "Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy," Oberdorster et. al., *Particle and Fibre Toxicology,* October 2005.

Technical and Commercial Names. A descriptive name (e.g., AB-123 or surface-treated nano rutile TiO_2) should be used to distinguish the material from similar materials or those in bulk form. Similarly, if a series of samples of different compositions has been generated, a unique designation should be used for each so that their corresponding physical properties can be tracked.

Common Form. Is the nanomaterial a loose powder, contained in a liquid dispersion, agglomerated into larger-size particles, or aerosolized? The form of the material will have implications for the potential route of human or environmental exposure.

Chemical Composition. What are the concentrations of elemental chemicals or chemical compounds — particularly those known to be harmful — in the nanomaterial? Moreover, accompanying substances should not be overlooked; surface treatments and lattice doping are often used in nanomaterials and should be reported, as they may affect toxicity and exposure. Note too that chemical composition may change as nanomaterials are incorporated into products or break down, either during use or after disposal or recycling. Impurities in the material, and the extent of contamination, should be identified as well.

Crystal Phase/Molecular Structure. How elements or molecules are arranged physically in a nanomaterial can influence its potential toxicity. Early understanding of phase and molecular structure can lead to better understanding of potential structure-property relationships.

Physical Form/Shape. Is the nanomaterial crystalline or amorphous? Are the edges round or angular? What are the dimensions of the materials — e.g., are they plates, fibers, or particles? Physical form and shape influence how the materials flow, interact with other particles (to agglomerate), how easily they disperse when entering various media or the environment, and how they interact with plants and animals.

Size and Surface-Area Distribution. What are the mean particle size, the mean surface area, and the distributions around the means? What are the mass and number-count distributions? These measures are important because an increased surface-area-to-mass ratio of nanomaterials appears to be a critical feature in understanding some aspects of their toxicity,[46] particle surface energy, [47] and reactivity. [48]

Particle Density. What is the mass of particle per unit volume? This physical property, used in the determination of how easily the material is dispersed in air and water and how easily it settles *from* air and water, has implications for the behavior of the material in gases and liquids.

[46] Günter Oberdörster et al., "Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles," 113, *Environmental Health Perspectives,* 823-839 (2005)

[47] Günter Oberdörster et al., "Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy," *Particle and Fibre Toxicology,* October 2005

[48] M. C. Daniel & D. Astruc, "Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-size-related Properties, and Applications toward Biology, Catalysis, and Nanotechnology," 104 *Chemicals Review,* 293-346 (2004).

Solubility. Does the nanomaterial dissolve in water or other substances? Whether the material is soluble in acids, bases, organic solvents, or biological media may be important at various stages in its lifecycle as it interacts with other product components, materials, organisms, or the environment. Solubility plays a role not only in determining how the material behaves during its useful life but also in affecting its potential persistence in the environment thereafter.

Dispersibility. This property is "the ease with which an insoluble solid or liquid material may be dispersed uniformly in a liquid." [49] The dispersibility of a nanomaterial, particularly in water, has implications for exposure and fate throughout the product lifecycle. It will influence the partitioning of the nanomaterial should it enter an aquatic environment.

Bulk Density. An easy measurement to make, bulk density provides a quick indication of how much dust the nanomaterial may generate when being handled in its powder form. Low bulk-density materials often have a higher degree of dusting than high bulk-density materials of the same chemical composition.

Agglomeration State. This measure gives another indication of how much dust the nanomaterial may generate when handled in its powder form. Moreover, the agglomeration state provides information on the likely size distribution of inhalable particles as well as on their relative ease of dispersion.

Porosity. This measure is an indication of the fraction of the particle that is devoid of material. The porosity and pore-size distribution of the material has implications for its interaction with substances in its surroundings.

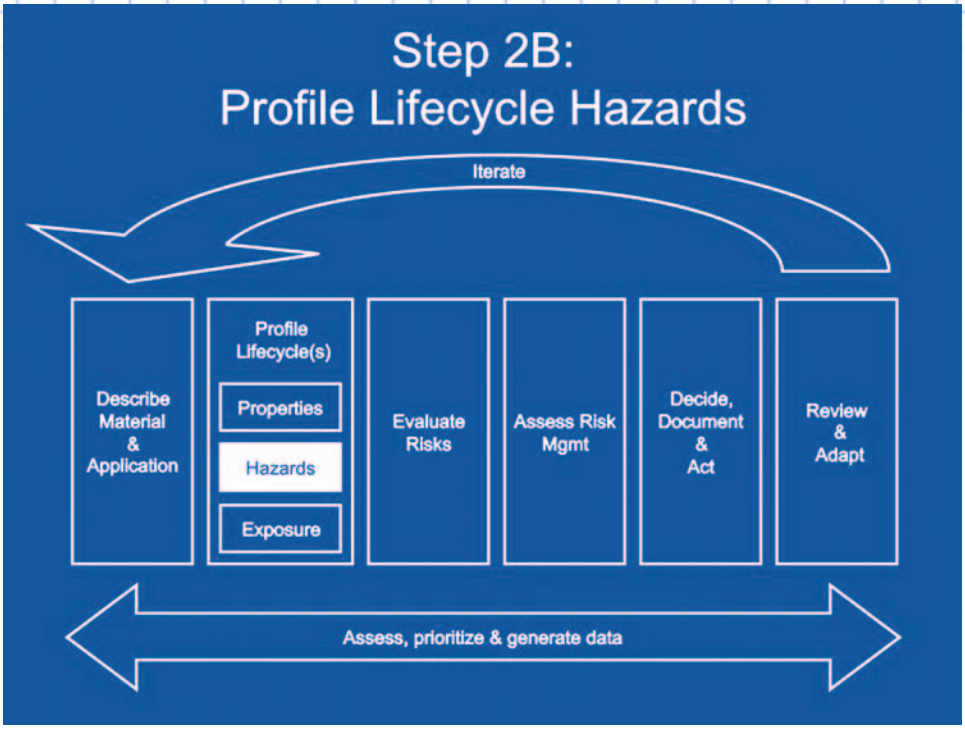
Surface Charge. The electric potential of a nanomaterial also suggests its likelihood of interacting with other materials. In solution, the surface charge — often determined by measuring the zeta potential [50] — has implications for the stability and aggregation of particles.

Surface Reactivity. This measure provides an indication of the likelihood and nature of a nanomaterial's interaction with other materials. Specific assays may need to be tailored to specific nanomaterials; examples include a Vitamin C test, a hemolysis test, and a reactive oxygen species (ROS) assay.

[49] FAO Plant Production and Protection Paper 173, Pesticide Specifications, Manual on Development and Use of FAO and WHO Specifications for Pesticides, First Edition, Prepared by the FAO/WHO Joint Meeting on Pesticide Specifications, World Health Organization and Food and Agriculture Organization of the United Nations, Rome, 2002; see http://www.fao.org/docrep/007/y4353e/y4353e0g.htm

[50] See http://www.colloidal-dynamics.com/CDElTut1.pdf

STEP 2B
Develop Lifecycle Hazard Profile



In this critical step, information is gathered and integrated into a hazard profile that characterizes the material's potential health, environmental, and safety hazards over the entire lifecycle. As part of this procedure, the needs for additional data are determined and prioritized, and actions are taken to fill those needs or to develop default assumptions.

Maximizing the quality and completeness of the hazard profile is fundamental to considering the new application's potential risks. While exposure parameters may vary with changing processes and uses, hazard is essentially an intrinsic property of the material and is therefore a relevant starting point. Scientifically valid data may not always be available, however, for a particular nanomaterial. Therefore professional judgment may be needed in order to conduct realistic evaluations of the potential hazards associated with the applications being considered and to determine what measures should be taken.

In any case, a hazard profile alone is not sufficient for a full risk evaluation, having been made without full information on potential routes and magnitude of exposure, which is developed in Step 2C. In order to make sounder and more informed product-development decisions, the hazard profile should be combined with exposure information from Step 2C to develop the risk *evaluation* in Step 3. Before reaching Step 3, however, a user may decide to conduct multiple

iterative rounds of Steps 2B and 2C to develop more hazard-profile data relevant to potential routes of exposure. The result of such iteration should be that by the time of commercial launch the full base set of hazard data will have been addressed.

The Process

Step 2B proceeds as follows:

For each lifecycle stage, as appropriate to stage of development:

- *Determine knowns and unknowns.* An initial literature review on the base material, as well as on any variations or impurities that arise as a result of sourcing, industrial processing, or environmental/biological transformation, is performed. This information is then compared to the base sets of hazard data needs, shown below in Boxes 3, 4.1, 4.2, and 5. Note that these base sets represent health hazards, environmental hazards (two sets), and safety hazards, respectively. Users of the Framework may consider potential triggers for obtaining additional data, as described in Box 1 (shown above in the Step 2 introduction, "Profile Lifecycle(s)"). In order to determine what critical data elements are missing, the available information may be entered into the Output Worksheet (see Appendix), which is a blank form that specifies the kinds of data needed for ultimate documentation.

- *Prioritize data needs.* Where data gaps exist, determine how best to fill them. For example, information from the properties profile (see Step 2A) and exposure profile (see Step 2C) may be useful in prioritizing data gaps in the hazard profile. Key considerations include the most likely modes of release and routes of exposure, the nature of the material expected to be released or to which exposure may occur, the expected magnitude of release or exposure (e.g., number of exposed individuals, spatial and temporal extent), as well as the resources needed for testing the product. All decisions on data needs, the justifications for those decisions, and the means used to compensate for missing data elements are documented in the Output Worksheet.

- *Define protocols and conduct appropriate testing.* Given the information gathered thus far, specific test protocols needed to complete the hazard profile are selected. Possible sources for test protocols include those listed by International Life Sciences Institute [51] and by the U.S. National Cancer Institute. [52] All such data generated and resulting decisions, as well as their justifications, are documented in the Output Worksheet.

- *Characterize hazard.* Prior information based on existing literature is combined with any new data generated and entered into the Output Worksheet. A profile of the known hazard information on the material — including comparisons to reference, bulk, and incumbent materials

[51] Oberdorster et al, "Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy," *Particle and Fibre Toxicology,* October 2005

[52] See Assay Cascade of the Nanomaterial Characterization Laboratory of the National Cancer Institute (http://ncl.cancer.gov/working_assay-cascade.asp).

— is then generated. Significant gaps in the hazard profile are later filled during Step 3 by reasonable worst-case default values or assumptions (as described earlier, in the Step 2 introduction, under *Use of Default Values and Assumptions*), which themselves may be replaced by data generated in subsequent iterations of Steps 2B and 2C. Ultimately, the key "deliverable" from Step 2B should be a formal hazard characterization, available by the time of commercial launch. Even then, the profile will not be truly final; it may have to be updated thereafter as further new revelations of hazards or other information trigger warrant.

Base Set of Health Hazard Data

The base set shown in Box 3 been selected to provide critical information on potential health hazards.

Box 3. Health Hazard Data

Base Set:

- Short-term Toxicity. One or more of the following, depending on conditions (see discussion that follows for guidance on which tests to select):
  - 28-day inhalation study with full histopathology, over a 90-day observation period
  - Single-dose instillation study with full histopathology, over a 90-day observation period
  - 28-day repeated-dose oral toxicity test with full histopathology, over a 90-day observation period
- Skin sensitization/irritation
- Skin penetration, assuming valid methods exist or emerge
- Genetic toxicity tests

Additional Data to Be Developed as Needed:

- Biological fate and behavior
- Chronic (>1 year) inhalation/ingestion toxicity studies
- Chronic dermal irritation/sensitization studies
- Developmental and reproductive toxicity studies
- Neurotoxicity studies
- More extensive genotoxicity studies
- Focused toxicity studies
  - Susceptibility studies — animal models
  - Allergenicity and immunotoxicity
  - Organ-function bioassays
- Endocrine-disruption studies

Short-term Toxicity Bioassays

These bioassays evaluate the health effects from short-term exposures. Both the National Toxicology Program [53] and OECD [54] provide a variety of guidelines for acute and subchronic testing protocols. The principle route or routes of exposure should determine the specific protocol. For instance, if inhalation is known or expected to be a significant route, or if no dominant exposure route is known or expected, pulmonary testing should be performed, either through:

i) 28-day inhalation study with full histopathology, over a 90-day observation period
OR
ii) Single-dose instillation study with full histopathology, over a 90-day observation period.

If ingestion is virtually exclusive as the known or expected route of exposure, oral testing should be performed — specifically, a 28-day repeated-dose oral toxicity test with full histopathology, over a 90-day observation period. This extended period represents a modification designed to distinguish latent effects from the short-term exposures.

If both inhalation and ingestion are known or expected to be significant routes of exposure, a 28-day repeated-dose oral toxicity test with full histopathology, over a 90-day observation period, should be conducted *in addition* to either:

i) A 28-day inhalation study with full histopathology, over a 90-day observation period
OR
ii) A single-dose instillation study with full histopathology, over a 90-day observation period.

Skin sensitization/irritation

Users should consider alternatives to *in vivo* skin-irritation studies (see, for example, National Toxicology Program, Test Method and Evaluations, http://iccvam.niehs.nih.gov/methods/dermal/dermal.htm) as base-set skin tests. If these tests fail to show skin corrosivity, additional data on skin sensitization should be obtained.

Skin penetration

Skin-penetration testing should be conducted when valid methods exist or emerge.

