Woodrow Wilson International Center for Scholars
Project on Emerging Nanotechnologies

GMA
The Association of Food, Beverage and Consumer Products Companies

ASSURING THE SAFETY OF NANOMATERIALS IN FOOD PACKAGING:

The Regulatory Process and Key Issues

Project on Emerging Nanotechnologies is supported by THE PEW CHARITABLE TRUSTS

PEN 12
JULY 2008

ACRONYMS

ADI	acceptable daily intake
CEQ	Council on Environmental Quality
CEDI	cumulative estimated daily intake
CFSAN	Center for Food Safety and Applied Nutrition
CTP	comprehensive toxicological profile
EA	Environmental Assessment
EDI	estimated daily intake
EEC	expected environmental concentration
EIS	Environmental Impact Statement
ELISA	enzyme-linked immunoabsorbent assay
ENM	engineered nanoscale material
EPA	Environmental Protection Agency
FCN	food contact notifications
FCS	food contact substance
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FONSI	Finding of No Significant Impact
GMA	Grocery Manufacturers Association
GRAS	generally recognized as safe
MS	migrating substance
NEPA	The National Environmental Policy Act
nm	nanometers
OECD	Organization for Economic Coordination and Development
PEN	The Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars
ppb	parts per billion
ppm	parts per million
SN	safety narrative
TOR	Threshold of Regulation
USDA	U.S. Department of Agriculture
UV	ultraviolet

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The opinions expressed in this report are those of the author and do not necessarily reflect views of the Woodrow Wilson International Center for Scholars or The Pew Charitable Trusts.

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PREFACE

According to Helmut Kaiser Consultancy, in the next decade nanotechnology will impact 25 percent of the food-packaging market, which is currently estimated at $100 billion.[1] This report authored by Michael R. Taylor was a joint initiative between the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars (PEN) and the Grocery Manufacturers Association (GMA). It involved a dialogue among dozens of experts and stakeholders from government, industry and the public interest community, to better understand how the regulatory process would apply to nanotech food packaging materials and to identify issues that need to be addressed to ensure the process works effectively. The unique focus of this dialogue was "upstream" on products that had not yet been commercialized but which contained features of products that would likely move from development into the marketplace.

The novel properties that make engineered nanoscale materials beneficial for food packaging may also raise safety questions different from those raised by conventional scale versions of the same material. Companies developing engineered nanoscale materials for use in food packaging need to consider the state of the science and technology to better understand the behavior and properties of materials at the nanoscale. In addition, regulatory agencies like FDA, EPA, and the USDA need an overview of what products are heading towards commercialization, how nanotechnologies are used in these products, and what unique scientific questions may be raised by these uses.

This study showed that an open dialogue, based on case studies, and focused upstream in the product development process can help clarify environmental and safety issues and provide industry, government, NGOs, and other stakeholders with an opportunity to resolve emerging issues impacting testing and oversight. This report synthesizes over eight months of meetings and discussions, providing an initial roadmap through the regulatory process and insights into industry stewardship efforts for a new generation of nano-enabled food packaging applications.

—David Rejeski, Director, Project on Emerging Nanotechnologies

—Dr. Bob Brackett, Senior Vice President and Chief Science and Regulatory Affairs Officer, Grocery Manufacturers Association

1. Reynolds, G. "Future nanopackaging market worth billions, says study," Food Production Daily, May 15, 2007. http://www.foodproductiondaily.com/news/ng.asp?id=76538 last accessed May 21, 2008.

EXECUTIVE SUMMARY

Introduction

The new science of nanotechnology has potential applications throughout the U.S. economy, including the creation of food-packaging materials with new functional properties that can better protect the quality and safety of food. For purposes of this report, the term "engineered nanoscale material" (ENM) is used to describe a material purposefully manipulated at the nanoscale that exhibits novel properties and behaviors as a result.

One feature of ENMs is that the novel properties that make them beneficial for food packaging may raise safety questions different from those raised by conventional-scale versions of the same material or not easily answerable on the basis of what is known about the conventional-scale material. The food-packaging industry, food companies and consumers share an interest in assuring that any such safety questions are identified and, if present, are carefully evaluated and resolved before a new packaging material is marketed.

In the United States, the safety of food packaging is regulated primarily by the Food and Drug Administration (FDA), with the Environmental Protection Agency (EPA) playing a role in a limited set of cases. The central concern of this federal oversight is food safety, and specifically whether and to what extent any components of the packaging material migrate to food and, if so, whether the migrating substances are safe. Environmental impacts are also considered in various ways, depending on the product.

The regulatory system for food packaging is extraordinarily complex, legally and scientifically. That system is based on the principle of pre-market safety review and is rigorous in terms of the standards and data requirements it imposes on product sponsors and on the scientific reviews FDA and EPA conduct. The system is not widely understood, however, and legitimate questions have been raised about how it would apply to nanoscale substances used in food packaging.

The Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars (PEN) and the Grocery Manufacturers Association (GMA) are collaborating on a project to help address these questions. The project has involved dialogue among experts and stakeholders from government, industry and the public interest community to build understanding of how the regulatory process would apply to nanotech food-packaging materials and to identify issues that need to be addressed to ensure the process works effectively.

The author of this report was retained by PEN to write it based on the discussions among project participants and on his own analysis of the issues, with the understanding that the author would be solely responsible for the report's content. While project participants generally agree on the need to address the issues identified in the report, they held differing perspectives on some points, such as the state of the science related to safety evaluation of ENMs. The experts and stakeholders who participated in the project did so as individuals, and neither they nor their employers were asked to endorse this report. Section I of the report provides additional information on the goals, scope and methodology of the project and this report.

The Regulatory Process for Food Packaging

Most substances used in food packaging are regulated by FDA as "food contact substances" under the "food additive" provisions of the Federal Food, Drug and Cosmetic Act (FFDCA). EPA sometimes has overlapping responsibility under the nation's pesticide law to regulate antimicrobial agents when used in certain food-packaging applications. The core concept underlying both statutes is that the burden rests on the sponsor of a new food contact substance to demonstrate its safety, with either FDA or EPA having the opportunity to review the sponsor's data prior to marketing. For antimicrobial agents, EPA's regulatory review must address not only the safety of food as potentially affected by the food contact substance but also the potential for adverse impacts on the environment.

FDA and EPA have provided product sponsors detailed guidance on the data required to demonstrate safety and to assess environmental impacts for food contact substances generally, although not in the specific context of nanotechnology-based food contact substances. On the central issue of food safety, the agencies require detailed chemistry data to determine which components of a packaging material might migrate to food and at what levels, coupled with data on the toxicity of those materials as needed to demonstrate their safety. Because of statutory differences, EPA and FDA food-safety data requirements differ in some respects. Moreover, for antimicrobial agents, EPA requires data related not only to human food safety but also to possible occupational exposures and possible impacts on plant and animal species.

The FDA and EPA regulatory processes and data requirements are summarized more fully in Section II of the report.

Issues Arising in the Application of the Regulatory Process to ENMs

The project explored legal and policy issues, as well as scientific and technical issues, that might arise in the application of the regulatory process to ENMs. The most challenging issues relate to how the scientific and technical criteria for evaluating the food-safety aspects of ENMs in food packaging will apply, in light of their novel properties. The few legal or policy issues also stem from the science. Section III discusses the issues in more detail.

LEGAL AND POLICY ISSUES

Application of Existing FDA Clearances to ENMs

Under FDA's regulatory framework, most food contact substances are listed in the agency's food additive regulations, in its inventory of "effective" food contact notifications (FCNs) or in other lists of substances cleared by FDA for use in packaging. These listings typically include product specifications that are silent on the range of permissible particle sizes. One issue is whether a nanoscale version can be marketed on the basis of such a listing.

With regard to food additives, FDA's traditional position is that if there is a change in the identity or composition of a listed food additive that goes significantly beyond the variation covered by the petition that gave rise to the regulation, a new petition is required, even if the changed substance remains within the terms of the existing regulation. The underlying idea is that the safety and other data supporting the original petition would not necessarily have demonstrated the safety of the changed substance.

Based on the assumption that the nanoscale version has different properties than the conventional scale material does and on the general understanding that nanoscale particles warrant their own case-by-case safety evaluation, FDA's traditional position would seem to mean that a new petition would be required to authorize use of the nanoscale particle.

A contrary conclusion could be argued as a matter of administrative law, however, on the ground that parties without ready access to the content of petitions are entitled to rely on the plain language of the regulation, with FDA retaining the option to amend the regulation as needed to assure safety. Questions of scope of application could also be raised regarding current FDA regulations affirming the "generally recognized as safe" (GRAS) status of food contact substances and FDA's list of effective FCNs. An issue for consideration is whether the industry and other stakeholders would find it useful for FDA to issue guidance on these questions.

Independent GRAS Determinations for ENMs

The law and FDA policy explicitly recognize that developers of new packaging materials can make independent determinations that all the components of those materials are GRAS for their intended use and thus are not food additives and not subject to any FDA pre-market review. The legal standard is high, however, and not likely to be satisfied by an ENM with novel functional properties. An issue for consideration is whether FDA guidance regarding the possibility of independent GRAS determinations for ENMs in food packaging would be useful.

Requiring a Food Additive Regulation for an ENM

The FFDCA directs FDA to make listing decisions about food contact substances based on a food contact notification, without going through the lengthy process of issuing a food additive regulation, unless it determines that the complete food additive petition and rule-making process are necessary to provide an adequate assurance of safety or FDA and the sponsor agree that a petition should be submitted. An issue for consideration by FDA and potential sponsors is under what, if any, circumstances the petition process would be advantageous for ensuring safety and fostering public understanding and acceptance of novel products.

Defining Nanoscale

Most parties working on nanotechnology use the range of 1–100 nanometers (nm) as a benchmark for what they mean by "nanoscale," but small particles do not necessarily stop having novel properties just because they have dimensions of 101 nm, 110 nm or 200 nm. In the event FDA or EPA decides to provide nano-specific guidance to sponsors, the issue

will arise of how to define the scope of such guidance, such as by establishing benchmarks or criteria based on particle size, on possible novel properties associated with manipulation at the nanoscale that may be relevant to safety or on both.

SCIENTIFIC AND TECHNICAL ISSUES

Most of the scientific and technical issues arise under FDA's chemistry and toxicology guidance and are driven by the fact that ENMs typically have novel properties when compared to their bulk counterparts, and that these properties may affect how the materials interact with other substances and biological systems and how they can be measured and tested for purposes of safety evaluation. Related issues also arise in connection with the assessment of environmental impacts.

Chemistry Issues

1. Adequate Characterization of the ENMs' Identity and Properties—Characterizing a substance's identity and properties is the first step in exposure assessment and in designing and evaluating toxicity studies. Data beyond FDA's current guidelines are likely to be needed since the properties of ENMs could affect the design of migration studies and the identity of substances likely to be present in food. The parallel issue is whether adequately validated analytical methods yet exist to collect the additional data.

2. Defining and Describing ENM "Impurities"—Some ENMs, such as carbon nanotubes, are particularly likely to be associated with impurities generated during the manufacturing process, and these would have to be identified and quantified. In addition to such familiar consideration of chemical impurities, the properties of ENMs may necessitate an expanded view of what constitutes a manufacturing impurity that may be relevant to safety. For example, should nanoparticles that fall outside the range of particle sizes associated with the optimal functionality of an ENM be defined as impurities?

3. Migration Study Methodology and Validation—The project identified several issues that potentially affect the manner in which migration studies are performed and whether they produce reliable information. The potential for nanoparticles to change their surface charge or particle-size characteristics depending on their context or surroundings creates challenges in assuring that what is tested for safety is what the consumer is exposed to, and that it is related in a reliable, reproducible way to what is in the food contact substance. For example, if the ENM agglomerates in food simulants or changes properties in the simulant in other ways, the sponsor would have to consider whether the conventional migration study protocols recommended by FDA need to be altered to work for ENMs. Another issue might be whether the analytical methods used in the migration study adequately detect and quantify what the consumer would be exposed to. In any event, migration study protocols need to be validated for ENMs.

Toxicology Issues

Like the chemistry issues, the nano-specific toxicology issues stem from the novel properties of ENMs, in particular their tremendous surface area in relation to mass, their surface reactivity and insolubility and their potential to agglomerate or change particle size in different media, to distribute in the body and possibly to persist and accumulate in ways that conventional-scale substances might not. These properties do not prove harm, and case-by-case assessment will remain the norm, but the novel properties and their context dependence raise challenging scientific questions that may require new kinds of data and new or supplemental toxicological tools to address.

1. The Appropriateness of Current Exposure Triggers for Toxicity Testing—FDA's toxicology guidance uses a dietary concentration of 50 parts per billion (ppb) as the trigger for toxicity testing of food contact substances, with testing requirements increasing as estimated potential exposure increases. This value is based on knowledge accumulated by toxicity testing of many different structural classes of chemical compounds over many years. The issue for ENMs is whether their reactivity, possible persistence or other properties might justify a reduction in the testing triggers, either as a general rule for ENMs or on a case-by-case basis.

2. Toxicological Data Requirements and Testing Protocols—Most of the toxicological research conducted to date on ENMs has addressed the inhalation and dermal, rather than oral, routes of exposure. This reflects scientists' expectation that occupational exposure through these routes (such as in a manufacturing setting) is likely to be significantly greater, and of correspondingly greater health concern, than is exposure through food, and is much greater than possible exposures from food contact substances. What is known about the properties of ENMs, however, raises the question of whether the standard toxicology data requirements for food contact substances need to be supplemented to evaluate safety by the oral route. For example, the potential of ENMs to persist and accumulate in the body in different ways raises the question of whether additional, product-specific data on ENM characteristics in biological matrices should be required as a foundation both for determining toxicity testing requirements and for evaluating the results.

While established approaches to toxicity testing provide the foundation for safety evaluation of ENMs, validation of assay applicability to ENMs will be needed in some cases, and some protocols may need to be adjusted or supplemented to fully characterize the materials and properly assess their potential toxicity. For example, in animal-feeding studies, additions to existing protocols may be needed to understand the distribution and transformation of ENMs in the body, including, for example, techniques for examining tissue accumulation. Moreover, additional dose metrics may be needed for ENMs, whose toxic potential may be influenced less by mass alone than by such factors as surface area/mass ratio, surface reactivity or number of particles.

As these and other methodology issues are resolved and any needed new or supple-

mented protocols are developed for regulatory purposes, those protocols will have to be standardized and validated for their application to ENMs.

3. Utility of Data on Conventional Scale Versions of ENMs—For many ENMs, toxicological data exist on the conventional-scale version, but the question is whether and under what circumstances such data can be used to help inform safety evaluations on the materials manipulated at the nanoscale. This remains a matter of debate and case-by-case scientific inquiry because of, among other things, the distinctive properties of ENMs, the context dependence of their properties and the current methodological uncertainties about ENM measurement and toxicity testing noted above.

Environmental Assessment Issues

Though operating under different statutory mandates, FDA and EPA face the same basic scientific issues in assessing the environmental impacts of ENMs. As do the chemistry and toxicology assessments required for food safety evaluation, the nano-specific environmental assessment issues stem from the novel properties of ENMs. They include the challenges of having adequate analytical methodologies and toxicity tests to assess what substances enter the environment, their environmental fate (including how they might change in form or composition) and their impacts on plant and animal species.

CONCLUSION ON KEY ISSUES

Cumulatively, these issues pose a significant scientific challenge to developers of ENM food contact substances as well as to FDA and EPA. The applicable laws are by design stringent: they impose on sponsors the burden of proof of the safety of food contact substances. FDA and EPA implement these laws in keeping with sound safety assessment principles that impose significant data collection requirements on sponsors. This approach provides a high level of consumer protection, but, given the current state of scientific knowledge and need for case-by-case evaluation, it also will require scientific investment and innovation in order to satisfy established regulatory standards. Efforts are underway within national and international organizations to address scientific issues related to safety evaluation of ENMs. For the foreseeable future, however, early consultation with FDA is advisable for parties seeking to develop and market ENM food contact substances.

The Role of Industry Stewardship

PRODUCT LIFE CYCLE MANAGEMENT OF ENM FOOD PACKAGING

FDA's pre-market regulatory review focuses on specific aspects of product manufacturing and use, rather than on a comprehensive assessment of "product life cycle" issues, such as occupational exposure and health during manufacturing, safe distribution, storage and proper disposal. These issues can nevertheless have great impact on businesses and society, especially if something goes wrong and people or the environment are harmed. Recognizing this, the chemical industry and other industries involved in manufacturing have developed product stewardship programs through which they take responsibility for addressing these issues in a preventive manner.

Participants in the PEN-GMA project initiated a discussion of the possible elements of nano-specific stewardship programs and developed a draft "points to consider" document on this subject (see Appendix E). The document, drafted by the Industry Stewardship Working Group, one of three expert groups convened for this project, outlines general principles for product life cycle management by companies and embraces transparency and outreach to stakeholders. This draft document is intended not to establish new industry standards but rather to serve as a starting point for discussion of how ENMs intended for food applications can be responsibly and safely managed throughout their life cycles.

Conclusion

This report is only a springboard for discussion. It is clear that those developing ENMs for use in food packaging have significant scientific and technical work to do. It is also clear that this work needs to be done in close consultation with FDA and EPA, and with an eye on the emerging scientific knowledge about the behavior and properties of materials at the nanoscale. One of the positive lessons from this study is that open dialogue can bear fruit in clarifying the issues and ultimately mapping the way to solutions that are protective of consumers and the environment.

I. INTRODUCTION

Nanotechnology and Food Packaging: Why This Study?

In just the past few years, nanotechnology has come to media and public attention as potentially one of the most significant technological advances of our time. And for good reason: grounded in fundamental scientific and engineering breakthroughs, nanotechnology has potentially far-ranging applications throughout our economy. One of these is food packaging, the subject of this study.