Two genetic-toxicity tests

We recommend using a gene mutation test in prokaryotic cells, with and without metabolic activation; and a chromosomal-aberration assay, either in mammalian cells grown *in vitro* or using *in vivo* methods such as the micronucleus test or metaphase analysis of bone-marrow cells.

[53] NTP. 2005. Descriptions of NTP Study Types. http://ntp.niehs.nih.gov/index.cfm?objectid=72015D9F-BDB7-CEBA-F4EB4F9BF507820C

[54] OECD. Undated. OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects. http://puck.sourceoecd.org/vl=5507610/cl=26/nw=1/rpsv/cw/vhosts/oecdjournals/1607310x/v1n4/contp1-1.htm

Beyond Base Set: Additional Data to Be Developed as Needed

Depending on the outcome of the above testing and other considerations, additional data may need to be developed.

Biological fate and behavior

The development of test methods for gaining an understanding of the fate and transport of nanomaterials in the body is a widely recognized critical-information need and a priority for near-term research. [55, 56] This information is particularly important for nanomaterials that exhibit significant potential for chronic or repeated exposure to workers, consumers, or the general population. Hence, where nanomaterials are to be used in ways that can result in significant exposure, undertaking these types of studies may be warranted even in advance of the development of standardized methods.

A broad spectrum of study designs and methods has been routinely used to assess biological fate and behavior of non-nanomaterials, and a number of studies have more recently been conducted to assess the biological disposition of certain nanomaterials. Technical challenges in applying such approaches specifically to nanomaterials are significant, and development of suitable bioassays is at an early stage of development.

Some believe that short-term toxicity tests, coupled with full histopathological evaluation, generally suffice to identify potential concerns about systemic circulation and unique pathological effects related to nanomaterial exposures. They believe that biological fate and behavior studies should be triggered by results derived from base-set toxicity tests, or where widespread exposures are likely. Others believe that biological fate and behavior information is so fundamentally important that it should — methodology allowing — be conducted early in hazard evaluation. They also suggest that such information can help to target and interpret the results of toxicological studies and inform the need for further, in-depth examination of biological fate and behavior. They further believe that — based on ongoing work to apply biological fate and behavior study techniques to nanomaterials, primarily in pharmacological applications [57] — these types of studies will become increasingly feasible for non-pharmacological applications as the science of measurement advances.

[55] National Nanotechnology Initiative (NNI), 2006, Environmental health and safety research needs for engineered nanoscale materials. Nanoscale Science, Engineering, and Technology Subcommittee, Committee on Technology, National Science, and Technology Council, September 2006

[56] United States Environmental Protection Agency, 2007, Nanotechnology White Paper, February 15, 2007, http://www.epa.gov/osa/nanotech.htm

[57] See, for example:
Cherukuri P, CJ Gannon, TK Leeuw, HK Schmidt, RE Smalley, SA Curley, and RB Weisman. 2006. "Mammalian pharmacokinetics of carbon nanotubes using intrinsic near-infrared fluorescence." *Proceedings of the National Academy of Sciences.* 103: 18882–18886.
Singh R, D Pantarotto, L Lacerda, G Pastorin, C Klumpp, M Prato, A Bianco, and K Kostarelos. 2006. "Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers." *Proceedings of the National Academy of Sciences.* 103: 3357–3362.
Elder A, R Gelein, V Silva, T Feikert, L Opanashuk, J Carter, R Potter, A Maynard, Y Ito, J Finkelstein, and G Oberdörster. 2006. "Translocation of Inhaled Ultrafine Manganese Oxide Particles to the Central Nervous System." *Environmental Health Perspectives.* 114:1172-1178.

Chronic (>1-year dosing) inhalation/ingestion studies and chronic dermal irritation/sensitization studies

Chronic dosing or exposure studies may be necessary to identify health risks if chronic exposures of the worker, consumer, or general public are expected to occur, or if there is evidence of toxicity following the acute exposure studies included in the base set. OECD test guidelines for chronic testing are available online. [58]

Reproductive and developmental toxicity

OECD has guidelines both for one- and two-generation reproductive-toxicity assays. [59] The U.S. National Toxicology Program utilizes a study design, termed Reproductive Assessment by Continuous Breeding, that is a two-generation study to identify effects on male or female reproduction, characterize toxicity, and define the dose-response relationships for each compound. [60]

By contrast, developmental toxicity study designs are more variable. Chemicals are tested in pregnant animals such as mice, rats, or rabbits; and offspring are assessed for indications of toxicity during fetal development. Exposure duration may be from implantation to the day before delivery, or it could continue to a specific postnatal period. [61] In addition, OECD has two methods for a combined reproductive/developmental toxicity test. [62]

Neurotoxicity studies

Neurotoxicity is the study of effects of chemicals on the nervous system, including the brain. Significant damage to nervous-system tissue may be detected through an extended histopathology following a repeated-dose toxicity test of the type included in the base set. More subtle damage may not be detected through histopathology, however.

If neurotoxicity emerges as a concern, available neurotoxicity tests, such as the OECD Neurotoxicity Test Guideline, [63] should be evaluated for applicability and adapted as needed. This guideline is designed to detect major neurobehavioral and neuropathological endpoints, some of which would not be apparent on histopathological examination, in adult rodents.

More extensive genotoxicity studies

Positive results in the initial genotoxicity studies can trigger additional genotoxicity studies or possibly a carcinogenicity bioassay.

Focused toxicity studies

The results of the initial base sets, in combination with known or expected patterns of exposure, could trigger more focused toxicity studies. If, for example, evidence of allergenicity or immunotoxicity is seen in the initial toxicity studies, then an endpoint-specific bioassay may be warranted. If ingestion is considered to be a significant route of exposure, then additional testing on the

[58] OECD. Undated. See footnote 54.
[59] OECD. Undated. See footnote 54.
[60] NTP. 2005. See footnote 53.
[61] E.g., see NTP 2005 (footnote 53).
[62] OECD. Undated. See footnote 54.
[63] OECD. Undated. See footnote 54.

interaction with or effects on the gut should be pursued. If organ-specific toxicity is identified in the short-term testing, then it could be prudent to conduct additional studies to further characterize such adverse effects. Studies could include organ-specific functional assays or the use of animal models to investigate susceptibility.

Endocrine-disruption studies

Such studies should be triggered by either of the following: 1) the bulk compound is a known or suspected endocrine disruptor; or 2) results of base-set tests, additional reproduction/developmental toxicity testing, or any other available information indicate a potential for endocrine disruption. Professional judgment would determine which endocrine-disruption tests should be applied, pending guidance from the U.S. EPA or other authorities. An endocrine-disruption test battery will soon be finalized by EPA for testing of conventional chemicals. It is likely that, as with most bioassays, methods may need to be modified to accommodate the testing of nanomaterials.

Base Set of Environmental Hazard Data

The base set shown in Box 4.1 is recommended for characterizing the environmental hazard data for nanomaterials. Once again, the need for testing at more than one lifecycle stage should be considered.

Box 4.1. Environmental Hazard Data

(Based on reasonably anticipated routes of exposure)

BASE SET:

Acute aquatic toxicity to:

- Fish (fathead minnow or rainbow trout)
- Invertebrates (Daphnia) — Acute or chronic toxicity test, depending on conditions (see discussion that follows for guidance).
- Aquatic plants (algae)

Terrestrial toxicity

Necessity for testing is dependent on conditions (see discussion that follows for guidance). Initial testing should focus on acute toxicity tests using:

- Terrestrial invertebrates (earthworms)
- Terrestrial plants.

ADDITIONAL DATA TO BE DEVELOPED AS NEEDED:

- ADME studies on aquatic organisms
- Chronic toxicity to aquatic and terrestrial organisms
- Chronic toxicity to soil microorganisms and sediment- and soil-dwelling organisms
- Further testing for toxicity using additional terrestrial species
- Avian toxicity testing
- Population/ecosystem-level studies

The aquatic and terrestrial testing elements and conditions described in Box 4.1, and in the text below, are taken directly from the Screening Information Data Set (SIDS) developed by the OECD. SIDS is utilized in OECD's HPV Program and in the U.S. EPA's HPV Challenge Program. SIDS was developed through international consensus and is considered the minimum data set needed to conduct a screening-level hazard assessment on a substance. Avian toxicity and population/ecosystem-level studies are considered data elements that are above and beyond the SIDS. See:

- OECD, Manual for Investigation of HPV Chemicals, Chapter 2: SIDS, the SIDS Plan, and the SIDS Dossier, available at www.oecd.org/dataoecd/13/18/36045056.pdf.
- EPA SIDS guidance is available at www.epa.gov/chemrtk/pubs/general/sidsappb.htm.

Aquatic toxicity elements

Inclusion of these elements in the Framework's base set — they also are present in base sets used in virtually every voluntary and regulatory program used throughout the world — is intended to provide an ability to determine whether nanomaterials are toxic to aquatic organisms. Our base set includes acute toxicity tests to three fundamentally different classes of aquatic organisms, which may well exhibit independent mechanisms and extents of toxicity. The specific organisms identified are those for which standardized, widely employed test protocols are available; thus these organisms should be used, barring a compelling justification for a different test organism. These three toxicity tests should be performed as standard procedure, unless release to aquatic environments at any point in a nanomaterial's lifecycle can be definitively ruled out.

Acute toxicity tests are limited in that they typically measure only lethality as an adverse effect; they are not capable of detecting sublethal effects, which may arise through entirely different mechanisms of action. For many nanomaterial applications, sublethal effects resulting from lower levels of exposure over a long period of time are more likely than lethality or other acute effects. Hence the base set provides that chronic toxicity to aquatic invertebrates *(Daphnia)* be assessed — in addition to or instead of acute toxicity — where evidence of possible persistence or bioaccumulation potential is available.

The three classes of test organisms are all residents of the water column in aquatic environments, whereas many materials with low water solubility — a typical feature of nanomaterials — are likely to accumulate in sediments, where exposure to sediment-dwelling or benthic organisms may occur. For this reason, toxicity testing using such organisms — e.g., *Hyalella azteca* (a shrimp-like crustacean) — may also be needed.

Toxicity to terrestrial organisms

Where there is evidence (monitoring data, for example) of the presence of nanomaterials in soil or other land environments, or there is reason to anticipate that nanomaterials may be released to or otherwise reach and accumulate in soil or other terrestrial environments, toxicity testing using terrestrial animals and plants may be warranted. Nanomaterials used directly on land, whether by themselves (for example, through fertilizers or pesticides) or in products that may lead to releases to land environments (e.g., from agricultural films or farm structures) are candidates for such testing. Similarly, waste products containing nanomaterials or associated products (such as wastewater sludge) that are intentionally applied to land, or could reach it, should be considered for such testing. Finally, the potential for transfer of nanomaterials from air or water to land (via deposition of airborne particles, for example, or use of untreated water for irrigation) should be considered.

Beyond Base Set: Additional Data to Be Developed as Needed

Where evidence emerges of toxicity to aquatic organisms, or of persistence or accumulation in these organisms or in aquatic environments, additional studies to better understand the longer-term toxicity, biological fate, and behavior of nanomaterials in aquatic organisms should be considered. For example, chronic toxicity and ADME (absorption, distribution, metabolism, and excretion) studies may be triggered by such findings. Tracing methods, such as radiolabeling, or the use of new or experimental procedures may be needed to conduct these studies.

Likewise, where evidence becomes available of longer-term releases to or accumulation in soil or other terrestrial environments, or where there is evidence of acute toxicity to or frequent or ongoing exposure of soil-dwelling organisms or other terrestrial plants or animals, chronic toxicity to such organisms is warranted. Toxicity to birds may also be indicated, given their contact with water, soil, and land and their consumption of aquatic, soil-dwelling, and sediment-dwelling organisms and terrestrial plants and animals.

In addition to direct testing to detect toxicity to individuals, studies to determine population- or ecosystem-level effects may be needed where releases or exposures are found or anticipated to be greater or more widespread.

Base Set of Environmental Fate Data

The base set shown in Box 4.2, which characterizes the environmental fate of nanomaterials, is recommended but should not be viewed as an all-inclusive requirement. Depending on the degree of uncertainty in particular types of environmental outcomes from nanomaterials, different elements of the base set may be used for each life-cycle stage.

Box 4.2. Environmental Fate Data

BASE SET:

Environmental fate based on physical-chemical properties

- Complete physical and chemical properties (Box 2)
- Adsorption-desorption coefficients in release medium (soil or sludge)
- Nanomaterial aggregation or disaggregation in applicable exposure media (e.g., air, water, soil, sludge, sediment)

Persistence-potential screen

- Organic-based nanomaterials only
  - Biodegradability test
- Both organic-based and inorganic-based nanomaterials
  - Photodegradability/phototransformation
  - Stability in water (hydrolysis)
- Bioaccumulation-potential screen

ADDITIONAL DATA TO BE DEVELOPED AS NEEDED:

Activated sludge respiration-inhibition test *(if release to wastewater treatment)*

Microorganism toxicity *(if release/deposition/transport to soil or sediment)*

Persistence potential in relevant media *(e.g., along expected exposure pathways)*

- For organic-based nanomaterials — "inherent" biodegradability test or simulation test (if practical) or other relevant biodegradability test
- Aerobic/anaerobic soil or sediment biodegradability test (if applied or deposited to soil or sediment)
  - If in sediment, also determine adsorption-desorption coefficient

For inorganic nanomaterials, conduct testing to determine potential for transformations via oxidation-reduction reactions

Standard methods not currently available. At this time, there are no standard methods, or even widely accepted methods, for assessing nanomaterials' environmental fate (i.e., where nanomaterials can be found in the environment, and their transformation/persistence potential). There is also uncertainty about whether established methods for bulk materials can be applied to nanomaterials. As suitable analytical methods become available, it may be possible to modify existing environmental-fate assessment methods for bulk materials so that they meet the needs of nanomaterials. In the interim, it will be necessary to conduct environmental-fate assessments using best-available scientific designs. Concurrently, we recommended that multi-stakeholder consortia (e.g., industry, NGOs, government, academia) should be formed to advocate for the development of standard methods.