Like most other major technological advances, nanotechnology could bring both new benefits and new challenges, especially when applied to the food-related and medical products regulated by the Food and Drug Administration (FDA). Most Americans are quick to embrace new technologies, but they also want new products to be safe, and they expect the regulatory process to assure that. The challenge for the U.S. regulatory process is to ask the right questions and to generate the answers needed to demonstrate safety, on a case-by-case basis, before the products enter the marketplace.[1]

In the United States, the long-established regulatory process for food packaging is based on the principle of pre-market review of safety. Its central concerns are whether and to what extent any components of the packaging material would migrate to food under conditions of use and, if so, whether the migrating substances would be safe. This study was initiated in anticipation of nanotech food-packaging materials entering that regulatory process. This report describes how the process is likely to apply to such materials and identifies issues that need to be addressed to ensure the process works effectively.

This study is motivated by the very nature of nanotechnology, which involves the intentional manipulation of matter at a very small scale—generally between 1–100 nanometers (nm)—to exploit novel properties and functions that can occur at that scale.[2] A nanometer is one billionth of a meter. A human hair is about 80,000 nanometers wide. Nanotechnology thus involves the purposeful use of matter down to the molecular and even atomic, scale. At this scale, many common elements and compounds behave differently than they do at larger particle sizes, and can be used in new and unconventional ways. For example, specially engineered nanoscale materials (ENMs) can combine to form substances of enormous strength or barrier properties. ENMs can be used for applications that are not possible or economic with conventional materials and manipulation technologies.

There is no single, universally accepted definition of ENM. As used in this report, however, the term describes a material that exhibits novel properties and behaviors (that cannot be predicted based on size alone) as a result of being manipulated at the nanoscale. Nanometer-scale particles—nanoparticles—are an important subset of ENMs, and form the basis for many current and emerging nanotechnologies. One reason matter acquires new and useful properties when reduced to very small particle size is that its ratio of surface area to mass increases exponentially. For example, the surface area of 100 grams of lead in a sphere 2.6 centimeters in diameter is 0.002 square meter (m^2). The same 100 grams of lead at a particle size of 50 nm have

a surface area of more than 1,000 m^2—about a half-million times greater.

Such dramatic expansion of the surface area/mass ratio typically makes ENMs much more reactive with materials around them, whether other chemicals or biological systems. In addition, the small size of many nanoparticles can cause them to take on unique physical and chemical properties that lie somewhere between those of individual atoms and molecules and those of much larger blocks of material and that cannot simply be extrapolated from the behavior of the component chemicals or the bulk substance.

While enhanced reactivity and other novel properties of nanoparticles can produce beneficial new functional attributes, these properties also raise the possibility that ENMs may have different toxicity than do conventional-sized particles of the same substance. For example, because they are so small, some ENMs have the potential to pass through membranes and go places in the human body where their conventional-scale counterparts cannot. This property creates nanotechnology's potential to produce highly targeted drug-delivery vehicles, but it could also raise safety questions. At the same time, the reactivity of ENMs means that their novel properties may be altered—or lost—as they move through environmental or biological media.

Based on what is known today about nanotechnology, the general consensus among knowledgeable scientists is that one should neither assume all ENMs are unsafe nor assume, on the basis of what is known about the conventional-scale material, that the nanoscale version is safe. Instead, assuring the safety of any ENM requires a careful, case-by-case assessment. Each ENM should be approached, in other words, as if it were an untested new material with unfamiliar properties or a significant new use of a material. While manipulation of material at the nanoscale does not necessarily make the material unsafe, it should prompt the asking of additional questions.

The regulatory process for ensuring the safety of food packaging is designed to make such a case-by-case assessment before new materials, or new uses of previously cleared materials, enter the market. The novel properties of ENMs make it fair to ask, however, whether they are likely to pose new scientific or technical questions that need to be addressed to ensure the regulatory system achieves its goals. This study attempts to identify such questions and to explore how they would be examined in the current regulatory process.

While the products used in this study are hypothetical ones, the issues are real. Helmut Kaiser Consultancy recently estimated that in the next decade nanotechnology will impact 25 percent of the food-packaging market, which is currently worth $100 billion.[3] In the future, nanotechnology will enable better and more intelligent food packaging. With nanoparticles, bottles and packaging can be made lighter and stronger, with improved thermal performance and less gas absorption. Nanostructured film can help protect food from bacteria and microorganisms, and embedded nanosensors in packaging may alert consumers to food-safety problems.

We are at the beginning of nanotechnology's possible impact—as far as we know, FDA has cleared only one ENM food contact substance, based on the likelihood of little or no migration and exposure—but that makes it the right time to understand and address any issues related to assuring the safety of this new technology.

Interests and Roles of the Study's Sponsors

This study is cosponsored by two organizations: the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars (PEN) and the Grocery Manufacturers Association (GMA).

The Woodrow Wilson Center is a nonprofit research center that addresses a wide range of domestic and international public policy issues. A joint initiative of the Woodrow Wilson International Center for Scholars and the Pew Charitable Trusts, PEN is engaged in a multi-year effort to build awareness of nanotechnology and the economic, scientific, regulatory and social issues it raises and to foster action by government and the private sector to address these issues as needed to help ensure that the benefits of nanotechnology are realized and the risks are well managed.[4] As a part of its effort, PEN has commissioned a number of studies on nanotechnology-related issues, of which this study is one.

GMA is a broad-based food-industry trade association that represents many of the largest brand-name food and grocery products companies in the United States and globally. GMA's food-industry members are potential customers of companies in the chemical, plastic and paper industries that manufacture and market food packaging who may be developing products that incorporate ENMs. GMA's members depend on the regulatory process to assure the safety of and maintain consumer confidence in food packaging and the food products GMA companies market. GMA is interested in assuring that the regulatory pathway for any food packaging that incorporates nanotechnology is well understood and well equipped to achieve these goals.[5]

Both PEN and GMA have played active roles in this project, contributing financial resources and staff time and facilitating the working group process described below. PEN retained the author of this study report, who bears sole responsibility for its content. PEN and GMA have both contributed significantly, however, to marshaling the information and expert analysis underlying this report and have reviewed and commented on drafts.

Scope and Goals of the Study

This study focuses on ENMs, materials that have been specifically manipulated at the nanoscale to produce the novel properties that come with small material structures—and especially small particle size. While most food-packaging applications of ENMs are regulated by FDA, antimicrobials used to protect food packaging are also regulated by the Environmental Protection Agency (EPA). The regulatory processes at both agencies are addressed here. The study focuses specifically, however, on the pre-market regulatory review of packaging containing ENMs. At EPA, this includes the registration of antimicrobial products under the pesticide law, but it does not include any possible application of other EPA laws, such as those covering clean air and water and hazardous waste.

As noted earlier, the primary purpose of the study is to identify ENM-specific issues that need to be addressed to ensure the regulatory system works as intended to ensure safety. The study also has an educational purpose and, through the discussion on industry

stewardship, it highlights "points to consider" as companies proceed to commercialization of products containing ENMs.

The regulatory process for food packaging is complex legally, procedurally and scientifically. It may not be well understood by stakeholders in industry and the consumer community, as well as the public at large, who may be interested generally in nanotechnology but unaware of its application to packaging. The study thus aims also to improve public understanding of the regulatory process and was designed to incorporate a broad-based participation of stakeholders. This was accomplished with the participation of 62 stakeholders (see Appendix A for participant lists) representing government (14), industry (40), academia (2), policy centers (3) and non-governmental organizations (3).

As is commonly the case with novel technologies, or novel applications of existing technologies, FDA and EPA will have to make case-by-case decisions about how existing standards and procedures apply to ENMs. This study describes and analyzes the regulatory process as applied to ENMs to a degree sufficient for its issue-identification and educational purposes, but it does not make scientific or policy recommendations. The hope is that the study can help inform necessary decisions, but it does not recommend what those decisions should be.

Study Methodology

This study relied primarily on expert working groups and hypothetical product scenarios to examine how the existing regulatory system applies to ENMs in food packaging.

Three expert working groups were organized around these topics: (1) law, policy and process; (2) science; and (3) industry stewardship. Each working group included representatives of FDA, EPA, the U.S. Department of Agriculture (USDA), the food and packaging industries and the consumer and environmental community (see Appendix A for working group participant lists). Group members participated as individual experts to share their knowledge and perspective; they were not there to represent their particular organizations, or, in the case of the agency experts, to convey official policy or regulatory conclusions or advice.

Each group met at least once and did additional work via e-mail and conference calls. The Law, Policy and Process Working Group and the Science Working Group made substantial contributions to the description of the regulatory process that follows and to the identification of ENM-specific issues. The Science Working Group carried the heaviest load, because most of the novel issues raised by ENMs are scientific or technical in nature. This group conducted its own analysis of the regulatory safety evaluation process and met with FDA and EPA review scientists to discuss the product scenarios and the issues they raise.[6] The project could not have proceeded without the helpful collaboration of FDA and EPA.

The Industry Stewardship Working Group was formed in recognition of the fact that companies developing and using ENMs have responsibilities not only under the specific regulatory statutes addressed here but also beyond. This group developed some stewardship "points to consider" related to nanotechnology, which are discussed below.

The author of this report participated in the discussions of all three working groups and was charged by PEN with writing this report based on the discussions of the groups and his own analysis of the issues. The author alone is responsible for the content of this report.

Hypothetical Product Scenarios

In order to provide factual context for the description and analysis of the regulatory system, the study participants developed three hypothetical product scenarios involving the use of ENMs in food packaging. These scenarios do not reflect any specific, known product, and they may or may not prove technically or commercially feasible; they are simply illustrative of theoretically possible applications. They were devised with a view toward raising a wide range of possible regulatory issues.

The scenarios have served the important purpose of stimulating discussion within the working groups, and they are used in this report to illustrate the functioning of the regulatory system and key issues. The study does not, however, provide a full "case study" analysis of each scenario, nor does it attempt to provide definitive answers to questions about how the hypothetical products would be evaluated and regulated by FDA and EPA. This would have required migration and toxicology data, which was beyond the scope of the project.

The three product scenarios are summarized here and described more fully in Appendix B.

SCENARIO ONE: "ACTIVE PACKAGING" THAT PREVENTS CONTAMINATION OF THE PACKAGING ITSELF

This hypothetical scenario involves affixing a nanoscale antimicrobial agent to the food contact surface of a plastic packaging film. The purpose is to protect the film from microbial contamination in order to reduce the likelihood that it could be the vehicle for introducing bacteria that cause spoilage or food-borne illness during the commercial handling and shipment of fresh produce or meat.

This scenario includes two versions of the active packaging. Version A involves affixing the antimicrobial peptide nisin to nanoscale (90-nm) plastic spheres, which are then used to coat the surface of the packaging film using an electrostatic process. Version B involves using as the antimicrobial agent metal nanoparticles (50 nm in diameter) that release positive metal ions into the immediate environment. As in Version A, these are then coated to the film's surface using an electrostatic process.

In both versions, the advantage of the nanoscale material is that it permits the use of very minute amounts of antimicrobial agent while still presenting a high surface area of the bioactive agent to the potentially contaminating bacteria.

SCENARIO TWO: "SMART PACKAGING" THAT DETECTS HARMFUL BACTERIA IN PACKAGED FOOD

Scenario Two involves affixing nanobiosensors to the food contact surface of a packaging film to react with and detect specific pathogenic organisms in food, such as *E. coli* O157:H7. Manufacturers or retailers could use such a film to monitor and screen products for contamination before releasing them to the marketplace.

The hypothetical biosensor is based on the widely used enzyme-linked immunoabsorbent assay (ELISA). It involves attaching one end of a rigid nanotube to a nanoscale version of an enzyme-antibody conjugate or complex. The antibody is capable of detecting the specific pathogen by binding to antigens on the surface of the bacterial cell. The enzyme part of the conjugate fluoresces (emits light) when it contacts a specific chemical known as its substrate. The opposite end of the nanotube

is encased in the substrate and fixed to the packaging film (see Figure 1 in Appendix B). This construct is designed so that, when the antibody on the end of the tube binds with the antigens on the surface of the bacteria of concern, the nanotube loses its rigidity and flexes, causing the enzyme to contact and cause fluorescence in the substrate. The degree of fluorescence is proportional to the number of bacteria present, allowing both the presence and level of bacteria to be read with an ultraviolet (UV) light (qualitative) or UV instrument (semi-quantitative).

The scenario includes two versions.Version A uses single-walled carbon nanotubes, while Version B uses silica or alumina nanotubes.

SCENARIO THREE: IMPROVED BARRIER PACKAGE FOR CARBONATED BEVERAGES

Scenario Three involves the use of nanoscale clay "platelets" to make a plastic bottle for carbonated beverages that has clarity, barrier properties and shelf life comparable to that of glass bottles, but that weighs less and is less likely to break. The bottle is made by embedding nanoscale clay particles in a polypropylene layer that is then sandwiched between external and internal polyethylene layers. The barrier helps maintain the integrity and quality of the product by holding in carbonation and water vapor in the product and keeping out oxygen, which reacts with and degrades flavorings and other ingredients.

II. OVERVIEW OF THE REGULATORY PROCESS FOR FOOD PACKAGING

Introduction

Any effort to identify and understand the regulatory issues raised by food packaging produced by nanotechnology must begin with an overview of the regulatory process as it applies generally to food packaging in general. This section provides that overview. The full story of food-packaging regulation is remarkably complicated—legally, procedurally and scientifically. The aim here is to provide the background necessary for discussion of regulatory issues raised specifically by nanotechnology, without attempting to provide a complete legal and scientific treatise on the subject.

Most substances used in food packaging are regulated by FDA under the food additive provisions of the Federal Food, Drug and Cosmetic Act (FFDCA).[7] EPA sometimes has overlapping responsibility under the nation's pesticide law to regulate antimicrobial agents used in certain food-packaging applications.[8] Some of the legal and procedural complexities of the regulatory system arise from how Congress has defined "food additive," drawn the line between FDA and EPA jurisdiction and over time established procedures and data requirements at EPA that differ from those of FDA in certain respects.

The core concepts underlying the statutory frameworks implemented by FDA and EPA are, however, similar and straightforward: the burden rests on the developer or other sponsor of a new packaging material to demonstrate its safety, with FDA or EPA having the opportunity to review the sponsor's data prior to marketing. This section briefly reviews the basic elements of the regulatory approaches and processes at FDA and EPA and describes how the core concepts underlying them have been given operational meaning through the implementing regulations, data requirements and other guidance the two agencies have issued over the years.

FDA Regulation of Food Packaging

FDA regulates food packaging through the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition (CFSAN). CFSAN's program is rooted in 50 years of experience regulating additives to food and in a set of widely accepted, risk-based scientific principles and practices that are reflected in detailed guidance FDA has given industry on the data and analysis required to demonstrate safety. FDA's legal and procedural framework and guidances are described here to provide the basis for identifying unique issues that might be raised by the application of nanotechnology.

LEGAL AND PROCEDURAL FRAMEWORK

Food Additive Regulation

Congress enacted the Food Additives Amendment of 1958 to the FFDCA to require that all substances meeting the legal definition of "food additive" be approved by FDA prior to marketing, based on the sponsor's demonstration that the intended use of the substance will be safe. Congress

cast the "food additive" net broadly to include not only substances added directly to food but also those whose intended use:

> … may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in packing, … packaging, or holding food …) …

Substances in food-packaging materials were explicitly covered, provided there is a reasonable expectation that some amount will migrate to the food. Regardless of whether a substance is added to food directly or indirectly, Congress recognized that the safety of substances with a long history of use prior to 1958 may be so well established in the view of experts that putting them through the FDA approval process would not be necessary. It thus excluded from the definition of "food additive" substances that are "generally recognized as safe" (GRAS) for their intended use based on their history of use. For substances lacking common use in food prior to 1958 to be considered GRAS, however, Congress required not only that their safety be generally recognized among qualified experts but also that the recognition of safety be based on "scientific procedures," which means the same quantity and quality of evidence required to demonstrate the safety of a food additive.[9]

FDA has recognized and listed in its regulations the GRAS status of a number of substances added directly to food and used in packaging and other food contact materials.[10] As a matter of law, however, sponsors are free to make independent determinations that a substance, or a new use of a substance, is GRAS and on that basis market it without prior review by FDA. The legal standard and the norms of the industry—in which commercial purchasers typically require guarantees and other forms of assurance that a packaging material or other food substance can be lawfully marketed —make it very difficult, however, for novel materials to enter the food supply without FDA approval. The implications of the GRAS concept for ENM-derived food packaging are discussed later in this report.

As a general rule, persons seeking FDA approval of a food additive are required to demonstrate that the intended use of the additive is "safe"[12] which, as Congress explained in legislative history, requires a demonstration of a "reasonable certainty of no harm" under conditions of intended use.[13] For direct additives and, until recently, food-packaging substances, the congressionally mandated procedure for seeking approval of a food additive is the submission to FDA of a petition containing information on the:

- Chemical identity and composition of the additive;
- Conditions of proposed use and specimens of proposed labeling;
- Intended physical or technical effect of the additive;
- Analytical methods for detecting the additive in food and substances formed because of its use; and
- Studies conducted to demonstrate the safety of the additive.[11]

If, based on its review of this information, FDA concludes that the intended use of the additive has been shown to be safe, the agency issues a regulation specifying the conditions under which the additive may be lawfully used, including as needed compositional specifications for the additive. Any party (in-

cluding members of the public) who consider themselves "adversely affected" by the approval regulation can file objections, request a hearing and ultimately seek judicial review.[12] Once final, FDA food additive regulations authorize use of the additive not only by the petitioner but by any other person as well (subject to patents or other applicable legal restrictions on use of the substance).

Based on this process, FDA has issued extensive regulations authorizing the use of thousands of substances, most of which are for uses in food packaging or other food contact situations rather than as direct food additives.[13]

Food Contact Substances

In 1997, Congress made an important change in how FDA regulates most food-packaging materials and other food contact substances. Recognizing the significant time and energy being expended by FDA to issue food additive regulations for components of packaging, which typically migrate to food in very small amounts, if at all, Congress directed that "food contact substances" (including, but not limited to, new packaging materials) meeting the definition of "food additive" would enter the market, in most cases, based on a "food contact notification" (FCN).[14]

Under the FCN process, the sponsor must satisfy the same safety standard and provide FDA the same information required to gain approval through a food additive petition.[15] After allowing 120 days for FDA review of a complete FCN, however, the sponsor may market the material unless FDA objects based on a finding that safety has not been adequately demonstrated.

This procedure enables FDA to conduct the same scientific safety review for a FCN as it would for a food additive petition but without the administrative burden of issuing a formal regulation. Because no regulation is issued, however, the right to market based on an FCN petition applies only to the specific material produced by the company that submitted the notification and the specific intended use. FDA posts on its website a list of packaging materials that have passed through the FCN process, with details on the identity, compositional specifications and allowable uses of the material.[16] In addition, after the 120-day review period, the safety data and data on the functional effect of the substance are available for public disclosure.[17]

If FDA later determines that available information raises a safety concern, it can declare the FCN no longer effective after giving the submitter an opportunity to rebut FDA's concern.[18]

While Congress made the FCN process the presumptive regulatory pathway for market entry of new packaging materials, it gave FDA discretion to require a food additive petition when it "determines that submission and review of a petition … is necessary to provide adequate assurance of safety."[19] In its regulations, FDA has exercised this discretion by requiring a food additive petition when the proposed use of a food contact substance increases the cumulative dietary concentration of the substance above 1 part per million (ppm) in the daily diet or above 200 ppb for a "biocide" (or antimicrobial) substance, or if existing data raise a new or unresolved question about the carcinogenicity or toxicity of the substance.[20]

Environmental Assessments

The National Environmental Policy Act (NEPA) requires federal agencies, including FDA, to prepare an Environmental Impact

Statement (EIS) in connection with agency actions that have the potential for significant impact on the environment.[21] NEPA assessments and findings serve the purpose of bringing to public attention any significant environmental impacts of such decisions so that the sponsor, FDA or others can consider mitigation measures.

Under FDA's regulations and guidance implementing NEPA, parties seeking FDA action, including approval of a food additive or review of an FCN ordinarily must submit to FDA an Environmental Assessment (EA) providing information that enables FDA to determine whether the requested action has the potential to significantly impact the environment.[22] Based on the EA, FDA decides either to issue a Finding of No Significant Impact (FONSI) without further analysis of environmental impacts or, if a FONSI cannot be supported, to proceed to prepare an EIS.

By regulation, FDA has granted a "categorical exclusion" from the requirement of an EA for categories of actions that it has determined are not likely to have significant environmental impact. Indirect food additive petitions and FCNs enjoy a categorical exclusion from the requirement of an EA in at least three circumstances: (1) when the substance is present in the finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with the finished food-packaging material through use by consumers; (2) when the substance is a component of a coating of a finished food-packaging material; or (3) when the substance is a component of another food contact substance intended for repeat use.[23]

FDA retains authority to require an EA for any agency action that ordinarily would be categorically excluded if available data indicate that "extraordinary circumstances" that would make the exclusion unwarranted exist and, thus, the proposed action may have significant impact on the environment.[24]

DATA REQUIREMENTS: FDA'S SCIENTIFIC AND TECHNICAL GUIDANCE

The statutes and regulations under which FDA operates establish legally binding standards and rules that, at a general level, control FDA's pre-market review of food-packaging materials and place boundaries on the agency's discretion. Within those boundaries, however, FDA has broad discretion in how it manages the pre-market review process, especially with regard to the scientific and technical issues it considers relevant to assuring safety and the data it requires for resolving those issues.[25]

As noted earlier, the potential safety concern about food packaging is that some components of the packaging could migrate into food and pose a safety hazard when the food is consumed. To address this concern, FDA's review focuses on answering these key questions:

1. What components of the food packaging are reasonably expected to migrate to food under intended conditions of use?

2. At what level are these components expected to be present in food?

3. What is the likely human exposure to migrating components?

4. Do available toxicology data demonstrate that the estimated level of exposure is safe?

While according to the laws of thermodynamics there is the theoretical likelihood

that, with sufficient time, some amount of any material in contact with food will migrate to the food, what actually migrates at what rate is affected by a host of factors, including the nature of the food (aqueous, acidic, alcoholic, fatty), the nature of the material (polymer, monomer, contaminant) and chemical bonds joining the materials, the temperatures at which the food and package will be held and time. Answering the first three questions requires detailed knowledge of the characteristics and physical properties of the food contact substance (FCS), careful chemical testing of migration potential under proposed conditions of use and analysis of the results to estimate exposure. FDA has issued detailed guidance to industry on these matters in its chemistry recommendations for food contact substances.[26]

The migration and exposure assessment provides the starting point for assessing safety and answering the fourth question. FDA has a long history of evaluating the safety of substances in food and doing so in accordance with the fundamental principle of toxicology attributed to the 16th-century Swiss physician Paracelsus: "The dose makes the poison." Thus, FDA requires varying levels of toxicity testing, depending on the anticipated exposure, and observes long-established, widely adopted approaches to evaluating safety based on the combination of exposure and toxicology information. As with the chemistry side of the equation, FDA has issued detailed guidance to industry on the toxicology information it should generate to support the safety evaluation of food contact substances.[27]

Together, FDA's chemistry, toxicology and environmental guidance play a central role in FDA's pre-market review of food-packaging materials, with the same guidance applying whether the material is submitted to FDA through a food additive petition, an FCN or a Threshold of Regulation (TOR) submission.[28] The guidance is not legally binding on FDA or the industry, and FDA closely guards its prerogative to adjust its recommendations as needed in particular cases to assure safety. It nevertheless provides a good road map of the scientific testing and review process for packaging materials.

The guidance documents have also played a key role in this study. It quickly became clear through the working group discussions that most of the new issues posed by the application of nanotechnology to food packaging arise in the technical arena. To identify nano-specific issues, working group members agreed it was important first to be clear about the chemistry, toxicology and environmental questions that have to be addressed for any packaging material and then to identify any new issues and challenges that arise when scientists seek to answer those questions with respect to materials manipulated at the nanoscale. Thus, the requirements of FDA's guidance documents are described briefly here to lay the foundation for identifying nano-specific issues later in the report.

Chemistry Guidance

FDA's chemistry guidance is a 40-page document full of highly technical detail. It is required reading for anyone seeking a full understanding of the chemical testing and dietary exposure analysis required to support a food additive petition or FCN. It will suffice here, however, to identify and explain the basic requirements, which fall into five categories: (1) identity of the food contact substance (FCS); (2) intended use of the substance; (3) intended technical effect; (4) testing and analytical methods to estimate migration; and (5) consumer exposure.

1. Identity—Detailed information on the identity of the FCS is needed to identify substances that may migrate to food. Identity information includes basic chemical identifying information on the FCS itself, such as chemical formula, structure and molecular weight, as well as details that relate to the potential for migration, including:

a. Method of manufacture—to assess the possibility that substances used in the manufacturing process, reaction products and other possible contaminants might be present and available for migration, concentrations of all impurities, as well as spectroscopic data to chemically characterize the FCS, must be provided.
b. Physical/chemical specifications—to understand the properties of the FCS that could affect the potential for migration, such as melting point and solubility. In cases where particle size is important to achieving the technical effect or may relate to toxicity, sponsors should describe particle size, size distribution and morphology, as well as any size-dependent properties.
c. Analytical methods—to determine the concentration of the FCS if it is being used as a component of another material.

Intended Use—Information on intended use is essential to assess the potential for migration and to select the tests appropriate to measure migration. Intended use information includes the maximum level of the FCS in the packaging material and the anticipated conditions of use, including the type of material (such as films, molded articles or coatings) in which the FCS will be used, the thickness of the material, the types of foods it will contact and the time and temperature of contact (including whether the packaging or other material is for single or repeat use).

2.Intended Technical Effect—Information is needed to verify that the FCS will achieve its intended effect and that the proposed use level is the minimum needed to accomplish that effect. This includes information on particle size and, if the technical effect is dependent on particle size, the specific functional properties of the particles.

3. Testing and Analytical Methods to Estimate Migration—Much of the preceding information is required to select an approach to migration testing and analysis that will produce an accurate estimate of the amount of the FCS expected to be in food, which is in turn essential to reliably estimating likely consumer exposure. FDA's guidance includes several conservative features intended to avoid underestimating migration and exposure. For example, sponsors may forgo migration testing if they are willing to assume that 100 percent of the FCS will migrate to food under intended conditions of use. To avoid overestimating migration and triggering toxicity data requirements that may not apply at lower, more accurate levels of migration and exposure, sponsors typically conduct migration studies on their FCS, commonly with food-simulating solvents.

FDA's chemistry guidance provides detailed recommendations on the design and conduct of migration studies, ad-

dressing such matters as the design of the "migration cell" (apparatus for exposing the FCS to the food or solvent), the test sample (which should include the maximum proposed concentration of the FCS), the appropriate food simulant based on intended uses of the FCS and on the types of foods with which it may be used, the temperature and time of the test (reflecting the most severe conditions anticipated for the proposed use and storage), how analysis of the migrating substances in the simulant should be conducted and reported and the need for validation of the analytical methods used in the study.

4. Consumer Exposure—The ultimate aim of FDA's chemistry guidance for FCS is to generate estimates of likely human exposure to substances migrating to food from packaging or other food contact substances, expressed as an "estimated daily intake" (EDI). To calculate the EDI, FDA first estimates the concentration of the FCS in the daily diet, taking into account (1) migration data showing the highest level of migration to food that might result from the anticipated use of the FCS and (2) the types of food and the fraction of the daily diet expected to contact the FCS, assuming the FCS captures the entire market for which it is intended.

The EDI is then determined by multiplying the dietary concentration of the FCS by the total weight of food a person is assumed to consume per day, with reference to U.S. food-consumption survey data. FDA uses the EDI as an integral element of its safety evaluation, including determination of the types of toxicity studies needed to establish safety. If other food uses of the FCS have already been approved by FDA, the agency combines the EDIs from all uses to determine a cumulative EDI (CEDI) and uses that to set toxicity data requirements and evaluate safety.

For some FCS, a possible outcome from the recommended migration studies might be that no migration is detected under conditions of intended use. This can lead to one of three conclusions, depending on a complete understanding of the chemistry data called for by the guidelines.[29] First, if the properties of the substance and the way it is incorporated in the packaging material are such that migration is reasonably expected, even if not detectable analytically, FDA ordinarily assumes for purposes of assessing exposure that the substance is present at the quantitative limit of detection of the analytical method that was used in the migration studies.

Second, if the FCS is relatively inert and insoluble, and thus less likely to migrate under intended conditions of use, FDA may assume that it is present at one-half the limit of detection. Finally, if the FCS is totally inert, not soluble in food-simulating solvents and not imbedded in or bound to the packaging material, FDA or the sponsor might conclude that the "reasonable expectation of migration" required to trigger the food additive definition is lacking. The regulatory implications of this last possibility are discussed later in the report.

Toxicology Guidance

FDA's toxicology guidance for food contact substances builds directly on the chemistry guidance and addresses selection of the test substance, safety testing recommendations based on anticipated exposure and the manner of presenting to FDA the toxicolo-

gy information needed to support an FCN or food additive petition for a food contact substance. In addition to the guidance document, FDA scientists have published two recent articles on the safety assessment and structure-activity relationship analysis of FCS. [30] These articles provide additional insight on the issues covered below and address carcinogenic evaluations of food additives and constituents, which, though not elaborated upon herein, are part of any safety assessment.

First, to ensure the relevance of the safety data, FDA calls for the test substance used in toxicity studies to be the same substance (or substances) expected to migrate. The detailed results of the migration studies, including the ability to accurately characterize the substance expected to be in food, thus play a critical role in designing proper toxicity studies.

Second, FDA recommends the studies that, at a minimum, should be conducted on the migrating substance (MS), are based on the CEDI estimated from the chemistry work. An important feature of this guidance is FDA's recognition that, below a very low threshold of exposure, namely 0.5 ppb in the diet (i.e., 1.5 µg/person/day), the possibility of any safety hazard is so low as to ordinarily not warrant safety studies on the substance. This position is based on FDA's analysis of a large universe of acute and chronic toxicity information and structure-activity relationships on a wide range of substances, from both peer-reviewed published literature and data in its own files, and on its conclusion that, at such low exposure levels, even the most potent acute or chronic toxic agents are unlikely to pose any safety concern.

Even when expected exposure is below 0.5 ppb in the diet, FDA still expects the sponsor of an FCS to submit a safety narrative focusing on the potential carcinogenicity, including structural similarity to known mutagens or carcinogens, of each MS (FCS and impurities).[31] This recommendation is usually fulfilled by searching scientific databases and regulatory agencies for publicly available studies. Any existing information relevant to the potential safety of the FCS should be submitted, but FDA does not normally require additional testing unless the FCS, or the proposed new use of a previously cleared FCS, poses new questions or potential safety concerns.

For cumulative dietary exposure to a MS greater than 0.5 ppb but not exceeding 50 ppb (150 µg/person/day), FDA recommends that, in addition to the 0.5 ppb recommendations, the potential carcinogenicity of the MS be evaluated using specified genetic toxicity tests, including a test for gene mutations in bacteria and an *in vitro* test using either mammalian cells or a particular mouse lymphoma assay.

For cumulative dietary exposure to a MS between 50 ppb and 1 ppm (3 mg/person/day), FDA recommends that, in addition to the less than 50 ppb recommendations, the potential carcinogenicity of the MS be evaluated in a third *in vivo* test using certain rodent cells. In addition, at this exposure level, FDA recommends two sub-chronic oral-feeding studies, one in a rodent and the other in a non-rodent species, with further testing requirements to be determined based on the outcome of these studies. These studies should be conducted to provide an adequate basis for determining an acceptable daily intake (ADI) for the substance, and, in all cases, studies are to be conducted in accordance with FDA's Redbook.[32]

At a cumulative exposure level above 1 ppm, which is not common for food contact substances, FDA recommends submission of a food additive petition, with data requirements

determined by the anticipated exposure and what is already known about the substance. Unless an applicable ADI exists, FDA may require a range of additional studies, including reproductive and developmental toxicity studies, chronic toxicity studies, carcinogenicity studies and any other special studies FDA considers necessary to evaluate the safety of the substance.

These trigger points for various levels of toxicity testing apply generally to migrating components of FCS. For biocides, however, including substances intended to have antimicrobial effects, FDA's guidance sets the trigger point at one-fifth the generally applicable level. Thus, for example, the threshold level of 1 ppm that ordinarily triggers the requirement of a food additive petition and a full battery of toxicity tests would be 200 ppb for the antimicrobials in Scenario One. The rationale for this is that biocides are toxic by design with respect to their target organisms and thus merit testing at even lower levels of exposure.

Finally, FDA's toxicology guidance calls for sponsors to prepare a safety narrative (SN) and a comprehensive toxicological profile (CTP) on the FCS. The SN is the sponsor's "concise summary" of the scientific bases for concluding the FCS is safe, including calculation of an ADI or performing a carcinogenic-risk assessment, where appropriate. The CTP includes all published and unpublished safety studies and other information relevant to the safety assessment of the substance, including but not limited to any testing done by the sponsor. All relevant data must be included for FDA's independent evaluation.

Environmental Guidance

As it has on chemistry and toxicology issues, FDA has issued detailed guidance for compliance with NEPA environmental assessment issues.[33] Most food contact substances qualify for one of the categorical exclusions from the requirement to prepare an EA as outlined earlier. FDA's NEPA regulations and guidance call for submitters of food additive petitions, FCNs or TORs to claim their categorical exclusion simply by citing the applicable exclusion regulation, stating compliance with the exclusion criteria, and stating that, to the submitter's knowledge, no extraordinary circumstances exist that would require the submission of an EA.

NEPA, the Council on Environmental Quality (CEQ) regulations and FDA regulations do not specify any environmental data requirements, but a demonstration of no significant impact on the environment is required using either actual data or prediction models. FDA's typical data recommendations for EAs are illustrated by its guidance with respect to one category of FCS that does not qualify for a categorical exclusion, namely, processing aids used in producing food-packaging materials that are not intended to remain as components of the finished packaging material.[34] As guided by NEPA and the CEQ regulations, FDA's primary concern is to understand what substances are likely to be introduced into the environment as a result of the use and disposal of the FCS, the fate of the substances in the environment and the potential for adverse environmental effects. FDA provides detailed guidance on the data and analysis required to address these matters, including calculation of the expected environmental concentration (EEC) of the FCS and its degradation products and comparison of the EEC to relevant toxicity endpoints for animals, plants and other organisms that might be affected.

FDA advises submitters to consult early with the agency to determine the EA format and environmental testing, if any, that will be best suited to satisfy the NEPA requirement. Reliance on data from the scientific literature, existing databases and company files is expected. FDA further recommends that the level of analysis be commensurate with the potential for environmental impact. For example, if the EEC is expected to be very small, less information on environmental fate and effects may be required.

ASSURING SAFETY: FDA'S SCIENTIFIC REVIEW

While the burden rests on the submitter of an FCN or food additive petition to marshal and submit data sufficient to demonstrate safety, the responsibility rests with FDA to evaluate the data and determine whether the statutory safety standard has been met. This evaluation is carried out by teams of consumer safety officers and chemistry, toxicology and environmental review scientists whose job it is both to scrutinize the quality of the studies and data submitted and to assess what those data say about the safety of the FCS.