Physical-chemical properties. For nanomaterials, there is still significant uncertainty about which physical-chemical properties affect partitioning and transport between environmental media (such as air, water, soil, sediments, and biota). For bulk materials, water solubility and vapor

pressure are key parameters. But considering that low water solubility and low vapor pressure are common characteristic of nanomaterials, other physical-chemical properties — such as agglomeration state, surface charge, dispersibility, particle density, particle size, size distribution, or surface area (see Box 2) — may be the key indicators for determining how a nanomaterial partitions in the environment. Sublimation may also be relevant in some cases. Further, the presence of natural organic matter (NOM) may play a role in the dispersal of carbon-based nanomaterials in the natural aqueous environment. [64]

There are still too many unknowns on how physical-chemical properties may influence behavior of nanomaterials in the environment. In time, when scientists can make accurate correlations between these properties of nanomaterials and their environmental behavior, it will be possible to develop reliable models for determining partitioning and transport of nanomaterials after their release. For now, an interim understanding of how nanomaterials behave in the environment may be established by determining the following:

- Adsorption/desorption coefficients in soil (if land-applied or deposited to soil) or sludge (if discharged from wastewater treatment),
- Degree of nanomaterial aggregation or dispersibility in applicable exposure media.

Persistence-potential screen. Factors such as a nanomaterial's organic or inorganic basis, its physical-chemical properties, and the analytical methodology available for determining presence in the environment of parent or transformation products will be the main determinants for choosing appropriate tests to determine persistence potential. Biodegradability assessments, for example, should only be conducted on organic-based nanomaterials. An EPA OPPTS (Office of Prevention, Pollution, and Toxic Substances) or OECD "Ready Biodegradability" or "Inherent Biodegradability" test is typically recommended, though it may be necessary to customize it. If radiolabeled nanomaterials are available for the biodegradation studies, this can be very helpful to the analysis.

For organic- and inorganic-based nanomaterials alike, photodegradability/phototransformation studies may be applicable if it is expected that the nanomaterial would be found in air, surfaces of water or soil, or anyplace else where exposure to sunlight is likely. Discrete nanomaterials would likely be stable in water, so hydrolysis may not be a factor. However, if the nanomaterial is tested with a carrier or is incorporated in a bulk material, then hydrolysis may be a consideration for potentially liberating the nanomaterial.

Bioaccumulation-potential screen. No standard methods have been developed for assessing the bioaccumulation potential of nanomaterials. The octanol-water partition coefficient is used as a surrogate for bioaccumulation of bulk materials, but whether or not it is applicable for nanomaterials remains unclear. If the appropriate analytical methodology can be developed, then a Bioconcentration Factor (BCF) test or Bioaccumulation Factor (BAF) test may be appropriate.

[64] H. Hyung, J.D. Fortner, J.B. Hughes, and J-H Kim, 2007, "Natural Organic Matter Stabilizes Carbon Nanotubes in the Aqueous Phase," *Environ. Sci. Technol.* 41, 179-184

Beyond Base Set: Additional Data to Be Developed as Needed

The following information is not part of the recommended base set, but it may be useful for clarifying the fate of nanomaterials in the environment:

Activated sludge respiration inhibition. The degree to which a nanomaterial will inhibit microbial respiration in activated sludge is an indicator of the material's potential for upsetting processes at wastewater-treatment plants.

Inhibitory effects (toxicity) to microorganisms in other relevant media. If a nanomaterial is released/deposited/transported to soils or sediments, then information about its potential inhibition of microorganisms is important for determining adverse ecosystem effects — on carbon or nitrogen cycles, for example.

Persistence potential in relevant media (i.e., along expected exposure pathways). For organic-based nanomaterials, an "inherent-biodegradability test," "simulation test," or other relevant biodegradability test is recommended if suitable analytical methods are available. But, as discussed above, there are no current standard methods for the biodegradability assessment of nanomaterials. Therefore adaptation of existing biodegradability guidelines (e.g., EPA OPPTS, OECD) or development of customized biodegradability studies may be needed. If a nanomaterial is applied or deposited to soil, then an aerobic-soil or anaerobic-soil biodegradability study would be recommended. If a nanomaterial is expected to pass through a wastewater-treatment plant as part of effluent entering a water body, or it is directly emitted, applied, or deposited (via air) to water, and if the particle density indicates a potential for settling to sediments, then the following testing is recommended:

- Adsorption/desorption coefficients in sediment
- Aerobic/anaerobic sediment biodegradability study.

Transformations in inorganic-based materials. As with inorganic bulk materials, inorganic nanomaterials would not be degraded via biodegradability, though there may be a potential for transformations via oxidation-reduction reactions in the environment. Because there are no existing standards for such tests at present, a customized design may be needed. Its form would depend on the physical-chemical properties of the nanomaterial, expected uses, and exposure media/pathways.

Base Set of Safety Hazard Data

The base set shown in Box 5 is recommended for characterizing the safety hazard data of nanomaterials.

Box 5. Safety Hazard Data*

BASE SET:

- Flammability
  - Ability of a material to readily ignite and burn.
- Explosivity
  - Material rapidly releases gas and heat when subjected to high temperature, pressure, or shock.
- Incompatibility
  - Material may create a hazardous reaction when in direct contact with another material.
- Reactivity
  - Material undergoes a chemical reaction with release of energy.
- Corrosivity
  - Material causes visible destruction or irreversible damage at site of contact.

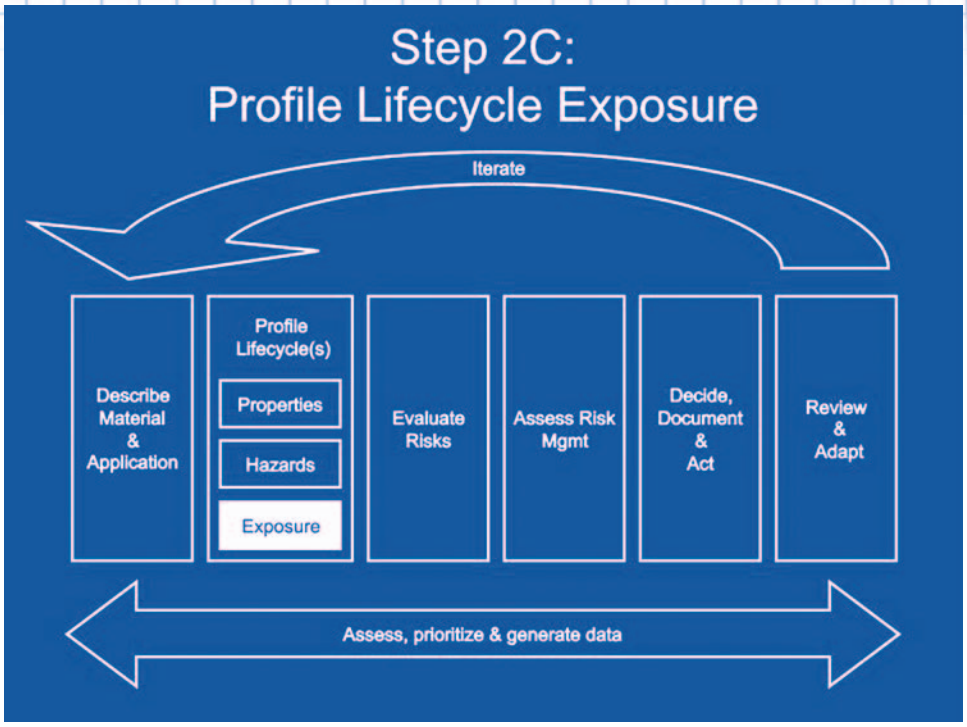
ADDITIONAL DATA TO BE DEVELOPED AS NEEDED:

- Stability
  - Ability of a material to remain unchanged during conditions of anticipated use.
- Decomposition
  - Material disassociates or breaks down into parts or simpler compounds.
- Polymerization (reaction whereby small molecules combine to form larger molecules)
  - Reaction in material may take place at rates that release large amounts of energy, which can cause fires or explosions.
- Photoactivity
  - Some materials, when exposed to light, generate electron-hole pairs that can produce free-oxygen radicals, subsequently oxidizing or reducing molecules in contact with their surfaces. This phenomenon may have implications for the material's interaction with the environment.

* ***Note:*** At this time, there are no standard methods or even widely accepted methods for assessing nanomaterials' safety hazards. There is also uncertainty about whether established methods for bulk materials can be applied to nanomaterials. As suitable analytical methods become available, it may be possible to modify existing safety-hazards testing methods for bulk materials so that they meet the needs of nanomaterials. In the interim, it will be necessary to conduct safety hazards assessments using best-available scientific designs. Concurrently, it is recommended that multi-stakeholder consortia (e.g., industry, NGOs, government, academia) should be formed to advocate for the development of standard methods.

Example: In European Community member states, producers of hazardous or dangerous chemicals are required by Directives 67/548/EEC and 99/45/EEC to provide industrial and professional users with detailed health, safety, and environmental information in the form of safety data sheets. Under the U.S. Occupational Safety and Health Administration's Hazcom standard — OSHA 1910.1200 — chemical manufacturers and importers shall evaluate chemicals produced in their workplaces or imported by them to determine if they are hazardous. Scientifically valid safety hazard data, detailed above, constitutes information that is to be included in safety data sheets and provided to employers, employees, and users of the material or products.

STEP 2C
Develop Lifecycle Exposure Profile



This step identifies and characterizes the potential for human and environmental exposures across the full product lifecycle.

Potential exposures may occur in two ways: when an opportunity arises for an organism to come into direct contact with a nanomaterial; or when a nanomaterial is released into a medium (e.g., air, water, soil, sediment, food, or a product) that may lead to contact. Exposure may be followed by actual entry into the organism via intake (inhalation or ingestion) or uptake (dermal penetration or absorption though other exposed tissue, such as the eye).

Regarding consumer usage, for example, the nature of the nanomaterial-based product may lead to various routes of exposure. Thus if the material is a component in a spray-product formulation, release from the spray can cause emissions into the ambient air and subsequent movement into the lungs or onto the skin. Or, if the material is ultimately intended to go down the drain — e.g., it is part of a cleaning product — water is a primary medium for exposure and ingestion (say, through drinking water or food fish). Furthermore, direct contact with residuals (left after the cleaning product is used) is a potential route of exposure.

Because the environmental fate and behavior of the nanomaterial are key factors in understanding exposure potential, information on key aspects of the material's pathway is needed:

- How a nanomaterial is released to the environment at any point in the product lifecycle
- How the nanomaterial is distributed after release to the environment, (i.e., how it partitions to air, water, soil, sediment, and biota)
- Whether or not the nanomaterial is transformed in the environment
- Whether there are "sinks" (accumulations in particular environmental niches) for the nanomaterial.

The Process

Step 2C proceeds as follows:

For each lifecycle stage, as appropriate to phase of development:

- *Assess potential for releases.* All known or reasonably anticipated processes involving the nanomaterial or nanomaterial-containing product are evaluated for the potential to cause exposure from direct contact or release to the environment.

  Because risk management and control measures affect exposure during manufacturing, answers to the following questions are needed when developing an exposure profile:

  - What engineering controls (e.g., dust collection, containment) are in place and what is the quality of their performance?
  - What personal protection equipment (e.g., specific filter cartridge, glove type) is in use?
  - What procedures (including housekeeping, decontamination of spills or releases, changing of filter systems, recycling, waste management and disposal methods) are in place to minimize exposure?
  - How effective are the engineering controls and protection equipment with regard to the particular nanomaterial under consideration?

- *Determine knowns and unknowns.* Each medium into which a release is expected to occur needs to be "mapped." That is, all known fates (e.g., transformations or transfers to other media) are identified. In this way, it is possible to determine what is *un*known about pathways, routes of exposure, dose, and other relevant factors.

  The quest to acquire information proceeds along two lines: human-exposure potential and environmental-exposure potential. The following types of questions should be considered when assessing potential for human exposure:

  - What are the potential routes of human exposure (e.g., inhalation, ingestion, and eye or dermal penetration)?
  - Are the nanomaterials present in a consumer product?
  - Can the nanomaterials have direct or indirect contact with food?
  - Can the nanomaterials be present in water used for drinking or recreational purposes?
  - Can the nanomaterials be present in the ambient air or surfaces of the workplace, home, and other locations where people may be exposed?
  - What sensitive populations (e.g., children, elderly persons) may be exposed?