When genetic toxicity testing is triggered by expected exposure, FDA must also assess whether those results raise any safety question that requires further testing to resolve. If oral studies sufficient to establish an ADI are triggered, FDA not only scrutinizes the exposure and genetic toxicity information but reviews the scientific validity of the ADI and assesses whether the anticipated exposure is less than the ADI.

In all of these review functions, FDA scientists are expected to exercise scientific judgment, identify unresolved safety issues and request whatever additional information or further testing are required to resolve the issue. Because the legal framework places the burden of proof regarding safety on the submitter, FDA holds the ultimate power in the process. It can decline to issue a food additive regulation or can issue an objection to an FCN based solely on the existence of unresolved safety questions, without having to prove that the FCS is harmful.

EPA Regulation of Food Packaging

EPA becomes involved in regulating food packaging when pesticides, typically antimicrobial agents, are incorporated to control microbes or other "pests" in or on the packaging itself or in packaged raw food commodities. EPA's jurisdiction arises primarily under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), which requires generally that pesticide products have an EPA-approved registration prior to use. In most cases where EPA is involved in regulating food packaging, it shares regulatory responsibility with FDA, which, with minor exceptions, retains responsibility for the safety of any migrants to food.

Implementation of FIFRA is a complex topic, and the interactions between EPA and FDA are the products of elaborate legal and regulatory provisions. Rather than attempt a complete description of this landscape, the following discussion summarizes the basic legal framework and EPA process in sufficient detail to set up analysis of issues that are specific to nanotechnology.

LEGAL AND PROCEDURAL FRAMEWORK

EPA's basic legal and procedural framework as applied to food packaging can be described more succinctly than FDA's because, for

practical purposes, new pesticide products have but one pathway to the marketplace, namely, product-by-product registration with EPA under FIFRA.[35] FIFRA requires that companies seeking registration demonstrate through a registration application that the pesticide product will not have "unreasonable adverse effects on the environment," which includes human health.[36] This standard requires a comprehensive evaluation of potential adverse effects to health and the environment, as well as of the potential health and economic benefits of the pesticide.

The burden rests on the applicant to provide the data EPA requires—by regulation and also at its discretion—to conduct this evaluation, and EPA has strong legal authority and wide scientific discretion in deciding what data are required. If, based on the application, EPA concludes that the product does not pose an unreasonable risk of adverse effects to human health and the environment, it grants the registration, which comes with approved product labeling that prescribes the permissible uses and any conditions or limitations on use EPA judges necessary to satisfy the standard for registration. The FIFRA registration is, in effect, a license that applies only to the particular pesticide product of a particular company.

Generally, for pesticide uses that may result in residues in food, EPA is also required to consider the safety of such residues separately, not under the FIFRA risk-benefit standard but under section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA). Section 408 establishes for pesticide residues the same basic safety standard—"reasonable certainty of no harm"—that section 409 establishes for food additives, but with some differences that make it even more stringent. For example, in calculating a pesticide's exposure, EPA must consider not only residues from all dietary uses but also exposure from drinking water and residential uses. In addition, EPA must include in its safety evaluation an additional 10-fold safety factor to further protect children and infants, unless scientific evidence is available that demonstrates such an additional safety factor can be reduced or removed.

The requirements of section 408 come into play in this study only indirectly. This is because it is assumed that the potential applications of nanotechnology in food packaging for pesticide purposes will involve antimicrobials, rather than insecticides or other types of agricultural pesticides, and because, in 1998, Congress gave FDA jurisdiction in most cases to regulate such antimicrobials under the food additive provisions of section 409 of the FFDCA.[37] EPA still must register the use of the antimicrobial under FIFRA, but FDA also must regulate the safety of any migrants into food under the section 409 system for FCS outlined earlier.

Under this dual-regulation scenario, EPA will not register an antimicrobial under FIFRA until FDA has evaluated it and either issued a food additive regulation or added the substance to its list of "effective" FCNs. EPA is also required, however, in making its FIFRA registration decision, to determine whether the more stringent safety provisions of section 408 have been satisfied. Thus, while FDA directly regulates the migrants in food, EPA must consider the section 408 criteria and require the registration applicant to submit whatever additional data are required to satisfy them. Typically, the data and analysis relied upon by FDA under section 409 can help satisfy EPA requirements under section 408, but the developer of the packaging is nevertheless in the position of having to demonstrate the

human food safety of the FCN to two agencies under two somewhat different sets of scientific criteria.

DATA REQUIREMENTS: EPA'S SCIENTIFIC AND TECHNICAL GUIDANCE

Like FDA, EPA has given operational meaning to the statutory standards it implements by providing detailed guidance on data requirements. In EPA's case, the requirements are codified in detailed regulations establishing the minimum data required to achieve registration under FIFRA.[38] Like FDA, EPA reserves the right to require additional data as needed to make the FIFRA risk-benefit assessment, as well as to waive data requirements that are not scientifically appropriate in particular cases.

EPA's data requirements for antimicrobials used to protect food packaging overlap FDA's requirements to some extent but are also more extensive, mainly because the FIFRA standard requires consideration of an additional array of potential human health and environmental impacts. EPA's requirements are outlined in the table at Appendix D and summarized here. They fall into the following categories:

1. Product Chemistry—This includes descriptive information on the identity of the pesticide product (including the active antimicrobial agent and any inert ingredients), including details on the manufacturing process, compositional specifications ("certified limits") for the amount of every active and inert ingredient, any impurities and analytical methods to detect and quantify the product's components. Much of the required information is similar to or the same as that required by FDA.

2. Physical and Chemical Properties— Like FDA, EPA requires information on the properties of the product to inform its analysis of the likelihood of migration to food and the likely behavior of the product's components in the environment. This includes information on such matters as physical state, particle size and dimensions, stability, reactivity, solubility and vapor pressure.

3. Human Health Exposure Assessment—For EPA, the exposure assessment must address both exposure through food and drinking water and exposure in occupational settings, such as in the facilities where the antimicrobial pesticide product is used. In addition, if the pesticide has residential uses, then EPA must perform an aggregate assessment that considers all potential exposures that could occur concurrently. For exposure through food, EPA uses the same basic approach to migration testing and calculation of the CEDI as FDA does. Approaches to obtaining data on possible occupational exposures are highly dependent on the nature of the substance and on the settings in which exposure might occur. EPA uses a surrogate database on occupational exposures to estimate exposures to antimicrobials.

4. Human Health Hazard Assessment—Like FDA, EPA has established toxicology data requirements that are dependent on the level of anticipated exposure. In contrast to FDA, EPA has not established a level of exposure in food below which no toxicity testing is required, reflecting the fact that EPA is required to consider human-health effects FDA does not have to address. Thus, EPA requires for

all exposures up to 200 ppb concentration in the diet a "Tier 1" set of testing that includes acute toxicity, mutagenicity, 90-day oral rodent and developmental studies, a literature search and structure-activity relationship analysis (See Attachment 1 to the table in Appendix D). For exposures at 200 ppb and above, EPA requires the full battery of testing required for registration of any food use pesticide, including all of the above plus additional sub-chronic, developmental, reproductive, chronic and carcinogenicity studies.

5. Environmental/Ecological Risk Assessment—To meet its duty under FIFRA to assess possible adverse environmental impacts, including an endangered species assessment, EPA generally requires data on the environmental fate of the product's ingredients, such as hydrolysis data, as well as toxicity data on non-target species, such as birds and aquatic species. EPA is considering and may propose additional data requirements for assessing environmental fate and the toxicity of antimicrobial pesticides to non-target species.

EPA REVIEW

Like FDA review scientists, scientists in EPA's Office of Pesticide Programs are expected to conduct a critical review not only of study results but also of the design and execution of the studies to ensure the quality of the resulting data. They are expected and empowered to make judgments about whether the data before them are adequate to answer the legitimate issues that arise under the FIFRA standard with respect to the particular product and to require additional testing and data as needed. Like FDA, EPA encourages applicants to consult with agency scientists early in the product development and testing process for guidance on what data will be required, or may be waived, in that particular case.

III. APPLICATION OF THE REGULATORY PROCESS TO ENMs

The preceding overview of the food-packaging regulatory process sets the stage for identifying issues likely to arise as the process is applied to ENMs. The issues identified in this section of the report emerged primarily from the working group process outlined earlier. This process included interaction with FDA and EPA regulatory officials and review scientists, who were very helpful in raising nanotech-specific issues, based on their examination of the hypothetical product scenarios. In addition, the Science Working Group produced the table in Appendix C, which lists many of the nanotech-specific issues arising in the FDA program. Following a similar format, EPA provided the table in Appendix D that summarizes questions that ENM antimicrobial products might raise under FIFRA. The author has drawn on all of these sources in the discussion that follows.

Most of the issues that have surfaced in this study relate to how the scientific and technical criteria for evaluating the safety of food packaging will apply to ENMs, in light of the novel properties of many nanoscale materials. In fact, the few legal or policy issues raised by nanotechnology stem from the science, in particular the understanding that nanoscale versions of conventional materials require their own case-by-case safety evaluations. Several legal, policy and procedural issues are described first, followed by the identification of a number of scientific and technical issues.

Legal, Policy and Procedural Issues

While the legal frameworks for food packaging are complicated, the basic regulatory pathways for ENMs in food packaging are generally clear.

In the case of the antimicrobial "active packaging" in Scenario One, for example, the dual FDA-EPA regulatory process applies: the antimicrobial active agents are subject to EPA's FIFRA registration process (including assessment of residues in food under the FFDCA section 408 criteria) *and* to FDA's process for pre-market review of food contact substances under section 409 of the FFDCA. The products in Scenarios Two and Three, on the other hand, because they do not involve an antimicrobial component, are subject solely to FDA oversight.

Under the FDA legal framework, however, both FDA and packaging developers have choices to make concerning the form of FDA's oversight. For example, it is possible for new packaging materials to enter the market without going through any FDA pre-market review if all their components are covered by existing food additive or GRAS regulations or by an effective FCN listing, or if the sponsor makes an independent GRAS determination. How these features of the FDA system might apply to ENM-containing packaging merits consideration. So, too, do the questions of whether FDA should ever exercise its discretion to require a food additive petition, rather than an FCN, for an ENM, FDA's likely approach to implementing NEPA, and whether FDA needs to define "ENM" or "nanoscale" for purposes of its regulatory process.

APPLICATION OF EXISTING FOOD ADDITIVE, GRAS AND FCN CLEARANCES

One of the first questions the developer of a new packaging material asks is whether the components of the material are already cleared for that use by an existing FDA food additive or GRAS regulation or FCN listing. It is a question worth asking. FDA maintains an inventory of over 3,000 substances that are listed for food contact use in FDA food additive regulations alone, and typically in multiple regulations for multiple purposes,[39] as well as a number of GRAS listings and an inventory of about 600 "effective" FCNs.[40]

For example, nisin, one of the antimicrobials in Scenario One, has been affirmed as GRAS by FDA for direct addition to food,[41] and FDA many years ago adopted a policy that substances affirmed as GRAS for direct addition to food would be deemed GRAS for indirect uses.[42] The GRAS regulation for nisin is silent, however, on the particle size of the nisin that was evaluated by FDA and affirmed as GRAS. Thus, the question arises of whether the existing FDA GRAS regulations cover the use of nisin on polyethylene nanospheres in Scenario One.

The same question could be raised with regard to nanoscale versions of any of the many substances approved by FDA as indirect food additives: If the intended use is covered by the indirect food additive regulation and, as is commonly the case, the regulation's identity and compositional specifications do not address particle size, can the nanoscale version be marketed under that regulation?

With regard to food additives, a fair reading of FDA's regulations is that if there is a change in the chemical identity or composition of a listed food additive that goes significantly beyond the variation covered by the petition that gave rise to the regulation, a new petition is required, even if the changed material appears to remain within the terms of the existing regulation.[43] The underlying ideas are that (1) the safety and other data supporting the original petition would not necessarily have demonstrated the safety of the changed substance and (2) parties introducing a new version of a material into interstate commerce have a duty to ensure the safety and legality of the material that goes beyond reliance on the literal terms of a technical regulation that could not reasonably have anticipated the new version.

Thus, suppose that the specifications in a food additive regulation are silent on particle size and that a nanoscale version retains the same chemical identity as the approved food additive and is otherwise covered by the terms of the regulation. Assuming that the nanoscale version has different properties than the conventional scale material, and given the general understanding that nanoscale particles warrant their own case-by-case safety evaluation, FDA's position would seem to mean that a new petition would be required to authorize use of the nanoscale particle.

A contrary conclusion could be argued as a matter of administrative law. Food additive regulations authorize use of a substance by any party (not just the petitioner), and parties other than the petitioner cannot reasonably be expected to know the details of how the petition described the material and what was actually tested. Thus, according to this argument, any substance covered by the plain terms of the regulation, including nanoscale versions of the covered material, should be considered legally authorized for use within the conditions of use spelled out in the regulation. Under this line of argument, FDA's remedy, if the agency felt that use of the nanoscale version should not be considered

covered by the existing regulation, would be to amend the regulation to make more explicit the limitations implied by the content of the petition or to go to court to prevent use of the nanoscale material on the ground that it is an unapproved food additive.

Notwithstanding this argument, it would be advisable for any party seeking to rely on an existing food additive regulation to market a nanoscale version of a listed substance to consult in advance with FDA.

Similar questions about scope of applicability could be raised with regard to FDA GRAS regulations and FCN listings, though the analysis and answers might differ. In the case of GRAS listings, FDA's rules say that if the substance in question "is used under conditions [e.g., technical effects or functional uses] that are significantly different from those described in the [GRAS] regulation, such use of a substance may not be GRAS."[44] This potential exclusion from coverage by the GRAS regulation would seem to apply to nanoscale versions of the listed substance, given their assumed novel properties. Moreover, the recognized need for case-by-case safety assessment of nanoscale materials would make it difficult for the nanoscale material to meet the high standard for "general recognition" of safety based solely on the data publicly available on the conventional-scale version.

The scope of effective FCN listings, as spelled out in FDA's administrative guidance, is limited to the particular manufacturer, substance and intended use identified in the notification.[45] FDA expects a new FCN to be submitted if "substantive" changes are made in the specifications, if changes in manufacturing method result in "substantive" changes in the identity of the product or its impurities, or if the product in question has conditions of use not included in the notification. A nanoscale version of a previously listed food contact substance that has new properties or uses would seem clearly to require its own FCN. In any event, it would be advisable to consult FDA regarding the need for a new FCN to cover the nanoscale version of an already-listed substance.

It is difficult to envision the situation in which a prudent manufacturer would attempt to market a nanoscale version of a food contact substance based on an existing food additive or GRAS regulation or FCN listing. This is because the norms of the industry—in which commercial purchasers typically require guarantees and other forms of assurance that a packaging material or other food substance can be lawfully marketed—make it very difficult for novel materials to enter the food supply without FDA approval. Nevertheless, FDA has not specifically addressed how the principles, rules and guidance outlined here would apply to nanoscale versions of previously cleared substances. Thus, there is potential for uncertainty about whether and under what circumstances nanoscale food contact substances could come to the market without any FDA review. An issue for consideration is whether it would be useful to the industry and other stakeholders for FDA, as it gains experience with nanotechnology, to issue regulatory guidance, or for commercial purchasers of packaging materials to establish stewardship principles and practices on this question.

INDEPENDENT GRAS DETERMINATIONS FOR ENMs

The FFDCA and FDA policy explicitly recognize that developers of new packaging materials can make independent determinations that the components are all GRAS for the intended use and thus are not food additives and not subject to FDA pre-market

review. They do so, of course, at the risk that FDA will later disagree and take action to remove the material from the market. To guard against that possibility, FDA has established a procedure by which developers can submit a GRAS Notification to elicit from FDA a statement of whether it has questions about or objects to the developer's GRAS determination.[46]

It is not unusual for packaging developers to make GRAS determinations when the safety of the substance is well established and well known among experts and the additional use does not add significantly to consumer exposure. In general, however, independent GRAS determinations are not likely to be a viable option for ENMs in food packaging, at least in the near future, for two reasons.

First, the legal standard is high. GRAS status requires (1) that safety be demonstrated on the basis of the same quantity and quality of data needed to gain FDA approval of a food additive and (2) that safety be "generally recognized," by experts qualified by training and experience, based on published studies, which may be corroborated by unpublished studies and other publicly accessible data and information.[47] Second, as will be made clearer in the later discussion of nano-specific scientific issues, a number of uncertainties remain concerning how both exposure and toxicity of ENMs should be measured and evaluated. In light of this, it would be very difficult for the developer of a new packaging material containing ENMs to justify a conclusion that its safety is both well established and generally recognized among qualified experts.

This conclusion seems particularly strong in the context of the ENMs in Scenarios One and Two, which involve ENMs in direct contact with food. In Scenario Three, however, the clay nanoparticles are embedded in a plastic material that is separated from the food by other plastic layers. This does not mean migration is impossible, but in that scenario or similar situations where a functional barrier exists between the ENM and food, a developer could argue that migration is, at most, so small as to not to raise a safety question and thus to support a GRAS determination, assuming the underlying data were publicly available.

Such a GRAS claim seems unlikely because of the difficulty of satisfying all elements of the legal standard for GRAS status and of the marketplace reality that a novel ENM packaging with important new properties will almost certainly need FDA clearance before being accepted by commercial customers. Food or beverage companies would not risk their brands on Scenario Three's high-barrier container without the assurance of safety and legality that comes with a successful FCN, GRAS Notification or food additive regulation.

In the future, however, the situation may not be as clear-cut. The question then is whether any further FDA guidance or industry stewardship principles are required regarding the possibility of independent GRAS determinations on ENMs in food packaging.

REQUIRING A FOOD ADDITIVE REGULATION FOR AN ENM

The FCN process has been an efficient way for FDA to conduct pre-market safety reviews of food contact substances. It gives FDA an opportunity to review all the data needed to evaluate safety and to pass judgment on a particular company's material without having to invest resources in a time-consuming rule-making process. If FDA raises no questions, the developer can market the product after 120 days from FDA's

acceptance of the FCN. There is no reason in principle that this same process will not work for ENMs. Indeed, it has already worked in one case involving use of a very low level (20 ppm) of nanoscale (20 nm) titanium nitride particles in plastic beverage containers, where the characteristics of the embedded particle were reportedly not amenable to migration.[48]

In more-complicated situations, however, FDA could find it advantageous to require a food additive petition for an ENM, which it has the legal discretion to do if a petition is required to provide an adequate assurance of safety or if FDA and the sponsor agree a petition should be submitted.[49] In Scenario Two, for example, the nanoscale construct is novel and complex and involves a functional effect—detecting harmful bacteria in packaged food—that has public health significance. Possible advantages of a food additive petition in such a case are that it removes from FDA the pressure of making a decision in 120 days, and that it provides an opportunity for public participation in the decision-making process through submission of comments when the notice of filing of the petition is published and the filing of objections and a request for a hearing when the regulation is issued.

FDA is entitled to make the decision of whether to require a food additive petition on a case-by-case basis. An issue for consideration by FDA and potential sponsors is under what, if any, circumstances the petition process would be advantageous for ensuring safety and fostering public understanding and acceptance of novel products.

NEPA COMPLIANCE FOR ENMs

Many components of packaging materials qualify for the categorical exclusion from the requirement of an Environmental Assessment. However, even when an ENM does qualify for one of the exclusions in its regulations, FDA is likely to make a decision on a case-by-case basis to require an EA, at least in the early stages of nanotechnology's application to food packaging. For example, titanium nitride, the one nanoscale substance known to have gone through the FCN process, fell within one of the categorical exclusions, but FDA required an EA.

Presumably, implementation of NEPA for ENMs in food packaging will evolve as FDA and sponsors learn more about the technology and the fate and effects of these substances once introduced into the environment, and FDA will continue to make case-by-case judgments about the need for an EA.

DEFINING NANOSCALE

Much of the public and scientific discussions of nanotechnology, including those in this report, proceed as though nanotechnology were a single, well-defined thing. It is true that most parties working on nanotechnology use the range of 1–100 nm as a benchmark for what they mean by "nanotechnology." But it is also true that, from a scientific and safety evaluation standpoint, any such boundaries are artificial. Small particles do not necessarily stop having novel properties just because they have dimensions of 101 nm, 110 nm or 200 nm.

The likely way FDA and EPA will deal with this reality is by focusing on size-dependent novel properties or behaviors that may be relevant for safety, rather than on absolute particle size ranges, and by continuing, in general, to take a case-by-case approach to applying their regulatory standards and procedures. In the event the agencies choose to provide nano-specific guidance on any of the legal, policy or procedural issues identified here, they will

need to address the difficult definitional issue in order to define the scope of such guidance.

The issue of what nanocharacteristics are potentially relevant for safety will also arise in the context of defining chemistry, toxicology and environmental data requirements, for reasons discussed in the next section.

Scientific and Technical Issues

Members of the Science Working Group discussed a number of scientific and technical questions that are likely to arise in the regulatory processes for ENMs in food packaging. All of these issues are driven by the central fact that nanoscale materials may take on novel properties that, depending on conditions, can affect how the materials interact with other substances and biological systems and how those properties can be measured and tested for purposes of evaluating their safety. The issues arise under FDA's chemistry and toxicology guidance for food safety evaluation and in the assessment of environmental impacts under NEPA and FIFRA. The broad array of scientific and technical issues identified by the Science Working Group underscores how important it is that packaging developers consult with FDA to determine how FDA's current guidance would apply to their particular use of nanotechnology.

FDA CHEMISTRY ISSUES

In general, FDA's chemistry guidance addresses the question of how to characterize the ENM, to identify migrants from packaging materials and to quantify consumer exposure to them for purposes of safety evaluation. EPA relies on the same basic approach in answering these questions, so most of the issues identified here arise in similar fashion in EPA's assessment of exposure due to migration of antimicrobials from packaging.

Most of the nano-specific chemistry issues identified by the Science Working Group relate to the difficulty of knowing, with respect to nanoscale food-packaging materials, exactly what substances will reach consumers, and thus what substances need to be subjected to toxicity testing. In ordinary cases, the data called for by FDA's chemistry guidance data will answer these questions satisfactorily. In the case of ENMs, the usual data may not suffice, and the reason is their potential for unusual reactivity or changes in their configuration and properties, depending on the materials and conditions around them.

For example, a nanoscale substance that is at one particle size and shape when incorporated in a packaging material may, when extracted by a food simulant in a migration study, agglomerate to form larger particles, dissolve to form discrete ions or molecules or react with other substances to form new ones. Similarly, over the life cycle of the product in actual use, the nanoscale substance may go through multiple transitions as it is incorporated in the package, used in contact with food and disposed of in the environment, and may not retain its nanocharacteristics. The chemistry data and analysis generated for the pre-market review process must anticipate these changes and provide reliable information on the substances to which consumers (and the environment) will be exposed and at what level.

To this end, the Science Working Group identified three broad, nano-specific sets of

issues: (1) adequate characterization of the ENM's identity and properties in the product and under conditions of use and exposure; (2) defining and characterizing ENM "impurities"; and (3) migration study methodology and validation. Much of the following discussion is drawn from the table in Appendix C.

1. Adequate Characterization of the ENMs Identity and Properties—Characterizing a substance's identity and properties is the essential first step in exposure assessment and in designing and evaluating toxicity studies. The general sense of the Science Working Group was that additional information would be needed in many cases to adequately characterize the identity and properties of ENMs, in light of their novel properties. This may include, on a case-by-case basis, the categories of information listed below. Because it is not yet clearly known which of these characteristics is most relevant to safety for any particular ENM, it is important to capture such information and analyze it in relation to the mass and chemical identity of the FCS.

- *Particle size and morphology*, including size distribution, morphology and crystalline form of the primary particle, surface area and charge (zeta potential) of the primary particle and any other size-dependent properties;
- *Surface chemistry and reactivity*, including coating, functionalization, catalytic activity and potential to form reactive oxygen species;
- *Aggregation/agglomeration potential* as measured in various media and pH, including pH 1 (stomach), 7.4 (blood) and 9 (intestine) and food simulants; and
- *Potential for binding with protein* in ways that might affect interaction with biological systems.

This information also helps address the issue of stability, in particular, whether, because of their potential for high reactivity and other size-associated properties, particular ENMs are likely to change properties (e.g., lose their nano-characteristics) in different media and/or over time. Such property changes could potentially occur during manufacturing (within batches or from batch to batch), during migration and toxicity studies or in actual use. Any such changes could affect consumer and environmental exposures, and thus the design and validity of the migration and toxicity studies.

In this area and most other chemistry areas where the Science Working Group identified the need for additional, ENM-specific data, the parallel issue is whether validated analytical methods exist to collect the data. The sense of the working group was that such methods do generally exist but that they may not have been standardized and validated for FDA purposes.

2. Defining and Describing ENM "Impurities"—Impurities are a fact of life for any chemical substance and must be identified and quantified for safety evaluation purposes, as well as possibly to ensure the substance is pure enough to perform its intended function. Single-walled carbon nanotubes, such as those incorporated in the Scenario Two nanobiosensor package, are known to be associated with metal impurities generated during the manufacturing process, and

these would have to be identified and quantified.

There is also a need for greater agreement on what constitutes an "impurity." The optimal functionality of ENMs is likely associated with some distribution of properties, e.g., particle sizes within a given range. Are particles outside that range, or shifts in the shape of the particle size distribution, "impurities"? Do the diversity and distribution of particle sizes affect migration or otherwise matter for toxicity testing and safety evaluation purposes? Can the distribution be controlled so that there is confidence that the test substance is the same as the one that will actually be used? These issues would have to be evaluated on a case-by-case basis.

3. Migration Study Methodology and Validation—Many of the chemistry issues already noted come together to potentially affect the manner in which migration studies are performed and whether they produce reliable information. Among the questions are whether the ENM dissolves in the food-simulating solvent or is released as nanoparticles, and whether extracted ENM nanoparticles agglomerate in food simulants or change their properties in the simulant in other ways. Whatever happens in the simulant, the sponsor would have to consider, on a case-by-case basis, whether the same thing is likely to happen in actual use and thus whether the conventional migration study protocols recommended by FDA remain valid for its ENM. Another issue might be whether the analytical methods used in the migration study adequately detect and quantify what the consumer would be exposed to. Modified or new migration protocols and analytical methods may have to be developed and validated to ensure that the study ultimately measures what would migrate to food under actual conditions of use and reach consumers (and would thus need to be tested for safety).

FDA TOXICOLOGY ISSUES

Once the identity and properties of the ENM are established and exposure to the substance is calculated based on migration studies that measure what may reach consumers, the developer and FDA can determine what toxicology information is needed.

FDA's detailed toxicology guidance for food contact substances was developed well before the advent of nanotechnology, however, and the general sense of the Science Working Group was that a number of points in the guidance may need to be clarified or adjusted and that the current toxicology testing approaches may need to be supplemented and expanded to appropriately evaluate the safety of ENMs in packaging. As the needed science continues to develop, FDA can be expected to make case-by-case judgments about toxicology requirements. The agency has full discretion to preclude marketing of an ENM packaging material if safety questions cannot be answered with available tools.

Like the chemistry issues, the nano-specific toxicology issues stem from the novel properties of ENMs, in particular their tremendous surface area in relation to mass, their surface reactivity and their potential to be absorbed, to go places in the body and to possibly persist and accumulate in ways that conventional-scale substances do not. These properties do not prove harm, and case-by-case assessment will remain the norm, but the novel proper-

ties raise challenging scientific questions that may require new kinds of data and new toxicological tools to address. This includes questions about (1) the appropriateness of current exposure triggers for toxicity testing, (2) toxicological data requirements and testing protocols and (3) utility of data on conventional-scale versions of ENMs.

1. The Appropriateness of Current Exposure Triggers for Toxicity Testing—FDA's toxicology guidance uses a dietary concentration of greater than 50 ppb as the trigger for animal toxicity testing of food contact substances, with testing requirements increasing as exposure increases. This value is based on knowledge accumulated by toxicity testing of many different structural classes of chemical compounds over many years. For biocides, FDA has set lower triggers (one-fifth of the norm) based on their intended toxicity to target organisms. The issue for ENMs is whether their reactivity and possible persistence might justify a similar reduction in the testing triggers, either as a general rule for ENMs or on a case-by-case basis.

2. Toxicological Data Requirements and Testing Protocols—Most of the toxicological research conducted to date on ENMs has addressed the inhalation and dermal routes of exposure. This reflects the expectation among scientists that occupational exposure through these routes (such as in a manufacturing setting) is likely to be significantly greater, and of correspondingly greater health concern, than exposure through food, and certainly much greater than possible exposures from food contact substances. It also reflects the dominant applications of ENMs that are currently being developed in response to the huge market potential in electronics, energy, materials and pharmaceuticals. The result, however, is that relatively little is in the peer-reviewed scientific literature about the *in vivo* toxicity of ENMs when ingested orally.

The properties of many ENMs investigated to date at least raise the question, however, of whether the standard toxicology data requirements and testing protocols are sufficient to evaluate safety. Current methods may need to be supplemented and expanded. For example, the potential of ENMs to persist and accumulate in the body in different ways raises the question of whether additional, product-specific data on the distribution and characteristics of ENMs in biological matrices should be required as a foundation both for determining toxicity testing requirements and for evaluating the results. In some cases, data may be needed to evaluate the transformation of ENMs in biological compartments (it is possible that nanoparticles may lose their nano-characteristics under certain conditions), In other cases, additional post-mortem examination of tissues may be needed to evaluate the potential for tissue accumulation of nanoparticles over time.

Closely related to the issue of data requirements is the question of whether standard testing protocols will need to be supplemented for assessing the toxicology of ENMs. While established approaches to toxicity testing provide the foundation for safety evaluation of ENMs, validation of assay applicability to ENMs will be needed in some cases, and some protocols may need to be adjusted or supplemented to fully characterize the materials

and properly assess their potential toxicity. In this regard, efforts are underway within the Organization for Economic Coordination and Development (OECD)[50] and other national and international groups to assess the applicability of the standard testing protocols to ENMs (see Appendix D, Attachment 5).

Another issue concerns dose metrics in toxicity studies. Doses in toxicity studies are commonly expressed as mass per unit of body weight of the test animal, but this measure of dose may not be sufficient for ENMs whose toxic potential may depend not only on the amount, or mass, of the substance but also on the surface area/mass ratio, the surface reactivity or charge density of the particle or the number of particles. Thus, one question is whether and in what manner it might be appropriate to modify or supplement dose metrics in existing test protocols.

As these and other methodology issues are resolved and current protocols are modified, those modified protocols will have to be standardized and validated for their application to ENMs.

3. Utility of Data on Conventional-Scale Versions of ENMs—For many nanoscale materials, including the polyethylene, metal and clay particles in the hypothetical product scenarios, abundant toxicological data exist on the atomic/molecular and conventional-scale versions of these substances. The question is whether and under what circumstances such data can be used to inform safety evaluations on the nanoscale materials. Some have suggested, for example, that if data from an oral-feeding study on the nanoscale version produce the same toxicological endpoints and other biological effects as seen in the data on the conventional material, then the body of data on the conventional material could be considered relevant to the nanoscale version. This remains a matter of case-by-case evaluation and scientific inquiry, because of, among other things, the distinctive properties of ENMs and the methodological uncertainties about ENM toxicity testing noted above. The question of possibly "bridging" from data on convention-scale materials to evaluate ENMs is important because its answer will help guide future efforts to generate data sufficient to reliably evaluate the safety of ENMs.

FDA ENVIRONMENTAL ASSESSMENT ISSUES

FDA's duty under NEPA is to ensure that the environmental fate and impacts of ENMs have been identified to a degree commensurate with their potential for adverse environmental effects. The first critical question that an EA would have to address is whether and to what extent the ENM used in a food contact substance would actually enter the environment, taking into account the manner in which it is bound to the packaging material and how the material is used and disposed of. The chemistry data required for an FCN would contribute to answering this question.

If the ENM is expected to enter the environment, the product's sponsor will face challenges closely analogous to those arising in the food safety assessment of the packaging, most of which stem from the same novel properties of ENMs. These include finding ways to track and measure the fate of the substance in the environment for the purpose of determining exactly what substances animals and plants might be exposed to and at what levels. If non-trivial exposure is expected, sponsors will then face the issue of how best to evaluate possible

effects, including what testing is appropriate. As with human food safety assessment, this will raise difficult issues of data recommendations, testing methodologies and relevance of data on conventional-scale versions of the ENM.

Data collection recommendations for EAs are determined even more commonly on a case-by-case basis than requirements for chemistry and toxicology data to support FCNs. FDA thus encourages sponsors to consult with it before initiating data collection on environmental fate and effects. It is reasonable to expect that requirements will evolve as FDA and sponsors gain experience with environmental assessment of ENMs.

EPA Registration Issues

With respect to ENMs in food packaging, the questions EPA must address under FIFRA are much the same as those FDA addresses under the FFDCA and NEPA.[51] Thus, it is not surprising that, in general, the nano-specific scientific issues EPA faces are very similar to those facing FDA. Initially, EPA is likely to use a case-by-case approach. Many of these EPA issues are reflected in the table in Appendix D.

With respect to the human safety assessment addressing potential migration of antimicrobial substances to food, EPA faces the same chemistry and toxicology issues FDA faces, as outlined above. The toxicology issues may have even wider impact at EPA, however, because EPA's toxicity testing requirements are more extensive. Generally, EPA does not recognize the 0.5 ppb EDI trigger for toxicity testing of antimicrobial food contact substances but rather requires a standard battery of tests in all cases to address its FIFRA responsibilities. In addition, EPA is required by the interaction of FIFRA and section 408 of the FFDCA to assess developmental toxicity, even in cases where FDA might not consider it a significant issue. Thus, for the antimicrobial food contact substances requiring FIFRA registration, there is a heightened need for sponsors to address the ENM toxicology issues related to human safety.

In assessing environmental impacts of ENMs under FIFRA, EPA faces the same set of scientific issues FDA would face under NEPA, except that, again, the immediacy and impact of the issues may be greater for EPA-regulated products, because the environmental impact assessment is decisional and contingent on specific data required in the FIFRA registration process.[52] The nano-specific scientific issues EPA must address, like those facing FDA, stem from the novel properties of ENMs. They include assuring the validity of analytical methodologies and test protocols to assess what substances enter the environment, their environmental fate (including how they might be change in form or composition) and their impacts on plant and animal species (see Appendix D).

Conclusion

The principal conclusion from this analysis is that developers of food-packaging materials that incorporate ENMs, along with FDA and EPA, face significant scientific challenges. The applicable laws are by design stringent in imposing on sponsors the burden of proving the safety of food contact substances, and FDA and EPA implement

these laws in keeping with sound safety-assessment principles that impose significant data collection requirements on sponsors. This approach provides a high level of consumer protection. But it also means that scientific investment and innovation will be needed to secure the necessary regulatory approvals in order to bring the innovation ENMs offer the food industry and consumers to the marketplace.

IV. THE ROLE OF INDUSTRY STEWARDSHIP

Product Life Cycle Management of ENM Food Packaging

This report focuses on the pre-market safety review of ENM-containing food-packaging materials by FDA and EPA. For products that do not involve antimicrobial substances, the FDA review ensures food safety. For antimicrobial ENMs in packaging, the typically dual FDA-EPA review both ensures food safety and precludes unreasonable adverse environmental effects.