When investigating environmental-exposure potential, consider these types of questions:

- What are the potential routes of entry into the environment (e.g., air, water, soil, sediment, and biota)?
- How does the nanomaterial partition in the environment (that is, how does it distribute itself between air, water, soil, sediment, and biota)?
- What are the potential exposure pathways?
- Does the nanoscale material undergo degradation or transformation in the environment?
- What is its ultimate fate and does it accumulate in particular environmental sinks?
- Will the material persist in the environment in a bioavailable form?
- Based on the above environmental-fate information, what are the populations (e.g., avian, aquatic, benthic, or terrestrial species) that may be exposed?
- What is the bioaccumulation potential?
- What is not known about the material's environmental fate and how could such unknowns best be addressed?

- *Prioritize data needs.* Where data gaps exist, determine how best to fill them. Key considerations include the most likely modes of release and routes of exposure, the nature of the material expected to be released or to which exposure may occur, the expected magnitude of release or exposure (e.g., number of exposed individuals, spatial and temporal extent), and the resources needed for testing the product. All decisions on data needs, the justifications for those decisions, and the means used to compensate for missing data elements are documented and recorded in the Output Worksheet (see Appendix).

- *Develop and implement a plan to address data needs.* After reviewing the key elements described above and identifying and prioritizing the critical unknowns, a plan is developed to fill the data gaps. It identifies information sources, technical experts, and budgetary resources for meeting the most critical data needs first; and, ideally, it provides maximum overall benefit in securing other currently unavailable data as well.

- *Characterize exposure.* The key deliverable from this step is an exposure characterization — a summary and synthesis of the gathered exposure information — available by the time of commercial launch and updated thereafter as changes in use or exposure information warrant. The exposure characterization includes:

  - A statement of purpose, scope, level of detail, and the approach used in the assessment, including key assumptions
  - Estimates of exposure and dose by pathway, both for individuals and populations
  - Evaluation of the overall quality of the assessment and the degree of confidence in the exposure estimates and conclusions drawn.

See Box 6 for the base set of data to gather as a function of stage of the lifecycle; and see Box 7 for guidance on nanomaterial monitoring and measurement methods.

Box 6. Exposure Data*

Manufacture

- Number and locations of manufacturing sites (A)
- Current (A) and expected annual production volumes
- Industrial functions (e.g., adhesive, coloring agent) of the substance (C)
- Stage of development (e.g., R&D, pilot scale, commercial scale)
- Percentages of production volume for each industrial function (C)
- Physical form(s) of the substance as it leaves the submitter's possession, along with the associated percentage of production volume (B)
- Maximum concentration of the substance in each industrial function as it leaves the submitter's possession (B)
- North American Industrial Classification System (NAICS) codes that best describe the industrial activities conducted by the sites that produce the substance (C)
- Description of manufacturing methods
- Number of employees working with the substance at the site of manufacture or import (B)
- Types of employees, handling practices, and environmental containment and control equipment used to mitigate exposure potential.

Processing

- Types of industrial processing or use operations at downstream sites (C)
- Approximate number of processing and commercial-use sites (C)
- The industrial functions of the substance during the processing or use operations (C)
- NAICS codes that best describe the industrial activities conducted by the sites that use or process the substance (C)
- The percentage of production volume, number of sites, and number of workers associated, whether for processing or use, with each NAICS/industrial-function combination
- Estimated number of employees working with the substance at sites where the substance is used or processed (C)
- Types of employees, handling practices, and environmental containment and control equipment used to mitigate exposure potential.

Use

- Commercial or consumer product types (e.g., paints and coatings, soaps, and detergents) in which the substance is used or present (C)
- Specific commercial or consumer products in which the substance is used or present
- The percent of production volume associated with each commercial or consumer use (C)
- Trade names of the products
- Settings for use (e.g., in manufacturing sites, in homes, outdoors)
- Use patterns (e.g., description of products or applications and how they are used)

Box 6 continues on next page

Box 6 continued. Exposure Data

- Numbers of commercial users (including workers) working with the substance (C) and consumers using the product
- Maximum concentration of the substance in each commercial or consumer product (C)
- Indication of whether the products are intended for use by children (C) or other sensitive populations
- Indication of whether the substance is intended for release during use or can reasonably be anticipated to be released. If so, what are the magnitude, frequency, duration, and mode (e.g., to air) of the expected release?
- Indication of whether there is potential for exposure to the substance in the product through inhalation, ingestion, skin absorption, or ocular uptake
- Required or recommended controls for use (e.g., training, engineering controls, personal protective equipment)
- Recovery/recall techniques (e.g., in case of misuse or new hazard data).

Distribution/storage

- Methods of delivery of substance or substance-containing products to customers
- Methods of storage by producer and by customers.

Environmental releases

- Reasonably anticipated releases — specified in terms of physical form, magnitude, frequency, duration, and media — from manufacturing, processing, transportation, and waste management
- Expected recycling or disposal methods for manufacturing waste and off-spec materials
- Maximum concentration of the substance in each waste stream.

Post-use management

- Expected disposal methods for manufacturing and processing wastes, for materials containing the substance that are generated and discarded during use, and for used or spent products
- Expected recovery/reuse/recycling methods for the above materials, products, and wastes.

***Key:**

Many of these elements are drawn from the kinds of basic use/exposure elements that the U.S. EPA requires to be reported for industrial chemicals under the Toxic Substances Control Act (TSCA) [64], but the information reflects more of a full lifecycle view.

(A) = Information elements that have been required for all Inventory Update Rule (IUR)-reportable substances

(B) = Additional information elements required for all IUR-reportable substances, starting with the 2006 IUR reporting cycle

(C) = Additional information elements required for all IUR-reportable substances above 300,000 lbs (136,000 kgs) per year per manufacturing site, starting with the 2006 IUR reporting cycle

[64] See EPA's guidance document "Instructions for Reporting for the 2006 Partial Updating of the TSCA Chemical Inventory Database," available online at www.epa.gov/oppt/iur/pubs/tsca_cheminv_database.pdf (especially Section 1 and Table 1-1).

Box 7. Suggested Guidance for Exposure Measurements/Monitoring

Methodology development is needed for gathering exposure-profile information — covering detection, sampling, and monitoring — on nanomaterials. A careful and well-documented design for this process will yield manifold benefits, including data training sets that can be used for model development. The monitoring program should be designed to focus on key uncertainties and target end-points identified in the other steps of this Framework. [65, 65, 67]

I. Workplace

a. Until methods for measuring worker exposure to airborne nanoparticles are more fully developed, the following measurements should be considered:
    i. Mass concentration
    ii. Particle-number concentration
    iii. Particle-size distribution
    iv. Surface area

b. Measurements should be taken before processes are started in order to ensure an adequate baseline against which to assess potential increases in airborne concentrations that result from nanoparticle handling. Worker-exposure air-monitoring data in particular should be collected to establish pre-manufacture concentrations (mass and particle number), and then again after operations have commenced. The data should include short-term exposure levels, maximal measured concentrations, and eight-hour time-weighted averages for workers with the highest potential exposures.

c. Based on the manufacturing and handling processes employed, a clear and rational sampling strategy should be developed that takes into account spatial and temporal variability, locations of anticipated maximal concentration, presence of potentially exposed workers, and availability and performance of engineering controls and safe-handling practices.

d. In order to assess the efficacy of the containment and control measures, data should be collected, whenever possible, both before and after the installation of any employed engineering controls.

e. Engineering estimates of materials released from accidents and spills within workplaces should also be conducted — particularly regarding those associated with maximal air and liquid concentrations — with results reported.

f. Workplace settings associated with waste handling, reclamation of materials, and recycling should also employ an appropriate monitoring and sampling strategy, with measurements obtained prior to and during operation.

Box 7 continues on next page

[65] Much of the content of this section reflects recent guidance from NIOSH contained in the following document: National Institute of Occupational Safety and Health, Approaches to Safe Nanotechnology: An Information Exchange with NIOSH, available online at www.cdc.gov/niosh/topics/nanotech/safenano/.

See also:

[66] ISO, Workplace atmospheres — Ultrafine, nanoparticle and nano-structured aerosols — Inhalation exposure characterization and assessment, International Standards Organization, Geneva, (2006) ISO/TR 27628

[67] Maynard, A. D. and Kuempel, E. D., "Airborne nanostructured particles and occupational health," *Journal Of Nanoparticle Research* (2005) 7(6):587-614 (basic information on exposure monitoring). Online, available: http://www.springerlink.com/content/700q5022523342j4/fulltext.pdf

Box 7 continued. Suggested Guidance for Exposure Measurements/Monitoring

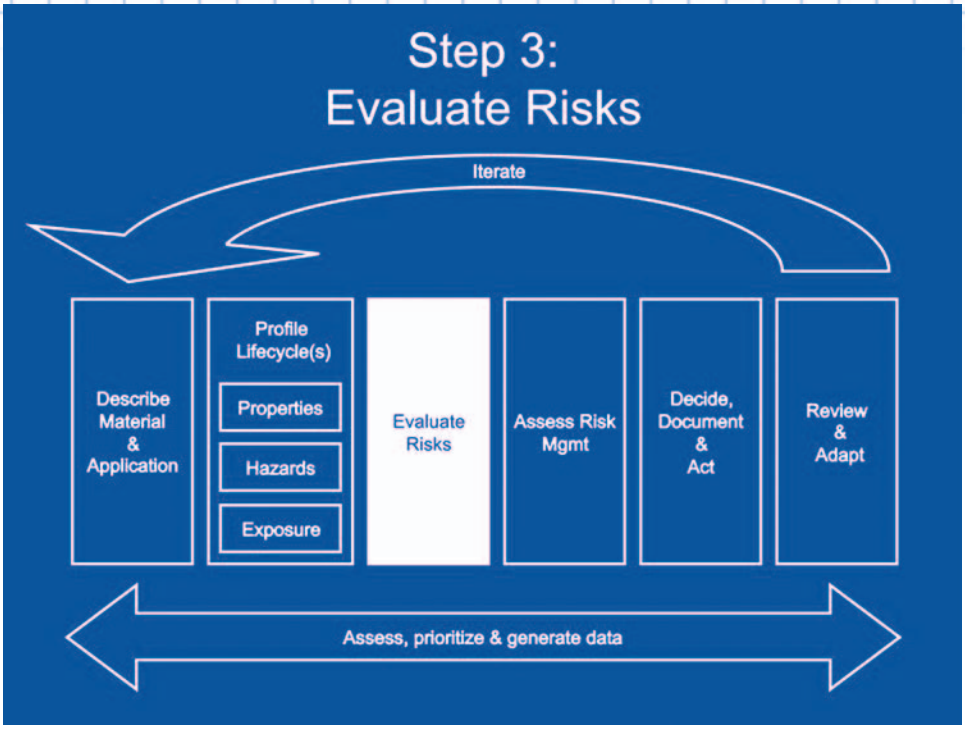
II. Environmental releases from manufacturing, processing, storage, transport, or waste handling

a. In processes and operations involving nanomaterials, gaseous emissions (e.g., from air ventilation and exhaust systems), waterborne discharges (e.g., to wastewater treatment), and solid wastes should be routinely monitored for the presence of nanomaterials. In order to assess the efficacy of the containment and control measures, data should be collected before and after the installation of any employed engineering controls.
b. For points of potential fugitive or other nonroutine releases, engineering calculations should be performed.
c. Engineering estimates of materials released from accidents and spills involving manufacturing, processing, storage and waste-handling facilities and transport containers/vehicles should be conducted, with results on associated maximal air and liquid concentrations reported.
d. Further monitoring or measurements, including field simulations and actual measurements of environmental concentrations, could be triggered by toxicity or initial monitoring data.

III. Consumer Use and Post-Use

a. For any applications during use or post-use stages of the lifecycle that can be anticipated to lead to releases to the air, water, soil, or sediment, or to deposition onto surfaces, simulations or calculations based on reasonably anticipated use patterns (including wear and degradation) should be performed. Full characterization of released or deposited materials, including particle-size distribution and other dose-relevant parameters, should also be conducted. For airborne releases, maximal and time-weighted average concentrations (mass and particle number) should be measured.
b. Applications involving direct skin contact should provide estimates of dose, frequency, and duration of application.
c. Applications with actual or potential presence in — or migration to — food or water should provide measured or calculated concentration data under reasonably anticipated conditions of consumer use.

STEP 3
Evaluate Risks



Step 3 of the Framework integrates the three products of Step 2: the lifecycle properties profile (from Step 2A), the lifecycle hazard profile (Step 2B), and the lifecycle exposure profile (Step 2C). Depending on the stage of development and availability of relevant hazard and exposure data, this step's analysis will result in qualitative, semi-quantitative, or fully quantitative estimates of the nature, likelihood, and magnitude of adverse effects on human health and the environment. Ideally, the early recognition of potential risks, at all stages of the product lifecycle, will provide better options for risk mitigation and management.

The Process

For each lifecycle stage, as appropriate to phase of development, Step 3 proceeds as follows:

- *Review hazard and exposure profiles.* The hazard and exposure profiles developed in Step 2 are reviewed in anticipation of integrating their contents. In order to facilitate this process, relevant information from the profiles can be organized in the Output Worksheet (see Appendix).

- *Match exposure situations with hazards and compare potential exposure levels to published or derived effect levels, where available.* For each exposure situation identified in the product lifecycle, the relevant routes of exposure and potential receptors (e.g., workers, children, elderly persons, specific ecosystems) are identified. All hazard data relevant to those routes of exposure or receptors are then assembled, and the hazard endpoint with the lowest observed-effect level (or highest "no-observed-effect level") is noted. Safety factors are applied to these effect levels, as appropriate, and then compared to the potential magnitude of exposures.