This government oversight is important to protecting the health of consumers and, for antimicrobials, protecting the environment. Such oversight also helps maintain consumer confidence in food safety and fosters consumer acceptance of new technologies. The FDA and EPA pre-market reviews do not, however, address the full range of circumstances in which possible adverse impacts could occur and in which preventive efforts are appropriate. For most food contact substances, issues such as occupational exposure and health, safe distribution and storage and proper disposal are not addressed through regulation on a product-specific basis.

Though lacking direct oversight, these product life cycle issues can have great impact on businesses and society, especially if something goes wrong and people or the environment are harmed. Recognizing this, the chemical industry and other industries involved in manufacturing have developed product stewardship programs through which they voluntarily take responsibility for addressing these issues in a preventive manner.

Participants in the PEN-GMA project considered it important to recognize the value of applying such efforts to ENM-containing food packaging, as well as to other possible food applications of nanotechnology, and they wanted to begin a discussion of the elements of nano-specific stewardship programs. To that end, the project formed a Stewardship Working Group, which developed a "points to consider" document on the subject of product stewardship (see Appendix E).

The working group's document defines "product stewardship program" as it relates to ENMs as follows:

A voluntary program that offers insight for responsible development and commercialization of products incorporating ENMs, through programs and practices that help protect people and the environment, and that typically involve going beyond applicable governmental requirements.

The document outlines general principles for product life cycle management by companies and embraces transparency and outreach to stakeholders. It is intended not to establish any new industry standards but rather to serve as a starting point for discussion of how ENMs intended for food applications can be managed responsibly and safely.

Industry Stewardship in the Regulatory Process

Companies also have what might be termed "stewardship" responsibilities with regard to decisions they are empowered to make under the FDA regulatory regime. The

GRAS concept, in particular, authorizes companies to make independent determinations that a particular new application of an ENM is GRAS and thus not subject to premarket review. Most companies take the responsibility that comes with this power very seriously, and the marketplace exerts its own discipline, as commercial customers of food packaging and food ingredients are generally strict in demanding strong documentation of either regulatory acceptance or GRAS status.

Moreover, in the 50 years since the food additive law was enacted, a widely recognized, though unofficial, standard of care for making independent GRAS determinations has evolved. It involves systematic compilation of all the necessary data in a GRAS monograph and review of that monograph by a representative panel of qualified experts, who are asked to pass independent judgment on the safety of the material and whose consensus statement can stand as general recognition of safety.[53]

Finally, FDA has created a GRAS Notification Program through which sponsors can submit the basis for their independent GRAS determinations to FDA. If FDA has no questions about the GRAS status of a food contact substance or other material, it will issue a letter stating that. Commercial customers commonly demand such letters if a substance is not covered by a food additive regulation, effective FCN or TOR. In 1997, FDA proposed a GRAS Notification rule that includes guidance on what is required to satisfy the technical elements of a GRAS determination.[54] Although this rule was never published in final form, FDA has been accepting GRAS Notifications, and the guidance is a widely used "standard of care" for GRAS self-determinations as well as for notifications.

These factors all contribute to a generally high level of industry stewardship in relation to assuring that food contact substances are lawfully marketed and to minimizing the likelihood that a significant new food contact substance will enter the market without FDA review. The novelty and emerging visibility of nanotechnology will make sustaining such stewardship particularly important with respect to possible uses of ENMs in food packaging.

V. CONCLUSION

This report has attempted to capture the essence of the discussions undertaken by the three project working groups and to identify key issues posed by ENMs that may be used in food packaging. It is a starting point for discussion. It is clear that those developing such ENMs have significant scientific and technical work to do. It is also clear that the work needs to be done in close consultation with FDA and, when applicable, EPA. One of the positive lessons from this study is that open dialogue can bear fruit in clarifying the issues and ultimately mapping the way to solutions.

ENDNOTES

1. For a review of FDA's regulatory programs as they apply to nanotechnology, see Taylor, M.R., "Regulating the Products of Nanotechnology: Does FDA Have the Tools It Needs" (The Woodrow Wilson Center Project on Emerging Nanotechnologies, October 2006). http://www.nanotechproject.org/publications/archive/regulating_products_nanotechnology_does/
2. FDA has not defined "nanotechnology" for regulatory purposes, but it participates in the National Nanotechnology Initiative (NNI), a White House–led program that coordinates federal agency efforts in nanoscale science, engineering and technology. The NNI's definition considers an activity to be "nanotechnology" if it involves all of the following elements: (1) research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1–100 nanometers; (2) creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and (3) ability to control or manipulate on the atomic scale. www.nano.gov. Lux Research, Inc. offers this succinct definition of nanotechnology: "The purposeful engineering of matter at scales of less than 100 nanometers (nm) to achieve size-dependent properties and functions." *The Nanotech Report 4th Edition*. New York, NY: LuxResearch, Inc., 2006, p. 1. The report of the FDA's Nanotechnology Task Force recommends that "FDA continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science." The report notes that, "while one definition for 'nanotechnology,' 'nanoscale material,' or a related term or concept may offer meaningful guidance in one context, that definition may be too narrow or broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products."
3. Reynolds, George, "Future nanopackaging market worth billions, says study," Food Production Daily, May 15, 2007. http://www.foodproductiondaily.com/news/ng.asp?id=76538
4. See the PEN website at www.nanotechproject.org
5. See the GMA website at www.gmabrands.com
6. The scope of this project did not include critical review by the Science Working Group of the emerging toxicology literature on ENMs or detailed discussions of the state of the science.
7. Food Additives Amendment of 1958, codified at 21 USC 321(s) and 348.
8. See The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 USC 136 et seq.
9. FDA's regulations in 21 CFR Part 170 include provisions that explain the safety standard for all food additives and eligibility for GRAS status.
10. 21 CFR Parts 182, 184 and 186.
11. Sections 409(b) and (c) of the FFDCA. The Delaney Clause is a proviso to the general safety standard in section 409(c) that prohibits the approval of a food additive that has been "found to induce cancer when ingested by man or animal."
12. Sections 409(d)-(g) of the FFDCA.
13. Direct food additives cleared by FDA are listed in 21 CFR Part 172. Indirect food additives are listed in 21 CFR Part 175 (Adhesives and components of coatings), Part 176 (Paper and paperboard components), Part 177 (Polymers) and Part 178 (Adjuvants, production aids, and sanitizers).
14. Section 409(h) of the FFDCA. Section 409(h)(6) defines "food contact substance" as "any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food."
15. The procedures for FCNs are codified in FDA's regulations at 21 CFR 170.100-106, and FDA has issued more detailed guidance on the FCN process in "Preparation of Food Contact Notifications: Administrative —Final Guidance (May 2002) (http://www.cfsan.fda.gov/~dms/opa2pmna.html).
16. CFSAN/Office of Food Safety, "Inventory of Effective Food Contact Substance (FCS) Notifications" (December 2007) (http://www.cfsan.fda.gov/~dms/opa-fcn.html) (last accessed January 26, 2008).
17. 21 CFR 170.102.
18. 21 CFR 170.105.
19. Section 409(h) (3) of the FFDCA.
20. 21 CFR 170.100(c)
21. 42 USC 4231 et seq.
22. 21 CFR 25.15 and 25.40. FDA's NEPA regulations are informed by regulations issued by

the Council on Environmental Quality (CEQ), which has government-wide responsibility for NEPA implementation. Information on the CEQ's regulations and FDA's guidance to industry for compliance with NEPA on food-related matters is in this guidance document: CFSAN/Office of Food Additive Safety, "Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition–Final Guidance" (May 2006) (http://www.cfsan.fda.gov/~dms/opa2eg.html) (last accessed January 26, 2008).

23. 21 CFR 25.32 (i) and (j).
24. 21 CFR § 25.21.
25. For an overview of the safety assessment process, see Twaroski, Michelle L., Batarseh, Layla I. and Bailey, Allan B. 2007. "The Regulation of Food Contact Substances in the United States." In *Chemical Migration and Food Contact Materials,* edited by D. Watson, K. Barnes, and R. Sinclair, pp. 17-42. Cambridge, UK: Woodhead Publishing Limited.
26. CFSAN/Office of Food Additive Safety, "Preparation of Premarket Submisions for Food Contact Substances: Chemistry Recommendations," (April 2002, revised December 2007). (http://www.cfsan.fda.gov/~dms/opa3pmnc.html) (last accessed January 26, 2008).
27. CFSAN/Office of Food Additive Safety, "Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations" (April 2002) (http://www.cfsan.fda.gov/~dms/opa2pmnt.html) (last accessed January 28, 2008). In addition to this specific guidance on testing requirements for food contact substances, FDA has issued detailed guidance in its so-called Redbook on how various types of toxicity tests should be conducted, including good laboratory practices, study design and execution, and reporting of results. CFSAN/Office of Food Additive Safety, "Toxicological Principles for the Safety Assessment of Food Ingredients–Redbook 2000" (July 2000, updated July 2007) (http://www.cfsan.fda.gov/~redbook/red-toca.html) (last accessed January 26, 2008).
28. Based on a supportive court case and analysis of an extensive body of scientific evidence, FDA has established by regulation a TOR procedure for exempting from food additive regulation food contact substances that result in dietary concentrations of 0.5 part per billion (ppb) or less on the ground that these levels are trivial from a safety standpoint. 21 CFR 170.39. The rule enables FDA, based on very low exposure alone, to exempt food contact substances that are not known carcinogens and that do not contain any carcinogenic constituents or impurities with a TD50 of less than 6.25 mg/kg body weight per day. The TD_{50} is the feeding dose that causes cancer in 50 percent of the test animals when corrected for tumors found in control animals. To obtain the exemption, sponsors must submit a request to FDA with essentially the same data and information required to support a FCN or food additive petition.
29. FDA Memorandum for the Record, Chemistry Review Branch, November 9, 1994 (on file with author).
30. Bailey, A.B., Chanderbhan, R., Collazo-Braier, N., Cheeseman, M., and Twaroski. M.L. The Use of Structure-Activity Relationship (SAR) Analysis in the Food Contact Notification (FCN) Program. Regulatory Toxicology and Pharmacology. 2005 July;42(2):149-252; and Twaroski, Michelle L., Batarseh, Layla I. and Bailey, Allan B. 2007. "The Regulation of Food Contact Substances in the United States." In *Chemical Migration and Food Contact Materials,* edited by D. Watson, K. Barnes, and R. Sinclair, pp. 17-42. Cambridge, UK: Woodhead Publishing Limited.
31. For background on FDA's approach to structure-activity relationships, see Bailey, A.B., Chanderbhan, R., Collazo-Braier, N., Cheeseman, M., and Twaroski. M.L. The Use of Structure-Activity Relationship (SAR) Analysis in the Food Contact Notification (FCN) Program. Regulatory Toxicology and Pharmacology. 2005 July;42(2):149-252.
32. http://www.cfsan.fda.gov/~redbook/red-toca.html also See note 28. For food substances, the ADI is a value calculated by applying safety factors to the lowest "no observed effect level" seen in animal studies and represents the level of daily intake deemed safe for humans. For further information on ADIs, see http://www.ific.org/publications/qa/adiqa.cfm
33. CFSAN/Office of Food Additive Safety, "Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition–Final Guidance" (May 2006) (http://www.cfsan.fda.gov/~dms/opa2eg.html) (last accessed January 28, 2008).
34. Appendix C of CFSAN/OFAS environmental guidance.

35. Section 3 of FIFRA. EPA's extensive regulations governing the registration process are at 40 CFR Parts 150-180.
36. Section 2(bb) of FIFRA, 7 USC 136(bb).
37. The one exception is that EPA retains section 408 jurisdiction over pesticides in food packaging that are intended to control pesticides in raw agricultural commodities, but packaging components that are intended to have a functional effect in food rather than in the packaging itself are beyond the scope of this study.
38. 40 CFR Part 161.
39. http://www.cfsan.fda.gov/~dms/opa-indt.html.
40. http://www.cfsan.fda.gov/~dms/opa-fcn.html.
41. 21 CFR 184.1538.
42. 21 CFR 174.5(d)(1) and 184.1.
43. See 21 CFR 171.1(c)(para G), which explains that a supplemental food additive petition "must be submitted for any change beyond the variations provided for in the original petition and the regulation issued on the basis of the original petition."
44. 21 CFR 186.1(b)(1).
45. FDA/CFSAN, "Preparation of Food Contact Notifications: Administrative, Final Guidance (May 2002) (http://www.cfsan.fda.gov/~dms/opa2pmna.html#II-E).
46. FDA GRAS Notification Program (http://www.cfsan.fda.gov/~dms/gras-ov.html).
47. 21 CFR 170.30(b).
48. FCN 716 in FDA's Inventory of Effective Food Contact Notifications (http://www.cfsan.fda.gov/~dms/opa-fcn.html). <?>. Section 409(h)(3)(A) of the FFDCA.
49. Section 409(h)(3)(A) of the FFDCA.
50. www.oecd.org/env/nanosafety
51. The important difference legally, of course, is that under FIFRA the environmental impact issues directly affect the registration decision, while under NEPA FDA's environmental assessments and findings are informational.
52. EPA is not required to conduct a NEPA assessment per se, because courts have recognized that the assessment of environmental impacts required for registration under FIFRA is the functional equivalent of a NEPA assessment.
53. This process is summarized in J.T. Heimbach, "GRAS Determination: A Short Guide," *Prepared Foods* (January 1, 2004). (http://www.preparedfoods.com/CDA/Archives/9ee0ffe5d2788010VgnVCM100000f932a8c0).
54. 62 FR 18938 (April, 17 1997).

APPENDIX A Case Study Project and Working Group Participants

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APPENDIX B

Case Studies: Hypothetical Food-Packaging Products and Their Characteristics

Note: These case studies were constructed to illustrate aspects of the existing regulatory framework relating to food-packaging materials. The products described are hypothetical. They are not necessarily plausible or desirable from the standpoint of intended technical effect, efficacy or commercial viability.

CASE ONE: NANOSANITIZER THAT PREVENTS CONTAMINATION OF THE PACKAGING FILM USED TO WRAP FRESH PRODUCE OR MEAT

Pathogens on food-packaging films can be a source of food contamination. This new, "active" packaging product is designed to protect the surface of the packaging film from becoming contaminated during the commercial transport and storage of food products. The product is designed to inhibit microbial growth, thereby reducing the likelihood that pathogens will be present or will grow on the film surface. The outside surface of the film is composed of traditional materials; the inside film has an ultrathin layer of a microbial inhibitor formulated as functionalized nanoparticles. The nanoparticles consist of polyethylene spheres that are 90 nanometer (nm) in diameter and is coated with an antimicrobial substance. (The polyethylene sphere serves as a delivery vehicle for the antimicrobial.) A proprietary electrostatic coating process allows the nanoparticles to be applied and adhered to the inner layer at nanoscale thicknesses. The nanolayer offers a high surface area per mass of material used, which reduces the number of nanoparticles needed to cover large amounts of film at molecular-level thicknesses. The nanoparticles are physically bound to the inner layer of packaging material in contact with the food. (If the product is designed with the intent that the nanoparticles separate and migrate to the food, the food contact substance would be considered a food additive and would not be eligible for a Food Contact Notification. Food additives are the subject of a future case study series.)

Two versions of the functionalized nanoparticles are considered:

- Version A: The nanoparticle bears the purified polypeptide antimicrobial nisin on its surface.

- Version B: The nanoparticle is an antimicrobial metal particle (50 nm in diameter) that releases positive metal ions.

CASE TWO. PACKAGING FILM THAT DETECTS AND QUANTIFIES MICROBIAL PATHOGENS IN PRODUCTS AS THEY MOVE THROUGH THE FOOD-PROCESSING CHAIN

The food-packaging film has nanobiosensors incorporated into its inner (food contact) surface that have been engineered to react with and detect specific food-related pathogenic microorganisms. The binding between a microbe of interest and the corresponding receptor sensor that is specific to that organism triggers a qualitative and semi-quantitative fluorescence reaction. The intensity of the fluorescence enables one to estimate the bacterial load in a food without opening its package. A manufacturer or retailer would use a fluorescence reader to evaluate a product for the presence and level of bacteria on the food and within the package without destroying the product. For example, the system could detect the presence of *E. coli* O157:H7 and give an estimate of the total bacterial load in the food at the time of measurement.

The biosensor constructs are based on ELISA (enzyme-linked immunoabsorbent assay) principles of detection. A small section of the package has conjugated biosensor structures bound to the packaging material, giving an "intelligent package." The package protects the food. In addition, when the food's juice or fluid-containing bacteria saturate the biosensor and are examined under ultraviolet (UV) light, the sensor gives the bacterial status of the product within.