- Evaluate (quantifying, where possible) the nature, magnitude, and likelihood of identified potential risks. In cases where there are insufficient hazard or exposure data to do a full quantitative assessment of risks, a *qual*itative assessment of available data can be done, especially at early stages of product development. For hazard data, this may be accomplished either of four ways: by bridging (see discussion in Step 2) to similar nanomaterials, where feasible; by comparing the test material to a material with well-characterized toxicity judged to be more severe (as a benchmark); by characterizing results from *in vitro* or other screening-level tests; or by assuming, as a default, "reasonable worst-case" values for use in the risk assessment.

  For exposure data, parameters specific to a given situation may also be derived through the use of "reasonable worst-case" assumptions (e.g., a person lives in an exposed residence for an entire lifetime). But as the material is nearing commercialization, these alternative, qualitative, or semi-quantitative methods should no longer be relied upon; rather, adequate hazard or exposure profiles should be as complete as practically possible by this time.

- *Evaluate uncertainty in the risk assessment.* If the data are sufficient for conducting a quantitative risk assessment to generate a risk value, such as a reference dose or reference concentration, then the application of standard uncertainty factors should be considered to account for uncertainty.

  In the absence of adequate data, the risk assessment will be qualitative. In this case, it is extremely important that assumptions and default values be conservative (meaning to err on the side of caution by assuming a "reasonable worst case"). This policy will help ensure that the subsequent decisions are protective of public health and the environment.

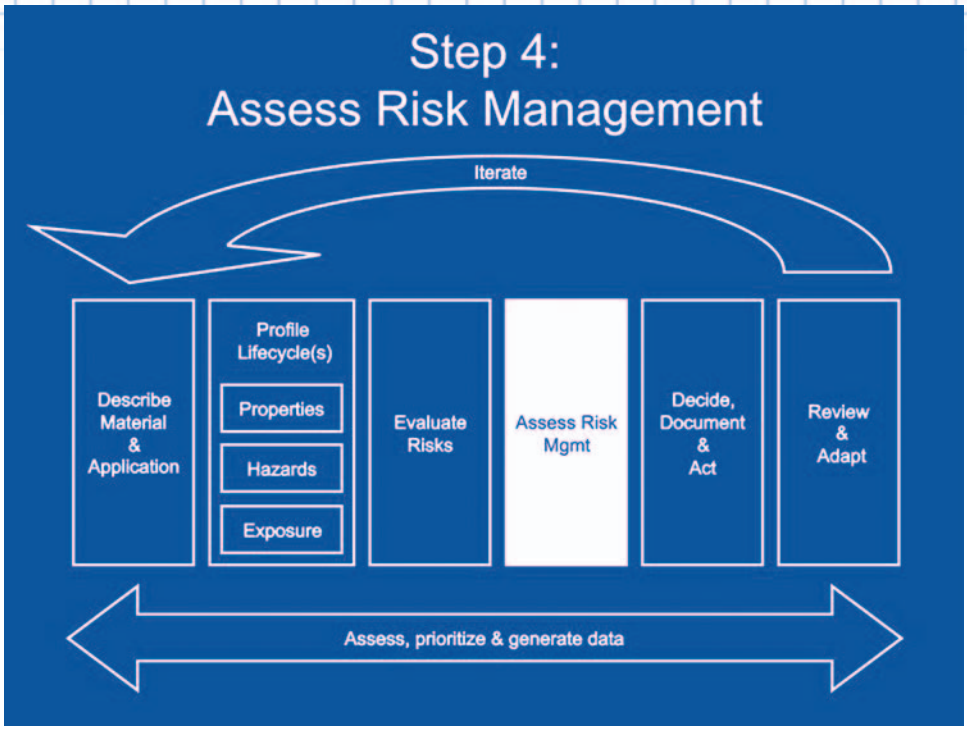
- *Assess potential for and consequences of deviations in material and applications.* This stage may involve a broadening of the lifecycle properties profile to take into account a variety of potential situations that might alter the likelihood, nature, or magnitude of potential risks. [68] Examples could include changes in the supplier of raw nanomaterials, leading to subtle changes in the properties of the product at some stage of the lifecycle; or shifts from applications with very little exposure potential (such as industrial catalysts) to ones with higher exposure potential (such as hazardous-waste-site remediation). While such changes cannot always be foreseen, they should at least be reasonably assessed as contingencies, as they could have significant impact on potential risks.

[68] There are a variety of methods and tools for doing this, including but not limited to failure analysis and scenario planning. For more information on these tools, see the following references:
UK HSE (Health & Safety Executive) Risk Management Home Page http://www.hse.gov.uk/risk/index.htm
American Insitute of Chemical Engineers (AIChE) — Center for Chemical Process Safety. Technical Guidelines and Publications. http://www1.lvs.dupont.com/SHE/psm&fire/process/training/reference_materials/aiche_ccps_publications.pdf

- *Identify knowledge gaps.* In the course of evaluating risks, there will inevitably be significant gaps in knowledge of exposure, or hazard, or both. But careful consideration of the stages of Step 2 should lead to identification of known and reasonably anticipated exposure and risk scenarios. These can then be prioritized for further data development. For example, a nanoparticle-based plastic additive may pose little exposure risk until the plastic starts to degrade. It may be difficult in early developmental stages to sufficiently characterize the nature of the degraded material, but this goal can be prioritized for further study prior to commercialization. All together, at this stage the user should have a prioritized list of data gaps.

- *Develop a plan to fill data needs or identify "reasonable worst-case" values, assumptions, and scenarios for use as benchmarks in risk management.* If the data are insufficient at this point for adequately assessing potential risks in specific scenarios developed in the lifecycle exposure profile, a decision must be made. Should the missing data be generated now? Or should the next steps be informed instead by the use of "reasonable worst-case" values, assumptions, and scenarios that can subsequently serve as benchmarks for control and mitigation efforts? Scenarios are a combination of data and assumptions to create situations that are reasonably foreseeable. The purpose of considering scenarios in Step 3 is to enable the team to consider what risk management measures could be needed in Step 4. We believe that as the product nears commercialization, priority should be given to completing the base sets for hazard and exposure profiles; in that way, the scenarios are based as much as possible on real data.

STEP 4
Assess Risk Management



Risk management comprises actions for reducing the potential risk to humans and the environment from a process or product — in this case, a nanomaterial-containing process or product. A risk management assessment should provide information sufficient for determining how best to pursue practices, conduct processes, and safely produce, use, and ultimately dispose of or recycle the product. In other words, the assessment should endeavor to eliminate or minimize any potential adverse impacts throughout the product's full lifecycle.

In performing the assessment, specialists in safety, occupational health, and environmental science, along with business managers familiar with the product and application under development, should work as a team. They should jointly determine the actions needed to reduce and control risks from known and reasonably anticipated activities associated with the product's or material's raw-material sourcing, manufacturing processes, expected uses, and disposal, recycling, or reuse pathways. Results of this assessment process may include product modifications, engineering or management controls, warning labels, or decisions to change or abandon the product. The current consensus in the literature for risk management is that the "most effective to least effective" controls are the following: 1) elimination, substitution, or reduction of the material, process, or condition that presents the hazard; 2) engineering controls; 3) warnings; 4) training, procedural, and administrative controls; and 5) personal protective equipment.

The Framework itself does not prescribe specific risk management tactics, which need to be decided on a case-by-case basis. The aim of the Framework is instead to provide a methodology for achieving a performance-based level of risk management. Several authoritative references (see Box 8) provide additional knowledge, guidance, and tools to guide risk management for nanoscale materials. Users of the Framework should consult these references and consider adopting their recommendations, as appropriate, to particular materials, applications, and conditions.

Box 8. Recommended Reading and Guidance

The following prescriptive references are recommended, with the acknowledgement that the list is not exhaustive. These references do provide, however, an excellent toolkit (based on the current state of knowledge) of available options for risk management that could be applicable to nanomaterials. Users of the framework should also consult with relevant experts (such as local, state, or federal authorities on risk management) for recommended guidance and information on required practices.

ASTM International — ASTM E56-03, "Standard Guide for Handling Unbound Engineered Nanoparticles in Occupational Settings," Draft of 30 September 2005
http://www.astm.org/cgi-bin/SoftCart.exe/DATABASE.CART/WORKITEMS/WK8985.htm?E+mystore

U.S. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, "Approaches to Safe Nanotechnology — An Information Exchange with NIOSH," Draft for comment, July 2006.
http://www.cdc.gov/niosh/topics/nanotech/safenano/

National (U.S.) Council for Occupational Safety and Health — Hierarchy of Health and Safety Controls
http://www.coshnetwork.org/Hierarchy%20of%20Controls%20Chart.PDF

Health and Safety Executive — United Kingdom Information Note: Nanotechnology
http://www.hse.gov.uk/pubns/hsin1.pdf

Health and Safety Executive — United Kingdom, COSHH (Control of Substances Hazardous to Health) — Achieving Control
http://www.hse.gov.uk/coshh/control.htm

German Federal Institute for Occupational Safety and Health (BAuA) and German Association of the Chemical Industry (VCI), Guidance for handling and use of nanomaterials at the workplace. Draft, March 2007.
http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Nanotechnology/Nanotechnology.html__nnn=true

For each lifecycle stage, Step 4 proceeds as follows:

- *Determine needed levels of protection.* Control measures should be commensurate with the risk. Decisions should be based on pre-existing standards of health and safety, and on the effectiveness of the chosen control method in reducing exposure to below the maximum level determined acceptable in the risk evaluation (or lower, if so indicated by management).[69] These decisions need to be made for each stage of the product lifecycle, and they should be based on the risk evaluation performed in Step 3.

  Elements to consider for the decision process may include a formal management policy that states a commitment to minimizing potential exposures to the nanomaterial; relevant safety, health, and environmental exposure standards that exist; and well-developed risk-assessment information. Additionally, reasonable judgment should be exercised; it should be based on the nanomaterial used, conditions of use, control measures implemented, exposure assessments, and the knowledge and experience of the users. All are workplace factors that have an impact on the potential for exposure. For example, handling nanoparticles incorporated or fixed in a polymer may reduce the potential for skin and inhalation exposure, whereas a mixing operation with nanoparticles in a non-fixed state will pose the potential for both skin and inhalation exposure. A user may decide, therefore, that working with nanoparticles fixed in a polymer would require less restrictive levels of protection (e.g., general ventilation, goggles, and gloves), while working with nanoparticles in a dry-mixing operation would require higher levels of protection (e.g., engineering controls).

- *Assess adequacy of current controls for reducing identified potential risks.* This phase of the process is a formal and ongoing review of current risk management practices relevant to the manufacturing process, product, and use of the product. A primary element to assess is management commitment. Is management providing leadership to ensure that an effective risk management program is in place? Do managers demonstrate a sincere and continuing interest in the program? Is "safety first" an internalized attitude and is prudent behavior mainstreamed in the organization? The review should also take into account the following: safety/health/environmental goals, policies, and procedures; safe-handling practices; suppliers; product distribution and transportation; customer use and misuse of the product; and recycling and waste management.

  Considerations include:
  - Are the hazards reduced or eliminated by changing the materials, chemistry, or process variables?
  - Engineering issues. For example, are local exhaust/ventilation systems performing according to specifications and effective at capturing airborne nanoparticles?
  - Administrative issues. For example, are hand-washing and other good-hygiene practices required prior to leaving the work area where nanoparticles are processed?
  - Personal-protection equipment issues. For example, are users of respirators with high-efficiency particulate filters wearing the equipment effectively?

[69] Many practitioners will be familiar with this approach as the ALARA principle ("As Low As Reasonably Achievable"). See http://www.ilpi.com/msds/ref/alara.html

- Is hazard and safe-handling information shared with those who have a need to know?
- Are procedures communicated to customers in order to inform them on how to safely use, dispose of, or recycle the product and manage environmental, health, and safety risks?
- Do labels and other safety-information communications indicate the extent of harm that could result from reasonably foreseeable misuse?
- Does packaging comply with transportation and risk regulations?

- *Assess adequacy of other available controls for addressing identified potential risks.* Other elements to be considered include facilities management; engineering controls (e.g., exhaust systems, filters, hoods, work practices, and emergency procedures); supply-chain communications; material-safety data sheet (MSDS) information; and product labeling. Users should also consider how modifying, redesigning, or replacing the material or application may reduce the potential hazard or exposure.

  Fundamental questions include:
  - Are workers and customers throughout the lifecycle adequately informed and protected?
  - Is the environment protected from the identified hazards?
  - Do customers and the general public have adequate information on the product's potential hazards and its safe and proper uses?
  - Are warnings (if applicable) available throughout the product lifecycle?
  - Are safety devices optional or standard?
  - Do customers have systems to handle spills or releases of the material?
  - Regarding customers' routine use, are gaseous-emission and solid-waste issues addressed effectively?

- *Determine best risk management options.* Once the above steps have been performed, the adequacy of existing risk management options, or the need to enhance or supplement them, must be evaluated. In that way, the user may determine whether the risks posed by a given product at any particular stage of its lifecycle can be managed, and how well. It is recommended that a re-check of Step 2C (exposure profile) be conducted to ensure that the selected risk management options adequately cover existing and potentially new exposure scenarios.

  The decision process is guided by the management objectives of manufacturing products that can be safely used and minimizing unintended exposures across the products' lifecycles. The process should include: implementation of procedures to achieve the expected level of protection; facilities and equipment improvements for containment control; and the availability of supporting equipment and other resources.

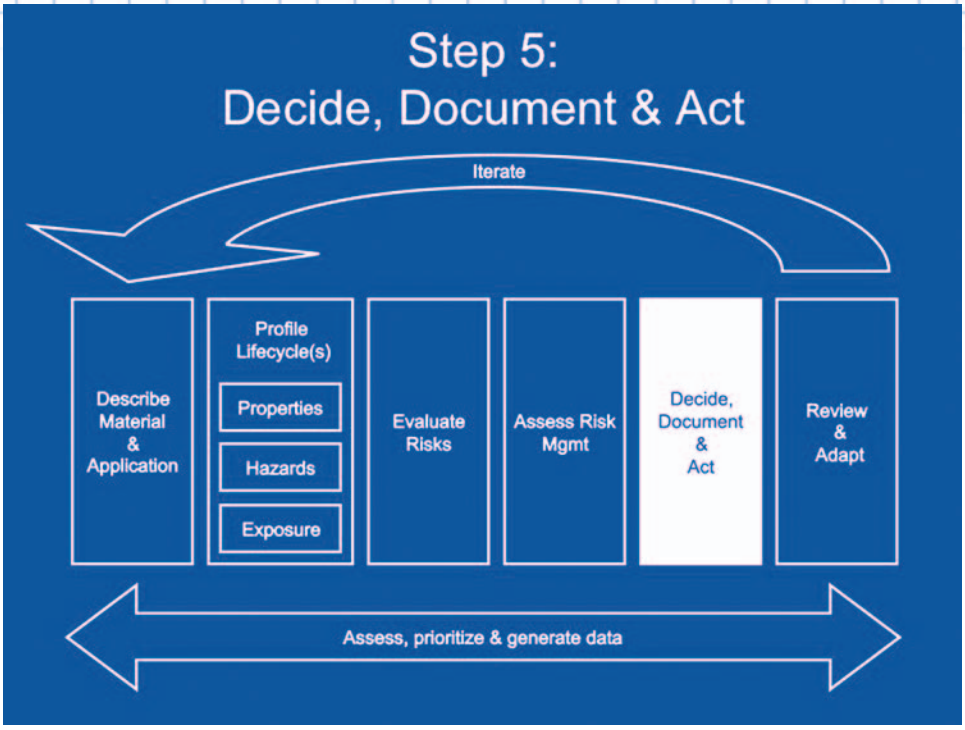
  Users should also consider whether there are needs for customer and distributor training; communications to guide customers on safe use, disposal, recycling, environmental control, and permitting recommendations; and first-aid and medical recommendations for overexposure.

  In the end, the user should be able to credibly document that the risk management measures chosen will adequately address the risks identified in Step 3.

- *Develop a plan for risk management, which includes monitoring, compliance, and reporting.* A formal risk management plan is a snapshot in time of the ongoing risk characterization/assessment/management process of this Framework. The plan is a means of determining and documenting (as well as attesting, through a written audit protocol) that appropriate and effective systems are in place for managing a product's safety, health, and environmental risks throughout its lifecycle. Note also that the monitoring program should be designed to focus on key uncertainties and target endpoints identified in the preceding steps.

  The documentation of the plan provides a frame of reference, both for communicating the current risk management program and considering whether future changes to the program may be warranted. The plan reflects elements such as toxicology; epidemiology; exposure standards, measurement, control, and prevention; lessons learned from exposure incidents; changes in workplace processes or personnel; and customer feedback.

STEP 5
Decide, Document, and Act



Earlier steps in the Framework involve compilation — typically, by the project leader or the product steward — of needed environmental, health, and safety information and assessments. In Step 5, key stakeholders, experts, and decision makers form a review team to critically examine those compilations, analyze the options, document the resulting analysis, make decisions, and take appropriate actions.

The scope of information that is considered and the composition of the review team should be appropriate to the stage of the project. Early-stage developments, for example, may have limited information to consider and small review teams, while late-stage developments are likely to generate substantial amounts of information and require more diverse complements of experts. In any case, it is recommended that outside perspectives and concerns be factored into the decision-making, when appropriate, as early in the process as possible. Such open sharing of non-confidential business information can facilitate transparency and result in shared understanding and more enlightened decisions.

It is expected that the deliberations of the review team will produce a number of "deliverables." They include:

- A decision to move ahead on, terminate, or redirect the development, manufacture, use, or sale of the product or application
- If moving ahead or redirecting, identification of specific actions to be taken
- Assignment of a product steward (if not already assigned)
- Specification of (along with rationale for) additional data to be collected, the needed mechanisms for such collection, and the expected timeline
- Endorsement of assumptions used in place of data; or recommendations for review and revision of assumptions
- Final implementation timeline for the risk management, monitoring, and compliance process
- Determination of an agreed-upon product-review cycle, including the timing and conditions for the next review
- A report that documents the review team's decisions and its recommended actions
- A plan to communicate this information across the organization and to other stakeholders.

These deliverables, as well as other products of the review team's deliberations, derive from Step 5's nine specific action elements, as detailed below:

1. Assemble a cross-functional decision-making review team.
The size and makeup of the review team will depend on the nature of the organization involved, the scope of the overall effort, and the stage of development. Ideally, the team will incorporate a broad cross-section of relevant environmental, health, and safety viewpoints, including technical, manufacturing, workforce, business, and legal perspectives (see Box 9). Its members, who may be drawn from across the value chain of the product under consideration, could include academic researchers, supplier representatives, consultants, or financiers, among others. The participation of team members with diverse perspectives and insights helps to increase the likelihood that no important factors will be overlooked in the decisions on whether and in what manner the project should proceed.

Box 9: Potential Review Team Roles

The types of roles that should be considered for the review team include the following:

- **Technical lead.** The person, typically involved in creating the nanomaterial or the product containing the nanomaterial, with the best knowledge of the technology
- **Product steward.** The person ultimately responsible for ensuring the safe promotion or sale of the nanomaterial or its product
- **Legal counsel.** A legally trained professional familiar with the policies and relevant background of the organization considering these decisions
- **Workforce representative.** A person with intimate knowledge of the handling of the material as it is processed
- **Manufacturing lead.** A person responsible for manufacturing the nanomaterial or its product
- **Administrative decision maker.** A leader of the organization who has ultimate accountability for the safe processing of the material
- **Safety officer.** An individual, knowledgeable in the laws and regulations surrounding the safe handling and use of chemicals, who is familiar with the organization's workplace or laboratory environments.

Ideally, the composition of the team will include a professional or professionals with expertise in risk assessment, toxicology, environmental fate, and industrial hygiene. It is recognized, however, that some SMEs may not have the resources to include such staff. One option is to engage outside experts to meet these needs (e.g., hiring consultants or partnering with university researchers). Additionally, the creation of consortia could function to leverage resources to ensure that these areas of expertise are covered.

2. Review information from Steps 3 and 4.

The risks associated with development, manufacture, use, reuse/recycling, and disposal of the nanomaterial were collected and evaluated in Step 3 (Evaluate Risks). The means to lessen or eliminate such risks were proposed in Step 4 (Assess Risk Management). Now the team must carefully review those risks and the options for controlling them. Different perspectives, reflecting different organizational roles, will likely surface, which collectively should aid in the determination of whether additional information or action is needed.

3. Discuss and consider business, legal, and stakeholder issues.

The cross-functional nature of the review team allows for examination of issues that may not have previously been considered. Examples include emerging regulations, public perceptions, worker perspectives, liability concerns, potential for design changes to reduce risk, and a variety of other influences.

Moreover, the review team facilitates interactions that might never occur if left to informal processes. The group dynamic often generates new ideas and derives better solutions. It is therefore best if meetings of the team provide for such interaction, with appropriate time allotted for open discussion.

Particularly important is attention to public and worker safety perspectives. It is good business to understand these issues early in the product-development cycle so that lines of communication are open and relevant information can be factored in. This results in product improvement and safer handling of materials throughout the product lifecycle.

4. Determine who is responsible for implementing recommended actions. Preferably, assign a responsible product steward.
A product steward, who ideally should have already been assigned during the previous steps, shepherds information from the early stages of development, is responsible for collecting the environmental, health, and safety data, and is a logical choice to carry out the recommendations of the review team.

5. Based on these inputs, decide whether to proceed; and if so, how to proceed.
Possible outcomes of the review team's deliberations include:

- Acceptance of the tentative recommendations as presented to the team and implementation of the project
- Provisional acceptance, with specified additional information required
- Provisional hold, with specified additional information required
- Redirection of the project
- Termination of the project.

In the case of provisional acceptance, provisional hold, or redirection, the review team should list criteria that must be met, or hurdles to overcome, for the project to proceed.

6. Determine additional data needs and initiate data collection, as necessary.
These data could include physical and chemical property data, hazard data, exposure data, or risk management information. Staff involved in the product development must then go back and uncover or produce this information to present to the review team.

7. Establish and implement appropriate risk management, monitoring, compliance, and reporting processes.
If the project and plan for risk management, monitoring, compliance, and reporting are approved in Step 5 and moved forward, mechanisms — including those related to accountability — should be established to ensure that the plan is executed. As stated in Step 4, the monitoring program should be designed to focus on key uncertainties and to target endpoints identified in the other steps of this Framework.

8. Determine the appropriate product-review cycle.
Levels of understanding change with time, as do end uses, production processes, and disposal and recycling practices. For this reason it is essential that the review team establish an appropriate product-review cycle. Periodic reviews should be triggered not only by the passage of time but also by significant events or changes that provide new information or affect previous assumptions. This allows the experts to scrutinize the most recent data, evaluate performance and compliance to date, and revise previous decisions, if indicated, concerning the material.

The schedule for regular review should be based on the degree of risk and uncertainty associated with the particular material and application. A lack of data or a high degree of uncertainty would require frequent reviews (e.g., fewer than two years between reviews), while well-characterized, low-risk materials and applications may require less frequent reviews. For at least the next several years, however, given the early and evolving state of knowledge about nanomaterial behavior, it is expected that most nanomaterial applications will merit frequent reviews. The schedule should also be flexible enough for any new data to be promptly reviewed and acted on.

Additional information on systems for ongoing evaluations and management of risk are described in Step 6 (Review and Adapt).

9. Document and report decisions and actions.
The result of Step 5 is a report that documents the decisions made and the bases for those decisions. The report itemizes the technical results of the risk evaluation and risk management assessment, and it summarizes decisions relevant to future development or commercialization of the product. The results of all studies, regardless of the conclusions they support, should be included in the report. Additionally, all assumptions should be clearly articulated. Advantages and limitations of each test, measurement, model, or estimate employed should be identified, and residual uncertainty caused by the nature or source of the data — as well as data gaps and potential biases — should be noted.

A written record allows those not present at the meetings to understand the decision-making process, its outcomes, and the resulting actions. The report can also serve as a transparency tool for assuring stakeholders (e.g., customers, the public, workers, government agencies, nongovernmental organizations) that potential risks have been identified and addressed and that needed management measures are in place. The relevant information in the report should be communicated throughout the participating organizations. It is especially important that workers who research, develop, or manufacture the product have access to the decisions, and their rationales, and that appropriate feedback mechanisms are in place to address worker concerns.

As products move into commercialization, it is recommended that a broader range of stakeholders have access to the decision-making rationale. Framework users may choose simply to make the report publicly available or to excerpt or summarize the report for specific audiences in order to facilitate ease of understanding. In either case, stakeholders should be able to request back-up documentation if they wish to dig deeper into the rationale behind certain decisions.

While a transparent decision-making process is crucial for credibility with stakeholders, it is also recognized that users have a need to protect legitimate CBI [70]— that is, to prevent competitors from capitalizing on the nanomaterial developers' efforts. A balance must be struck between providing transparency to foster public trust and withholding CBI to protect an investment. In certain cases, it may be desirable to have a responsible independent third party examine the CBI to validate conclusions to stakeholder groups. Where CBI has been withheld in stakeholder reports, this should be noted. Whenever possible under such circumstances, a non-proprietary description of the information (e.g., a description of the type and class of material that does not reveal its exact chemical composition) should be provided.

Still, in order to gain shared awareness of the risks and precautions, it is in everyone's best interest that users provide as much summary information as possible without compromising CBI. The summary should be sufficiently detailed to convince a reasonable person that the user's risk management decisions are adequate, given the potential risks of the material. The Output Worksheet included in the Appendix (or a variation thereof) may be used as a means of summarizing the information that the team considered, the assumptions it made, the risk management decisions it came to, and the rationales behind those choices.