The biosensor is a functionalized nanoparticle consisting of three components (see

Figure 1. Nanotube-Biosensor based on ELISA

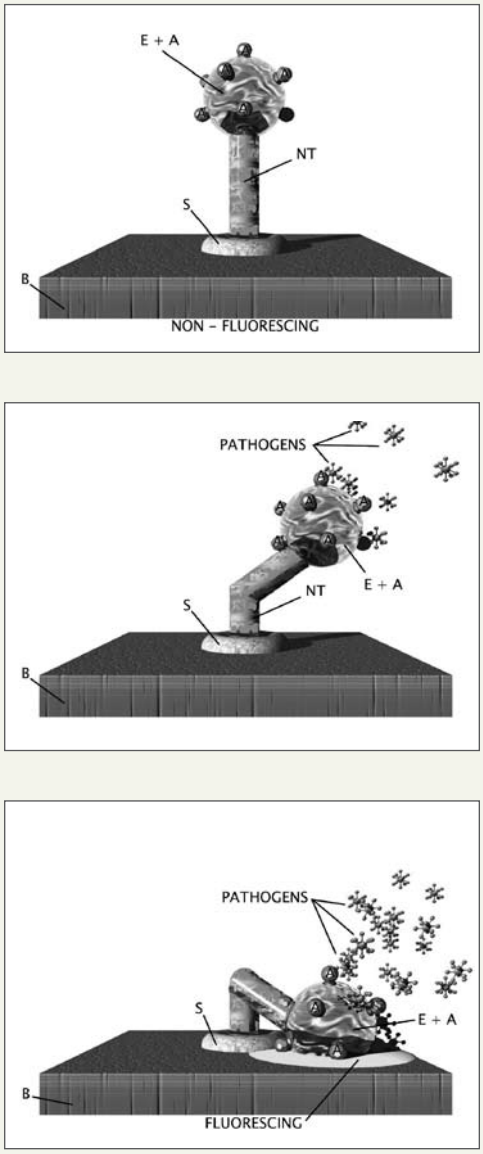

Figure 1). A rigid nanotube (NT) has an enzyme-antibody conjugate at one end (E+A). The antibody provides the specificity to a particular pathogen or bacterium. The other end of the nanotube, which is attached to the biosensor portion of the package, is encased in the substrate to which the enzyme has an affinity (S). This substrate's molecules fluoresce when the enzyme and substrate come into contact. This fluorescence indicates that bacteria are present. When a target organism is present, the antibody-conjugate on the end of the nanotube binds with the organism's surface antigens. This antibody-substrate binding induces the nanotube to lose rigidity and flex, moving the enzyme into contact with substrate particles. The number of nanotubes that flex sufficiently for the enzyme to contact the substrate and cause fluorescence is proportional to the amount of antibody bound by the target bacteria; thus, the intensity of the fluorescence is proportional to the bacterial load. Fluorescence can be read visually with a UV light (qualitative value) or by UV instrumentation (semi-quantitative value).

Two versions of the nanotubes are considered:

- Version A: Single-walled carbon nanotubes
- Version B: Silica or alumina nanotubes.

CASE THREE: BARRIER PACKAGE FOR CARBONATED BEVERAGES

Nanoclays, found in some natural clay as platelets, can be dispersed in a plastic matrix so that they are intercalated (separated into individual platelets) and exfoliated, forming a barrier to the passage of gaseous molecules. A relatively small mass of nanoclay can create a barrier that provides commercially significant reductions in water vapor, oxygen and carbon dioxide permeation. Researchers have developed an improved barrier for carbonated beverages packaged in rigid plastic bottles. The barrier material is composed of multiple layers of polyethylene with an inner layer of polypropylene that contains embedded nano-sized clay particles that is sandwiched between the external and interior polyethylene layers. The nanoclay/polypropylene layer has high barrier properties for gas, flavors, water vapor and carbon dioxide. Carbonated beverages packaged in this material have a shelf life approaching that of beverages packaged in glass bottles, but weigh considerably less and have less potential for breakage. The thickness of the nanoclay layer is optimized to give a film layer that has clarity and that contributes to the desired shelf life properties of the product. The nanoclay layer is nearly as impermeable as glass and as clear as polyester.

APPENDIX C: Science Working Group Identification of FDA Scientific Issues

Note: Columns 1 and 2 describe current FDA data requirements for a Food Contact Notification (see FDA Form 3840)*. Column 3 presents questions and associated scientific issues identified by the Science Working Group that are specific to engineered nanomaterials (ENMs) and may be pertinent in establishing the safety of an ENM food contact substance (FCS) on a case-by-case basis.

*http://www.cfsan.fda.gov/~acrobat/frm3480.pdf

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
A - Identity / characterization (composition)[2]	Full description of the FCS material (Purpose: quality control measures to inform subsequent steps. Assure consistency and function; determine exactly what consumer may be exposed to.)	In addition to the standard physical-chemical measurements, characteristics of the ENM relevant to its size-dependent characteristics and behavior, including purity, stability and potential toxicity, should be fully described. A menu of potential additional measurements that might be relevant for an ENM is in Attachment 1. Choose measurements on a case-by-case basis. Methodologies for the measurements in Attachment 1 exist but may not yet be standardized. Consult with FDA.

1. The components of a Food Contact Notification (FCN) are described here. These are also the essential components of a safety evaluation for a food additive petition or for a Generally Recognized as Safe (GRAS) determination (although the terminology used may be somewhat different).

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
B – Manufacture / impurities[3]	Essential manufacturing specifications for the product (Purpose: quality control measures to inform subsequent steps. Assure consistency and function; determine exactly what consumer may be exposed to.)	Besides the standard physical-chemical measurements, any characteristics of the ENM relevant to its purity, stability and potential toxicity should be fully described. The critical requirement is to assure that the range of what is tested must be the same as/encompass what is manufactured and sold and what impacts consumers and the environment. Compared with conventional materials, the definition of what constitutes "impurity" for an ENM may include any size-dependent characteristics, e.g., particle size (polydispersity[3]), charge distribution, surface coating, surface charge (zeta potential) and agglomeration and aggregation characteristics. Consider aggregation/agglomeration estimates for biological fluids, including blood, intestine and toxicity test articles. If the manufacturing process introduces new functional groups to a cleared polymer, bridging to safety data on the conventional material may not be appropriate (see Toxicology, below). A technical challenge is that nanoparticle properties may be context-dependent and change under different conditions, e.g., agglomeration depending on medium, pH, over time. Select measurement methods on a case-by-case basis. Until standardized methods are developed and validated, consult FDA for recommendations. NIST guidance is currently available for measuring impurities in carbon nanotubes.

2. Guidance for Industry, Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. April 2002; December 2007. http://www.cfsan.fda.gov/~dms/opa3pmnc.html.
3. Sphere size.

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
C – Physical / chemical properties[3]	(Purpose: quality control measures to inform subsequent steps. Assure consistency and function; determine exactly what consumer may be exposed to.)	A menu of potential new/additional measurements that might be relevant to an ENM is in Attachment 1. Measurements must be selected on a case-by-case basis. Select measurement methods on a case-by-case basis. Until standardized methods are developed and validated, consult FDA for recommendations.
D - Intended use[3]	Data to show the intended technical effect of the FCS on the food contact article (e.g., for Case Study #1, the effect of the functionalized nanoparticles on the behavior of the film in which they are incorporated).	Provide information on the antimicrobial efficacy of the ENM FCS. A technical challenge is that nanoparticle properties may be context-dependent and change under different conditions, e.g., agglomeration depending on medium, pH, over time. In the case of functionalized nanoparticles, must consider whether the nanoscale alters the behavior/efficacy/safety of each individual component. Select measurement methods on a case-by-case basis. Until standardized methods are developed and validated, consult FDA for recommendations.

4. Note that the technical effect of an FCS is to sanitize the (surface of) the package. If the technical effect were on the food in the package, the substance would be a food additive, not an FCS, and an FCN would not be allowed.

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
E - Stability[3]	Data to show if the physical/chemical properties change over time, within batches and from batch to batch. (Focuses the safety assessment on the correct material, i.e., that to which the consumer may be exposed *under intended conditions of use*. Do the changes affect migration? Toxicological properties?)	A technical challenge is that nanoparticle properties may be context dependent and may change under different conditions, e.g., agglomeration depending on medium, pH, over time, etc. Does an ENM exhibit size-dependent properties in the FCS? Are these nano-characteristics still exhibited when the ENM migrates? If extraction studies are performed, do the migrating materials (ENM, impurities, breakdown products, etc.) exhibit nanocharacteristics in the food simulants throughout the test? If so, are these properties stable during the test and the intended use of the FCS? Measurement issues—demonstrate validity of any migration study, i.e., that the analytical method measures what would migrate to food under conditions of use, and what the consumer would be exposed to. This may demand a wider range of testing than conventional materials do. Consider the stability of size-dependent nanoparticle characteristics/behavior in toxicology test media. Confirm that what is evaluated for safety is the same as what migrates to food under intended conditions of use.

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
F – Migration to food[3]	"The concentration of an FCS in the daily diet may be determined from measured levels in food or in food simulants, or estimated using information on formulation or residual levels of the FCS in the food-contact article and the assumption of 100% migration of the FCS to food. Although FDA always has accepted reliable analyses of FCS in real foods, in practice, many analytes are difficult to measure in food. As an alternative, notifiers/petitioners may submit migration data obtained with food simulants that can reproduce the nature and amount of migration of the FCS into food. Because an FCS may be used in contact with many foods with different processing conditions and shelf lives, the submitted migration data should reflect the most severe temperature/time conditions to which the food-contact article containing the FCS will be exposed" [5]	Address migration and impurities of each component of a functionalized nanoparticle. Standard wet chemistry methods would be the first line approach to see whether there was any migration, irrespective of nano-characteristics. If results are non-detectable, the limit of detection (LOD) is used in the exposure assessment. A worst-case approach would be to assume nanoparticles are present at the LOD. If a migrating moiety is quantifiable in the extraction solvent, characterize nanoparticles (see Attachment 1 for menu). Address agglomeration/aggregation. Measurement issues—do nanocharacteristics interfere with the analytical methods? Demonstrate validity of any migration study, i.e., that the analytical method must measure what would migrate to food under conditions of use, and what the consumer would be exposed to. Measurement issues—select measurement methods on a case-by-case basis. Until standardized methods are developed and validated, consult FDA for recommendations

5. Guidance for Industry, Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. April 2002; December 2007. http://www.cfsan.fda.gov/~dms/opa3pmnc.html

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
G – Estimated daily intake (EDI) and cumulative EDI (CEDI)[3]	(The toxicity assessment and safety evaluation are informed by what migrates.) "FDA uses the following approach for calculating the concentration of the FCS in the daily diet. The concentration of the FCS in food contacting the food-contact article, <M>, is derived by multiplying the appropriate f_T values by the migration values, M_f, for simulants representing the four food types. This, in effect, scales the migration value from each simulant according to the actual fraction of food of each type that will contact the food-contact article. $<M> = f_{aqueous\ and\ acidic}(M_{10\%\ Ethanol})+f_{alcohol}(M_{50\%\ Ethanol})+f_{fatty}(M_{fatty})$ where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant. The concentration of the FCS in the diet is obtained by multiplying <M> by CF. The EDI is then determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day. FDA assumes that an individual consumes 3kg of food (solid and liquid) per day (see Appendix IV. for sample calculations): EDI = 3 kg food/person/day x <M> x CF *CUMULATIVE EXPOSURE (CEDI).* If the FCS already is regulated for other uses in 21 CFR Parts 170-199, has been exempted from the need for a regulation under the Threshold of Regulation (21 CFR § 170.39) or has been the subject of previous effective FCNs, the notifier/petitioner should estimate the cumulative exposure to the FCS from the proposed and permitted uses (see the example in Appendix IV). Information on the regulatory status of an FCS may be obtained by inspection of 21 CFR Parts 170-199, searching the CFR on the Government Printing Office (GPO) website at http://www.access.gpo.gov/nara/cfr/index.html or contacting FDA directly. Information on effective FCNs or Threshold of Regulation exemptions for an FCS may be obtained through the FDA website or by contacting FDA directly. An estimate of cumulative exposure for the regulated, notified and exempted uses of an FCS can be obtained by contacting FDA. FDA also maintains a database of CEDIs for FCSs.	CEDI calculations are currently based on chemical mass (measured concentrations in the food simulants or, in the case of nondetects, LOD or half LOD). If the substance that migrates retains nanocharacteristics, what dose metric is appropriate for nanoparticles—surface area, particle number or other characteristics? In the case of nanoparticles functionalized with a GRAS or prior-approved biocide (e.g., Case Study 1a), include prior uses of the biocide in the CEDI estimate.

6. Guidance for Industry. Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations. Final Guidance. April 2002. http://www.cfsan.fda.gov/~dms/opa2pmnt.html

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
H - Toxicology **H-1) Toxicology literature summary** **H-2) Toxicology data summary**	Data requirements depend on estimated CEDIs. See Attachment to this appendix for detail from FDA Toxicology Guidance. [6]	Nanoparticles do not fit neatly into the existing FDA Toxicology Guidance, so decisions can be expected to be made on a case-by-case basis. Depending on the migration studies, the nanocharacteristics of the FCS/constituent may be relevant to safety assessment. The current CEDI cutoffs for toxicology testing will likely not apply to nanoparticles; FDA may require more testing at lower CEDIs on a case-by-case basis. There are currently exceptions for this threshold in cases of low-dose toxicity or biopersistence. There is evidence in the literature that oral absorption is higher for nanoscale materials. This is a potential toxicity concern. With respect to nanoparticles, a study in the literature could be cited only if the test article was known to be the same as the ENM. Tie what is evaluated for safety to manufacturing specifications, to what migrates to food under intended conditions of use and to what consumers are exposed to. Consider size-dependent nanoparticle characteristics/behavior in toxicology test media. Agglomeration potential, stability: in test medium, these affect the suitability of a test method, and in the gastrointestinal tract, they could affect bioavailability (precedent—absorption of genetically modified proteins at gastric and intestinal pH). Bridging to data on conventional material (publicly available from FDA files): on a case-by-case basis, there may be different options to establish a basis for bridging; e.g., parallel *in vivo* testing of nano and conventional materials; developing new 28-day repeated-dose data on the nanomaterial demonstrating similar behavior and endpoints to data on the conventional material. If genotoxicity studies are triggered, consult FDA. There is currently uncertainty as to the utility of certain *in vitro* studies, e.g., certain genetic toxicity screens, because the cytotoxicity of an ENM can make the results difficult to interpret. • The DNA interactions of nanoparticles may differ from the conventional/well-known electrophilic interactions that are the basis for current structure-activity modeling approaches. Such interactions, which may include, e.g., intercalation and strand separation, could potentially lead to heritable genetic defects. • Validate *in vitro* genotoxicity assays for the nanoparticle test material, with particular attention to excess cytotoxicity or precipitation. Submit full test article characterization with study reports. Ensure that what is tested is representative of the manufactured FCS and of what consumers are exposed to. • Issue of what are relevant dosimetrics: consider surface area and particle number, as well as (conventional) mass concentration. • Consult with FDA on the need for systemic toxicity testing for ENMs. • If systemic toxicity is observed, information on clearance from the body will probably be needed. Since standard approaches may not be technically feasible (e.g., radiolabeling), adding a recovery phase to the protocol (i.e., continuing to observe test animals for a period after discontinuing dosing) could be considered. • Current 90-day testing protocol may not reveal slow accumulation of nanoparticles in tissue over time may not be revealed. Consider electron microscopy. • In the case of nanoparticles functionalized with proteins, there may be potential for immunological effects (hapten[7] formation). Research is underway (e.g., NTP, OECD) to evaluate adequacy of existing test protocols required/recommended by regulatory agencies. Demonstrate in vivo the appropriateness of bridging to data on conventional material (e.g., compare results in a 28-day repeat-dose study). Work is underway to validate existing test protocols; some information on comparative toxicity of ultrafine and conventional materials is becoming available (see ED-DuPont database on TiO_2). Measurement issues—as discussed above, context-dependent behavior of nanoparticles; standardized, validated analytical methods. Consult FDA.

7. A **hapten** is a small molecule that can elicit an immune response only when attached to a large carrier such as a protein; the carrier may be one which also does not elicit an immune response by itself.

Major Scientific Requirements for FCS[1]	Description of Requirement and Relevant Details	Questions Specific to an ENM FCS and Associated Scientific Issues
I – Environmental information[8] **I-1) Categorical exclusion (21 CFR § 25.21)** **I-2) Environmental assessment (EA)**	FCS is present in finished food-packaging material at not greater than 5 percent by weight and is expected to remain with finished food-packaging material through use by consumers, unless "extraordinary circumstances indicate that the proposed action may have a significant environmental effect" (considering production, use and disposal). If FDA determines that extraordinary circumstances apply to a proposed action that would otherwise be subject to a categorical exclusion, FDA will provide the submitter with guidance on what information that the agency recommends be included in an EA.	Consult with FDA regarding whether "extraordinary circumstances" apply to nanoparticles and an environmental assessment would be required.
	FDA guidance says the level of analysis should be commensurate with the potential for environmental impact.	Test protocol and measurement issues. EPA research is underway to address issues in environmental fate and ecological-effects testing. Consult with FDA.

8. Guidance for Industry, Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition, FINAL GUIDANCE May 2006. http://www.cfsan.fda.gov/~dms/opa2eg.html

ATTACHMENT

MENU OF CHARACTERISTICS TO MEASURE THAT MAY BE PERTINENT TO SAFETY EVALUATION OF AN ENM ON A CASE-BY CASE BASIS

Size/Shape Category

- size and size distribution
- shape of the primary particle (which might include crystalline form)
- surface area of the primary particle
- how the material was prepared or the chemical composition (this could be part of the characterization that is routinely provided)

Surface Chemistry/Reactivity

- coating
- functionalization
- catalytic activity
- reactive oxygen species

Agglomeration Potential

- surface charge, zeta potential or agglomeration state at pH 1 (stomach), 7.4 (blood) and 9 (intestine)
- agglomeration state in medium used to treat test system

Protein Binding

APPENDIX D† Antimicrobial Pesticide Containing an Engineered Nanoscale Material* Issue Identification EPA Considerations

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
PRODUCT CHEMISTRY DATA REQUIREMENTS[1]		
Product Identity and Composition (guideline 830.1550)	Full description of the pesticide, including type	
Description of Materials Used to Generate the Pesticide (guideline 830.1600)	Description of starting materials used to produce the product	Is the ENM manufactured using top-down (i.e., large-scale materials are converted to nanoscale materials) or bottom-up (i.e., small-scale nanomaterials are converted to large-scale nanomaterials) methods? This information will help inform the particle size distribution.
Description of Production Process (guideline 830.1620)		Is the production process unique for ENM? If so, how?
Description of Formulation (guideline 830.1650)		Is it possible the 90-nm diameter polyethylene spheres coated with nisin would aggregate/ agglomerate?
Discussion of Formation of Impurities (guideline 830.1670)	Identify and quantify impurities, particularly metals at the lowest possible level.	What should be the appropriate definition of what constitutes an "impurity" for an ENM? Is the current definition of 0.1% appropriate for ENM, or should it be the limit of detection?
Preliminary Analysis (guideline 830.1700)	Same as 40 CFR 161.170	
Certified Limits (guideline 830.1750)		Specify the exact diameter of the nanomaterial; nanoproperties change significantly within nanometer range (± a few nm).