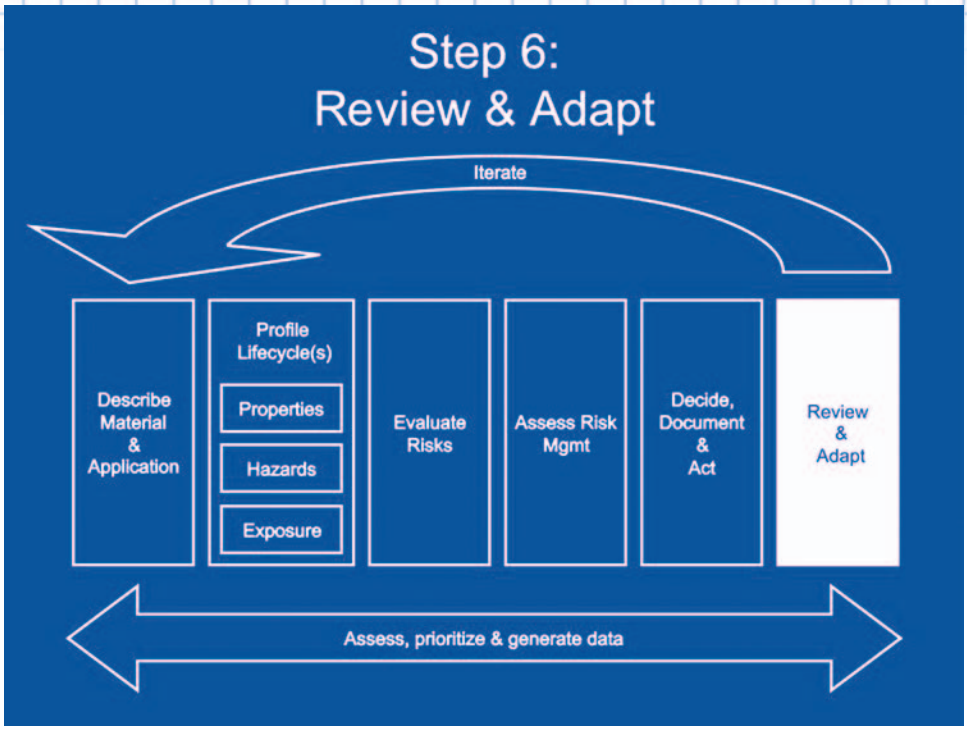
New data on nanomaterials are likely to be generated by Framework users. Because the literature on nanoparticles risks is nascent at this point, wherever possible it is recommended that users make such new data publicly available, especially as they apply to human health hazards, environmental hazards, environmental fate, physical hazards, and exposure. Publication in peer-reviewed journals will provide the greatest credibility for such findings.

[70] Consistent with U.S. EPA guidelines, users should consider information as legitimate CBI when:

- Disclosure of the information is likely to cause substantial harm to the user's competitive position (e.g., proprietary information on manufacturing methods)
- The information is not readily discoverable through other means (e.g., where chemical identity could be easily determined by reverse engineering).

See the Emergency Planning and Community Right-to-Know Act, Title 42, Chapter 116, Subchapter III, Section 11042 — Trade Secrets, at http://www.law.cornell.edu/uscode/uscode42/usc_sec_42_00011042----000-.html

STEP 6
Review and Adapt



Step 6 is key to institutionalizing the Framework within the user's processes for product development and stewardship. In this "review and adapt" step, the user implements a system of periodic and as-needed reviews to ensure that the information, evaluations, decisions, and actions of the previous steps are kept up-to-date.

The essence of these reviews is that the review team —whenever possible, the same one assembled for Step 5 — appraises new information that has been generated or has emerged and reassesses the adequacy of the risk management process for the material or application. In other words, does the current risk evaluation need to be revised in light of the new information? And if so, do the current risk management practices need to be changed as well?

A goal of Step 6 is to ensure that a material or product's risk profile and its associated risk management processes are constantly evolving with new knowledge and experience. Thus in time it may be appropriate to a relax risk management process developed under conservative assumptions, as long as those assumptions are obviated by actual data that suggest a lower level of risk. In other cases, new data may suggest that more conservative steps are needed to address previously unforeseen risks or deficiencies in the current risk management process.

As with the other steps in this Framework, it is expected that the user's level of detail in Step 6 will vary, depending on the phase of development for the given material or application. But even if a user works through Step 6 with relatively little information or data at early stages of development, the level of detail will increase — through repeated iterations of the Framework — as the material or application moves through the development process and the user gains more information. That is, the user should be seeking out new and additional information on an ongoing basis so that the risk evaluation and risk management for a material or application may continually evolve.

As-Needed Reviews

The user should conduct a risk management review whenever there has been a significant change in hazard or exposure information, production volume, or use profile. In general, "significant" means serious enough to potentially require a revision in the risk-evaluation or risk management procedures for the material or application. Examples include:

- A change in production, processing, or use patterns for the material or application that would alter the lifecycle exposure profile developed in Step 2C.
- The acquisition of new data relevant to the risk evaluation for the material or application, such as results from testing initiated by the review team in Step 5.

For pre-commercial materials or applications, a review should be included as part of the process to determine whether to move from one stage of development to the next — and if so, how. For example, upon the successful completion of the prototype phase, a review of the risk evaluation and associated risk management process should influence the decision on whether to begin test-marketing the product. Thus, as users move from one development phase to the next, they should be steadily developing a more complete package of lifecycle data on which to base risk evaluation and risk management decisions.

Regular Reviews

In addition to as-needed reviews that respond to unanticipated new information or situations, users should also establish a regular schedule for periodically reviewing recent data and the adequacy of the current risk management process. As noted in the discussion on Step 5, the schedule should be based on the degree of risk and uncertainty associated with the particular material or application, and it should align with any data-development activities initiated in previous steps so that the new data can be promptly reviewed and acted on.

In these regular reviews, the review team should:

- Analyze any new data on properties, hazards, exposure, or risk management.
- Decide on any additional data needs and how they are to be met.
- Determine whether previous decisions on development or deployment of the nanomaterial application remain valid.
- Determine any needed changes in the risk evaluation or the associated risk management practices.

These reviews should also include any information that will help assess how well the risk management practices selected in Step 5 are performing. In particular, the review team should consider any monitoring data that have been collected so that it may determine whether the risk management practices are keeping exposure levels below the maximum allowable exposure goals set in Step 4. In addition, the review team should consider any data from health screening or monitoring programs in order to ascertain whether the nanomaterial application may be causing any unexpected effects in employees or other monitored populations. Finally, the team should consider whether any new monitoring programs need to be initiated or existing monitoring programs require modification.

The team should also consider the broader issues noted in Step 5, including any new information on emerging regulations, public and worker perspectives, liability concerns, potential for design changes to reduce risk, and related influences.

Based on its review of any relevant new information or situations, the team should update the risk evaluation and then choose the most appropriate risk management options — new options may have become available since the previous review, for example, or information on previously reviewed risk management options may have changed. The project leader or product steward specified in Step 5 should be responsible for updating the risk management options. The team may also decide that new information or situations presented in the review indicate that additional data generation is needed.

Adapting Risk Management and Collecting Additional Information, as Appropriate
One way or another, the team should decide on what actions are to be taken as a result of the review. The decision is either:

- Confirm and continue ongoing actions, including the production, use, and marketing of the material or application as well as the current risk management practices.
- Provisionally continue ongoing actions, with additional information required.
- Put a provisional hold on current actions, pending generation and review of new information.
- Revise current actions in any part of product development — including the design, production, use, and marketing of the material or application — or revise current risk management practices.
- Terminate current actions (e.g., stop the development, production, or use of a material or application, initiate recall, or pursue other remediation activities).

Once the decision is made on how to proceed, the review team should determine and assign responsibilities for implementing it. In the case of a provisional hold or continuation that requires additional information, the team should designate how the required information is to be generated and set a follow-up date to review it and determine its consequences.

Documenting and Reporting any New Decisions and Actions

As in Step 5, each review conducted as part of Step 6 should produce documents that detail what information the team considered, along with the team's recommended actions and their rationales. A written record (which could be an update or expansion of the Step 5 results) allows all those not present at the team's deliberations to understand the outcomes. The Step 6 documentation should capture:

- Information reviewed by the team
- Significance of new information or situational changes
- Changes to the lifecycle profiles and risk evaluations (and reasons for the changes)
- Changes to assessments of risk management options (and reasons for the changes)
- Changes to risk management practices (and reasons for the changes)
- Updated decision to move ahead on, redirect, or terminate the development, manufacture, use, or sale of the product or application
- If moving ahead or redirecting, specific actions that will be taken
- Confirmation of the product steward or appointment of a new one
- Additional data to be collected, the needed mechanisms for such collection, and the expected timeline
- Endorsement of any assumptions used in place of data, or recommendations for review and revision of assumptions
- Updated implementation timeline for the risk management, monitoring, and compliance process
- Updated product-review cycle, including timing and conditions for the next review
- Updated plan to communicate this information across the participating organizations and to other stakeholders.

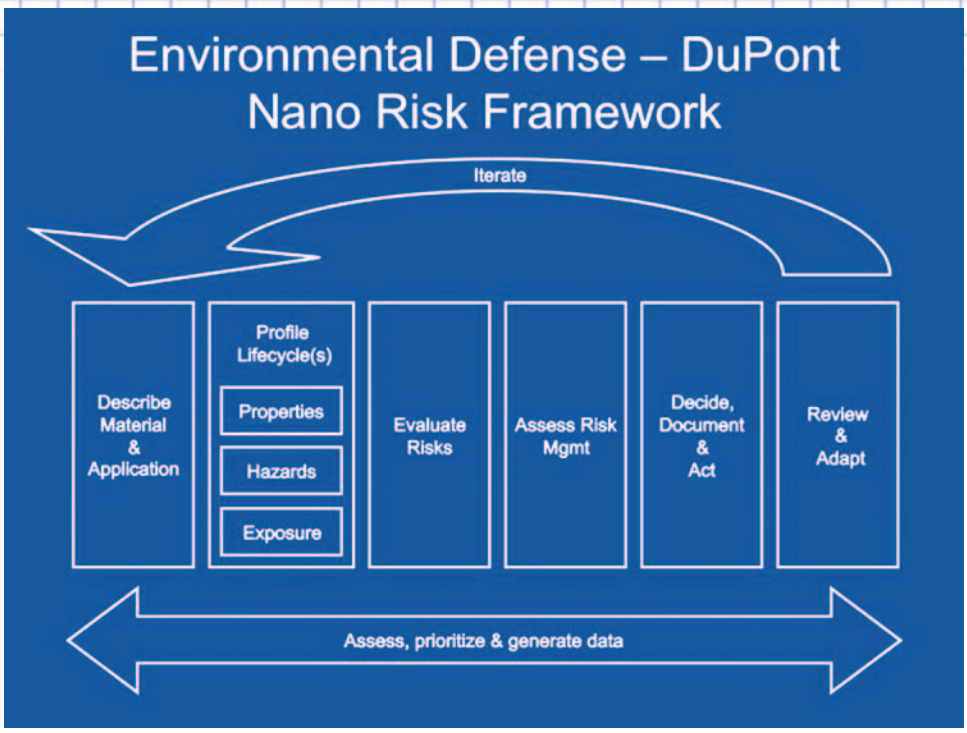
It is especially important for the review team to communicate any changes in the risk evaluation or risk management practices to those who will be affected. These audiences may include:

- Workers who handle the material or product
- Customers who purchase and use the material or product
- Other companies within the supply chain, including those involved in managing waste from the manufacture, use, recycling, or disposal of the material or product
- Members of the public who might be exposed to the material or product
- Regulatory agencies that have oversight over the risks presented by the material or product
- Public-interest groups (NGOs, governmental organizations) with a legitimate concern about the material or product.

The team should document any feedback it receives from the above groups, the company's responses to the feedback, and any actions or changes that result from them.

Finally, before completing any given review process, the team should set a date for the next scheduled review and specify the conditions that would trigger the next as-needed review. Moreover, the team should establish clear responsibility for monitoring those conditions.

CONCLUSION



Implementing this Framework will provide users with a comprehensive, effective, and flexible system for addressing the potential environmental, health, and safety risks of nanomaterials and their applications. The Framework identifies key questions and issues that a user should consider in determining how to manage those risks. And the Framework provides a means for discussing these risk evaluations and risk management decisions with other stakeholders.

The Framework offers flexibility in addressing data-generation needs. Hazard information may already be available in the literature for some nanoparticles or applications, or it may be possible to develop such data by "bridging" to other, better-characterized materials. The amount of information required in the Framework is directly related to the potential extent and degree of exposure of the specified application. Where a particular route of exposure or exposed population can be ruled out, the user would not need to develop hazard elements specific to that route or population. The Framework allows for using reasonable worst-case assumptions in lieu of newly generated information. Materials intended for single or few applications will likely engender a smaller set of exposure scenarios and thus require less hazard information for making informed risk management decisions. In sum, data should be gathered only if those data are deemed relevant to determining the potential risks associated with the nanomaterial, and its application or product, based on the stage of development.

The Output Worksheet (in the following Appendix or available for download as a Microsoft Word document at www.NanoRiskFramework.com) is meant to facilitate evaluation, management, and communication. The Worksheet provides a template for organizing all the information requested by the Framework, capturing overall evaluations of that information, and recording management decisions on how to act on it. The Worksheet can also be used as the basis for sharing information and decisions with stakeholders.

As described in the introduction, the Framework will be most effective when incorporated into or paired with a system to ensure its execution. That system may be an existing product-development or product-stewardship process, or it may be a new system designed specifically to implement the Framework. The key point is to ensure that responsible and accountable individuals should see to it that the implementation in fact occurs. Moreover, in keeping with the Framework's iterative nature, these individuals should also ensure that it is revisited on a periodic and as-needed basis. In that way, the Framework can accommodate new developments and information.

Appropriately, we expect that the Framework itself may also need to evolve in order to account for new information about nanomaterials. The field of nanotechnology is still a young one, and as such we expect that there will be ways to improve upon the Framework as the field develops. The base sets, for example, have been established in accordance with the best and most appropriate tests now available. But as new ways to test nanomaterials emerge, the base sets may be updated so that their thorough reviews of potential environmental, safety, and health risks may be accomplished through better, faster, or less expensive means. Thus we believe that this Framework will advance and mature, providing an ever more comprehensive, systematic, effective, and flexible means for reviewing, managing, and communicating nanomaterial risks.

List of Acronyms

ADME	Adsorption, distribution, metabolism, and excretion
AIChE	American Institute of Chemical Engineers
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CBI	Confidential business information
CNT	Carbon nanotube
COSHH	Control of Substances Hazardous to Health
CVD	Chemical vapor deposition
DEFRA	U.K. Department for Environment Food and Rural Affairs
EEC	European Economic Community
EHS	Environmental health and safety
EPA	U.S. Environmental Protection Agency
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
HPV	High production volume
HSE	U.K. Health and Safety Executive
ILSI	International Life Sciences Institute
ISO	International Organization for Standardization
IUR	Inventory Update Rule
LCA	Lifecycle assessment
LOAEL	Lowest observed adverse effect level
NAICS	North American Industrial Classification System
NGO	Non-governmental organization
NIOSH .	U.S. National Institute for Occupational Safety and Health
NCI-NCL	U.S. National Cancer Institute's Nanotechnology Characterization Laboratory
nm	Nanometer
NNI	U.S. National Nanotechnology Initiative
NOM	Natural organic matter
NPPTAC	U.S. National Pollution Prevention and Toxics Advisory Committee
NTP	U.S. National Toxicology Program
OECD	Organization for Economic Co-operation and Development
OPPTS	U.S. EPA Office of Prevention, Pollution, and Toxic Substances
OSHA	U.S. Occupational Safety and Health Administration
R&D	Research and development
ROS	Reactive oxygen species
SETAC	Society for Environmental Toxicology and Chemistry
SIDS	Screening information data set
SME	Small/medium enterprise
TiO_2	Titanium dioxide
TSCA	U.S. Toxic Substances Control Act
WHO	World Health Organization

OUTPUT WORKSHEET

An editable version of this Output Worksheet is available at www.NanoRiskFramework.com

Nanomaterial Risk Assessment Document — [nanomaterial]

Section 1: Describe Material and Its Applications
Develop basic descriptions — general overviews — of the nanoscale material and its intended uses.

General Overview: [71]

Material Description:
Material source or producer:
Manufacturing process:
Appearance:
Chemical composition:
Physical form/shape:
Concentration:
Size distribution:
Solubility:
State of aggregation or agglomeration:
Material CAS number (if applicable):

Material	CAS Number	Composition

Main applications (current or expected):

Stage of development:

General physical and mechanical properties of this material:

Past experience with this material or a similar material:

Potential benefits/positives of the material:

Potential risks/negatives of the material:
Health:
Environmental:

Sources of additional information:

[71] The general overview should contain descriptions sufficient to guide development of more detailed profiles of the material's properties related to hazard and exposure potential at various lifecycle stages (such as manufacture, use, and end-of-life). This overview should be developed from information in the possession of the user or available in the literature.

Section 2: Profile Lifecycles

Define and catalog the known and anticipated activities in a material's lifecycle in the following table, detailing both the product form and the operations and activities that occur at that stage of the product lifecycle. Include activities within the user's control as well as those activities upstream or downstream of the user.

Lifecycle Profile		
Material Lifecycle Stage	Material Form(s)	Operations and Activities
Material Sourcing (e.g., producer, supplier)		
Manufacturing Level I (e.g., processor)		
Manufacturing Level II (e.g. product fabrication)		
Manufacturing Level III (e.g., filling / packaging)		
Distribution (e.g., retailer)		
Use/Reuse/Maintenance (e.g., consumer)		
End of Life (e.g., recycling, disposal)		

Section 2A: Develop Lifecycle Properties Profile
Identify and characterize the nanoscale material's physical and chemical properties, including property changes, throughout the full product lifecycle.

Summary:

Data needs and actions:

Lifecycles Properties — Summary Table			
Lifecycle Stage*			
Technical or Commercial Name			
Common Form			
	Result	Method	Remarks***
Chemical Composition			
(including surface coatings)			
Component 1:			
Component 2:			
Component n:			
Crystal Phase/Molecular Structure			
Physical Form/Shape			
Particle Size and Size Distribution			
Surface Area			
Particle Density			
Solubility			
Bulk Density			
Agglomeration/Aggregation State			
Porosity			
Surface Charge			

User may create rows for data on additional properties, if available.

**Repeat table entries for each lifecycle stage if properties change.*
*** *E.g., reference, source of data, degree of certainty.*

Additional Notes:

Section 2B: Develop Lifecycle Hazard Profile

Gather information and characterize the material's potential health, environmental, and safety hazards over the entire lifecycle.

Summary:

Data needs and actions:

Nanomaterial Lifecycle Hazard Profile — Base Set		
Route	Hazard (characterization [e.g., low, moderate, high] and quantification if available [e.g., LOAEL=x mg/kg])	Source of Information (e.g., report number)
Health Hazard Data		
1. Short-term Toxicity		
a. Pulmonary toxicity		
b. Oral toxicity		
2. Skin senstitization/irritation		
3. Skin penetration*		
4. Genotoxicity		
a. Gene mutation in prokaryotic cells		
b. Chromosomal aberration		
Environmental Hazard Data		
Aquatic Toxicity		
1. Fish (fathead minnow or trout)		
2. Invertebrate (Daphnia)		
3. Aquatic Plant (algae)		
Terrestrial Toxicity (if significant release to terrestrial environments)		
1. Earthworms		
2. Plants		
Environmental Fate Data		
Water Solubility		
Vapor Pressure		
Adsorption/Desorption Coefficients in Release Medium (Soil/Sludge)		
Persistence potential screen		
Bioaccumulation potential screen		

Base Set of Safety Hazard Data
Flammability
Explosivity
Incompatibility
Reactivity
Corrosivity

Additional tests on an "as needed" basis

Nanomaterial Lifecycle Hazard Profile — Additional Tests		
Route	Hazard (e.g., low, moderate, high)	Source of Information (e.g., report number)
Health Hazard Data — *Additional tests as needed*		
Biological fate and behavior		
Chronic inhalation studies		
Chronic oral studies		
Chronic dermal irritation/ sensitization studies		
Reproductive and developmental toxicity		
Neurotoxicity Studies		
More extensive genotoxicity studies		
Focused toxicity studies		
Environmental Hazard Data — *Additional tests as needed*		
ADME studies on aquatic organisms		
Chronic toxicity to soil microorganisms and sediment- and soil dwelling organisms		
Further testing for terrestrial toxicity		
Avian toxicity		
Population/ecosystem level studies		
Environmental Fate Data — *Additional tests as needed*		
Activated sludge respiration inhibition		
Microorganism toxicity		
Persistence potential in relevant media		
Potential for transformations via oxidation-reduction reactions **		

***User may create rows for additional data, if available.*

Section 2C: Develop Lifecycle Exposure Profile

Assess potential for exposure from direct human contact or release to the environment at each stage of the lifecycle. The key deliverable from Step 2C is the ***Exposure Characterization*** — a summary and synthesis of the gathered exposure information.

Summary:

Data needs and actions:

Potential for Direct Human Contact — Summary Table			
Lifecycle Stage*			
Material Form			
Material			
Step (e.g. process step, transfer step, cleanup/disposal procedures)	Engineering Controls	Personal Protection Equipment (PPE)	Exposure Potential

**Repeat table entries for each lifecycle stage.*

Elaboration

Lifecycle Stage:

Step Name:

Material Form:

Number of People Potentially Exposed:

Potential Routes for Exposure (e.g., inhalation, ingestion, eye, dermal):

Personal Protection Equipment:

Engineering Controls:

Procedures:

Exposure Potential:

Estimated Exposure and Dose:

Unknowns and Uncertainties:

Potential for Environmental Release — Summary Table			
Lifecycle Stage*			
Material			
Step (e.g. process step, transfer step)	Potential Release Medium (e.g., Air, Water, Soil)	Engineering Controls	Release Potential

**Repeat table entries for each lifecycle stage.*

Elaboration

Lifecycle Stage:

Step Name:

Potential Release Medium (i.e., routes of entry):

Engineering Controls:

Procedures:

Release Potential:

Map Fates of the Material (e.g., degradation, transformations, or transfers to other media):

Estimated Exposure and Dose:

Unknowns and Uncertainties:

What is the ultimate environmental fate of the material?

Does it accumulate in a particular environmental sink?

What are the populations that may be exposed?

What is the bioaccumulation potential?

Exposure Data — Summary Table					
Nanomaterial Manufacture					
	Information				
Stage of Development					
Number and Location of Manufacturing Sites					
Annual Production Volumes *(current and expected)*					
Manufacturing Site's NAICS Code					
Manufacturing Method					
Number of Workers Handling Nanomaterials at the Manufacturing Site					
Industrial Functions (e.g., adhesive, coloring agent)	Percent of Production	Physical Form & Concentration			
Function 1:					
Function 2:					
Function 3:					
Function n:					
Material Processing					
Type of Downstream Industrial Processing or Use					
Number of Processing or Commercial Use Sites					
NAICS Code of Processors					
Industrial Functions	Percent of Production	Number of Sites	Numbers of Workers at Site	Number of Workers Exposed	
Function 1:					
Function 2:					
Function 3:					
Function n:					
Material Use					
Commercial or Consumer Product Types	Percent of Production	Setting for Use (homes, outdoors)	Concentration in Product	Released During Use?	Est. Number of Exposed Users
Product Type 1:					
Product Type 2:					
Product Type 3:					
Product Type n:					

Distribution/Storage		
Methods of Delivery and Storage		
Manufacturer		
Processors		
Distributors		
Retailers		
Consumers		
Post-Use Management		
	Expected disposal methods	Expected Recovery/ Reuse/Recycle Methods
Manufacturer		
Processors		
End-Users		

Elaborate on the types of employees, handling practices, and environmental containment and control equipment used to mitigate exposure potential at the manufacturing site(s) and the downstream processing site(s).

Elaborate on the use of the material in commercial and consumer products. Is there potential for exposure to the nanomaterial? If so, describe the circumstances. Describe any recommended controls for use. Describe recovery or recall techniques. Are the products intended for use by children or other sensitive populations?

Elaborate on the post-use management of the material across the lifecycle:

Section 3: Evaluate Risks

Using a synthesis of information collected in Step 2, produce a ***Risk Evaluation*** — estimates of the nature, likelihood, and magnitude of adverse effects on human health and the environment.

Summary:

Data needs and actions:

Risk Type	Nature, Magnitude, and Probability	Source(s) of Risk Assessment
Human		
Respiratory	Nature: Magnitude: Probability:	
Dermal	Nature: Magnitude: Probability:	
Ingestion	Nature: Magnitude: Probability:	
Other health (e.g., reproductive, developmental, neural)		
Environmental		
Aquatic		
Avian		
Mammalian		
Terrestrial		
Other (e,g., sludge)		

**Information contained in this table is based on existing studies. Where no information is available, a reasonable worst case assumption may be made.*

Section 4: Assess Risk Management

Determine how to minimize or eliminate any potential adverse impacts throughout the product's lifecycle. The key deliverable from Step 4 is the ***Plan for Risk Management, Monitoring, Compliance, and Reporting,*** based on the gathered exposure information.

Summary:

Data needs and actions:

Review cycle and conditions:

Plan and timeline for risk management, monitoring, compliance and reporting:

Material Safety and Handling (manufacturer of nanomaterial)		
Material Hazard Event	Recommended Precaution/Action	Expected Effectiveness of Recommended Action (e.g., what level of exposure will be achieved)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Disposal *(including packaging materials)*		
Other:		

Material Safety and Handling (nanomaterial user)		
Material Hazard Event	Recommended Precaution/Action	Expected effectiveness of recommended action (e.g., what level of exposure will be achieved)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Disposal *(including packaging materials)*		
Other:		

Material Safety and Handling (end-product user)		
Material Hazard Event	Recommended Precaution/Action	Expected effectiveness of recommended action (e.g., what level of exposure will be achieved)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Disposal *(including packaging materials)*		
Other:		

Material Safety and Handling (end of life)		
Material Hazard Event	Recommended Precaution/Action	Expected effectiveness of recommended action (e.g., what level of exposure will be achieved)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Disposal *(including packaging materials)*		
Other:		

User may add tables for additional steps in the value chain as appropriate

Section 5: Decide, Document, and Act
Cross-functional review team critically examines compiled information, analyzes the options, documents the resulting analysis, makes decisions, and takes appropriate actions.

Go/no-go/redirect decision and rationale:

Additional data needs:

Additional data-collection assignments:

Product steward:

Review team:

Product review cycle:

Needed actions and responsible persons:

Section 6: Review and Adapt
User implements a series of periodic and as-needed reviews to ensure that the information, evaluations, decisions, and actions of the previous steps are kept up-to-date.

List of reviews held (dates):

Conditions that triggered review(s):

Changes made in report and rationale (e.g., changes to lifecycle profiles):

Actions taken and rationale (e.g., revised risk management practices):

Additional References:
User may add additional references as appropriate

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