† Content provided by EPA.
* Antimicrobial pesticide containing an engineered nanoscale material (ENM) that is a food contact substance.

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
Enforcement Analytical Methods (guideline 830.1800)	Present methods like scanning electron microscopy (SEM), transmission electron microscopy (TEM), STM, X-ray diffraction (XRD), atomic force microscopy (AFM), UV-VIS spectrophotometry, Fourier transform infrared (FTIR), C-13 nuclear magnetic resonance (NMR), etc.	Are the analytical methods capable of both detection and quantitation of ENM?
Submittal of Samples (guideline 830.1900)	Same as 40 CFR 161.190	
SELECTED PHYSICAL AND CHEMICAL PROPERTIES DATA REQUREMENTS (40 CFR 161.190)[2]		
Physical and Chemical Properties		In addition to standard physical-chemical characterization, what if any "nanoproperties" of the pesticide should be characterized and what methods should be used? Does the ENM have increased reactivity/catalytic activity, which might result in a faster rate of degradation? What are the degradation products? Would a lower application rate of a pesticide containing ENM be sufficient to achieve the same antimicrobial activity of the macro-sized compound? Is the degradation pathway different than the macro-sized particle?
Physical State (guideline 830.6303)	1a. The antimicrobial substance (purified polypeptide antimicrobial nisin) coats a 90-nm diameter polyethylene sphere that is an inert substance. 1b. The metal nanoparticle, mean diameter 20 nm, is fixed to an inert polyethylene film substance.	

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
Stability to Sunlight, Stability at Room Temperature and Elevated Temperatures (guideline 830. 6313)		Is the ENM: a) stable to (UV-VIS) light?; b) stable or decomposes at elevated temperatures? What are the identities of the degradation products, if any?
Oxidation-Reduction Potentials (guideline 830.6314)		Does the ENM exhibit a new or different redox potential? What is the method of measurement reported?
Storage Stability (guideline 830.6317)	Measure long-term stability (shelf life: one year); report conditions for storage stability; apply cautionary label for storage.	Does the ENM aggregate/ agglomerate during storage? And if not, what conditions are required to keep it from non-aggregating? Does the ENM degrade during storage?
Corrosion Characteristics (guideline 830.6320)	Identify conditions under which corrosion may occur, particularly those pesticides containing nanomaterials that are metallic, metallic oxides, inter-metallics and composites that have metallic composites.	
pH of Water Solution or Suspensions (guideline 830.7000)		What is the pH at which the pesticide containing nanomaterials is stable? At what pH does it not aggregate/agglomerate? What is the duration of stability at a given pH?
UV-Visible Absorption (guideline 830.7050)	Condition under which absorption spectra obtained: a) natural sunlight; b) artificial light; c) absorption coefficient.	

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
Particle Size, Fiber Length, Diameter Distribution (guideline 830.7520)	Specify: a) particle size; b) length; c) diameter; d) diameter distribution. Ensure the particle size distribution is representative of the substance. More than one technique may be necessary to describe the particle sizes accurately.	Do the ENM show some unique changes such as: 1) increased surface area per unit mass?; 2) increased surface activity?; 3) increased chemical reactivity? Including: a) optical properties; b) magnetic properties; c) electronic properties; d) photochemical changes; e) mechanical properties; f) does catalytic activity become more pronounced? What is the morphology of the ENM? Does the surface area increase depend on the following parameters? 1) manufacturing method?; 2) percent purity of the ENM?; 3) nanorange of the product?; 4) quality control steps, including methods employed to avoid aggregation/agglomeration of the nanoparticles? Is more than one technique necessary to describe the ENM particles accurately? Is there aggregation/ agglomeration during sampling?
Kow/Octanol/Water Partition Coefficient (guidelines 830.7550, 7560, 7570)	Measure/report exact Kow or log Kow with any of the guideline methods.	
Vapor Pressure (guideline 830.7950)	Exact measured number is critical; it is more important for workers' exposure and inhalation toxicity.	
HUMAN HEALTH EXPOSURE ASSESSMENT FOR ENM		
1) Dietary Assessment		

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
Migration to Food[3]	EPA uses the FDA methodology to estimate migration to food. "The concentration of an FCS in the daily diet may be determined from measured levels in food or in food simulants, or estimated using information on formulation or residual levels of the FCS in the food-contact article and the assumption of 100% migration of the FCS to food. Although FDA always has accepted reliable analyses of FCS in real foods, in practice, many analytes are difficult to measure in food. As an alternative, notifiers/petitioners may submit migration data obtained with food simulants that can reproduce the nature and amount of migration of the FCS into food. Because an FCS may be used in contact with many foods with different processing conditions and shelf lives, the submitted migration data should reflect the most severe temperature/time conditions to which the food-contact article containing the FCS will be exposed."	a) Does the ENM retain its nanocharacteristics when it migrates? For example, if extraction studies are performed, does the pesticide containing an ENM maintain its nanocharacteristics in the food contact substance and in the food simulants throughout the test? What other characteristics of migrating nanoparticles (e.g., solubility, aggregation/agglomeration) potentially relevant to safety by ingestion should be measured and how? b) Is the migration study methodology appropriate for the detection of the ENM (size, quantity and shape)? c) Has the migration study methodology been validated for the ENM (i.e., the analytical method must measure what would migrate to food under conditions of use, and what the consumer would be exposed to)? d) Are wet chemistry methods necessary or appropriate to detect ENM? e) Is it conceivable that nanocharacteristics might interfere with the analytical methods?
Estimated Daily Intake (EDI) and Cumulative EDI (CEDI)[4]	EPA uses the FDA methodology to calculate the EDI and CEDI to assess dietary exposure and risk. See Attachment 2 for details.	CEDI calculations are currently based on chemical mass (measured concentrations in the food simulants or, in the case of non-detects, LOD or half LOD). If the substance that migrates retains nanocharacteristics, what dosimetric is appropriate for nanoparticles? Is existing guidance adequate?

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
2) Occupational Exposure		
Exposure Assessment for Workers[4]	The case study indicates: The polyethylene packaging film is coated with the prepared polyethylene/nisin particles using a continuous electrospray process in an enclosed environment. The metal nanoparticles are applied to the packaging film using a continuous electrostatic deposition process. This process is contained and kept at negative pressure to prevent aerosol release. This process allows the nanoparticles to be applied and adhered to the inner layer of the packaging film at the nanoscale thickness. The polyethylene/nisin particles are formulated as a liquid suspension. The metal nanoparticles are formulated as a dust.	a) Are workers exposed to the ENM during mixing/loading or application via inhalation and/or dermal contact during the manufacturing of the food-packaging material? For example, does the ENM become airborne, or is there potential for spillage of liquid product during the coating of the food-packaging material? b) How is the material delivered to the spray tank (e.g., open pour versus closed system transfer)? c) What are the proposed label language requirements? Are engineering controls required (e.g., closed and ventilated system) to reduce potential worker exposure? d) Does the ENM aggregate/ agglomerate or transform? e) Would existing Pesticide Handlers Exposure Data (PHED) or American Chemistry Council (ACC) data be relevant for nano materials? The existing data report exposure on a mass basis (i.e., mg/lb ai handled) Should another exposure metric (e.g., surface area or number of particles) be considered? f) Can nanoparticles of this material be detected and quantified?

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
HUMAN HEALTH HAZARD ASSESSMENT : **1) Toxicology Data Summary [5]**	Safety summary and comprehensive toxicological profile Toxicology data requirements depend on estimated CEDIs. See Attachment 1 for details.	**a) What substance migrates from food-packaging material? Nisin? Polyethylene spheres? Complex? Metal nanoparticle? Want to assure safety for same substance that migrates.** b) Does the FCS/constituent maintain its nanocharacteristics in the simulant? c) Do migration studies show nanomaterial aggregates/agglomerates or solubilizes in the simulant? **d) Is the current CEDI of 200 ppb relevant for nanomaterials?** e) Can a comparative approach to the non-nano form of same material be used as a basis for safety determination (e.g., for each required study, run a parallel study on the same substance in non-nano form and compare responses)? f) Do standard EPA testing protocols apply to ENM? Are these testing protocols adequate to determine health hazards? g) Should EPA toxicology study guidelines be modified to include additional measurements or pathology (e.g., the literature suggests potential for inflammation or immune system responses with some nanomaterials)? **h) Dosimetrics for nanoparticles: Should the toxicity studies evaluate surface area and/or particle number instead of, or in addition to, mass (mg/kg) as part of characterization?** **i) What is the role and significance of the vehicle used in delivering ENM in toxicity studies?** j) Does the ENM bind to protein (an indicator of potential to cause immunological effects)? What is the surface reactivity (this may inform the hazard potential)? k) Since many reactive nanoparticles are cytotoxic, this may affect the mutagenicity study results. Are *in vitro* tests useful for reactive ENMs? Has the potential for agglomeration of ENM been considered in mutagenicity studies? Is it possible that negative results could be due to the ENM agglomerating and not getting into the cell? l) If there is ENM inhalation exposure to workers, EPA may have heightened concern for inhalation toxicity based on available scientific literature. Is an inhalation toxicity study appropriate to address potential inhalation hazards to workers? m) What is the biopersistence and absorption/distribution/metabolism/excretion (ADME) for ENMs?

Current Major Scientific Requirements for Pesticide	Description and Relevant Details	Likely Key Questions Relevant to ENM Safety
2) Toxicology Literature Summary	Evaluate the published scientific literature.	Is information available for the constituents or impurities or the identical ENM?
ENVIRONMENTAL/ECOLOGICAL RISK ASSESSMENT		
Environmental/Ecological Risk Assessment [6]	Evaluate environmental impact of antimicrobial pesticide on wastewater treatment plants from effluent discharge during the manufacturing process of food packaging material. In addition to an ecological assessment of potential impacts by the EPA Office of Pesticide Programs (OPP), a National Permit Discharge Elimination System (NPDES) will likely be necessary from the EPA Office of Water to comply with the Clean Water Act. See Attachment **3** for a detailed list of EPA data requirements.	**a) What substance is released from the manufacturing facility? Nisin? Polyethylene spheres? Complex? Metal nanoparticle? Want to assure safety for same substance that is discharged. An environmental assessment may be necessary to evaluate the potential for movement, persistence and impacts of the nanoparticles in the environment.** b) Does the ENM aggregate/ agglomerate in effluent discharge? c) Does the ENM degrade faster or slower than the non-nano form? What are the environmental degradates? d) What is the impact on fish, birds, invertebrates and algae? e) What is the impact on endangered species? f) Can a "substantial equivalence" approach be used for environmental fate and effects? (e.g., for each required study, run a parallel study on same substance in non-nano form and compare responses)? g) Are the standard EPA testing protocols sufficient for ENMs? (i.e. are these testing protocols adequate to determine toxicity for aquatic and terrestrial organisms)? h) Should existing EPA ecotoxicity and environmental fate guideline study protocols be modified to include additional measurements or pathology (e.g., the literature suggests potential for inflammatory or immune system responses with some nanomaterials)?

ATTACHMENT 1

CURRENT EPA TOXICOLOGY REQUIREMENTS FOR LOW-EXPOSURE AND NON-FOOD USE ANTIMICROBIAL PESTICIDES*

A. Tier 1 for CEDI < 200 ppb:

Acute toxicity data (acute oral LD50, acute dermal LD50, acute inhalation LD50, dermal irritation, eye irritation and dermal sensitization) (870.1100/1200/1300/2400/2500 /2600);

Mutagenicity testing battery [bacterial reverse mutation test (870.5100—often substitute mouse lymphoma); in vitro mammalian mutation 870.5300/5375; in vivo cytogenetics (870.5380/5385/5395)

90-day oral rodent study (870.3100)

developmental toxicity study (870.3700)

literature search
structure-activity relationship (SAR) analysis

Reserved Data: 90-day inhalation study, 90-day dermal study, 90-day subchronic oral study (non-rodent); 2-generation reproduction study and other studies as warranted in the literature search/structure-activity relationship (SAR) analysis.

B. CEDI > 200 ppb: Food Use Data requirements: Above requirements in addition to a 90 day non-rodent study, second developmental study, two-generation reproduction study, chronic toxicity/carcinogenicity study (two species) and chronic non-rodent study. Additional studies in reserve (e.g., neurotoxicity studies and immunotoxicity studies).

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* EPA OPPTS Health Effects Test Guidelines. See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/index.html (last accessed March 24, 2008).

ATTACHMENT 2

EXCERPTS FROM FDA GUIDANCE FOR INDUSTRY,
PREPARATION OF PREMARKET SUBMISSIONS FOR FOOD CONTACT SUBSTANCES: CHEMISTRY RECOMMENDATIONS
FINAL GUIDANCE
DECEMBER 2007

A. FDA uses the following approach for calculating the concentration of the FCS in the daily diet. The concentration of the FCS in food contacting the food-contact article, <M>, is derived by multiplying the appropriate f_T values by the migration values, M_i, for simulants representing the four food types. This, in effect, scales the migration value from each simulant according to the actual fraction of food of each type that will contact the food-contact article. $<M> = f_{\text{aqueous and acidic}}(M_{\text{10\% Ethanol}})+f_{\text{alcohol}}(M_{\text{50\% Ethanol}})+f_{\text{fatty}}(M_{\text{fatty}})$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying <M> by CF. The EDI is then determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day. FDA assumes that an individual consumes 3kg of food (solid and liquid) per day (see Appendix IV http://www.cfsan.fda.gov/~dms/opa-2pmnc.html#aiv for sample calculations):

EDI = 3 kg food/person/day x <M> x CF

B. *CUMULATIVE EXPOSURE (CEDI).* If the FCS already is regulated for other uses in 21 CFR 170-199, has been exempted from the need for a regulation under the Threshold of Regulation (21 CFR 170.39) or has been the subject of previous effective FCNs, the notifier/petitioner should estimate the cumulative exposure to the FCS from the proposed and permitted uses (see the example in Appendix IV http://www.cfsan.fda.gov/~dms/opa2pmnc.html#aiv). Information on the regulatory status of an FCS may be obtained by inspection of 21 CFR 170-199, searching the CFR on the Government Printing Office (GPO) website at http://www.gpoaccess.gov/cfr/index.html (last accessed March 24, 2008) or by contacting FDA directly. Information on effective FCNs or Threshold of Regulation exemptions for an FCS may be obtained through the FDA website or by contacting FDA directly. An estimate of cumulative exposure for the regulated, notified, and exempted uses of an FCS can be obtained by contacting FDA. FDA also maintains a database of CEDIs for FCSs on the agency's website (http://www.cfsan.fda.gov) (last accessed March 24, 2008).

ATTACHMENT 3

CURRENT EPA ECOLOGICAL EFFECTS AND ENVIRONMENTAL FATE DATA REQUIREMENTS FOR ANTIMICROBIAL PESTICIDES*

Environmental Fate and Microbial Effects Tier 1 Data

Hydrolysis (OPP 161-1) (not appropriate for the metal nanoparticle)
Modified activated sludge, respiration inhibition (OPPTS: 850.6800)
Activated sludge sorption isotherm (OPPTS: 835.1110)
Ready biodegradability (OPPTS: 835.3110)

Nontarget Organism Effects Tier 1 Data

Avian Acute oral LD50 (OPPTS:850.2100)
Aquatic vertebrate acute LC50 (OPPTS:850.1075)
Aquatic invertebrate acute EC50 (OPPTS: 850.1010)
Algal toxicity (Using freshwater green algae, *Selenastrum capricornutum*) (OPPTS: 850.5400)

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* EPA OPPTS Ecological Effects Test Guidelines. See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/850_Ecological_Effects_Test_Guidelines/ (last accessed March 24, 2008).

ATTACHMENT 4

ADDITIONAL EPA PHYSICAL CHEMICAL DATA REQUIREMENTS FOR PESTICIDES NOT SHOWN ON TABLE 1*

Physical Chemical Properties (40 CFR 161.190):

Color (830.6302), Same as 40 CFR 161.190, guideline 63-02

Odor (830.6404,) Same as 40 CFR 161.190, guideline 63-04

Flammability (830.6315), Identify flash point; provide cautionary label language for flammability

Explodability (830.6316), Identify temperature at which explosion is likely; cautionary label language for safe use of nanopesticide

Miscibility, As per 40 CFR 161.190, guideline 830.6319

Dielectric breakdown (830.6321), As per 40 CFR 161.190, guideline 830.6321

Viscosity (830.7100)—same as 40 CFR for macro sized pesticides

Melting point /Melting range (830.7200)-- same as 40 CFR for macro sized pesticides

Boiling point/BP range (830.7220)-- same as 40 CFR for macro sized pesticides

Density/relative density/bulk density (830.7300)-- same as 40 CFR for macro sized pesticides

Dissociation in constant water (830.7370)-- same as 40 CFR for macro sized pesticides

Water solubility (830.7840 and 830.7860)

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* EPA OPPTS Harmonized Test Guidelines. Part 830 contains Physical and Chemical Properties (40 CFR 161.190) See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/830_Product_Properties_Test_Guidelines/index.html (last accessed March 24, 2008).

ATTACHMENT 5

OECD MINIMAL BASE SET OF ENDPOINTS FOR TESTING NANOMATERIALS*

The following list of endpoints is being used by the OECD Working Party on Manufactured Nanomaterials as a foundation data set for evaluation of the appropriateness of current testing approaches for the assessment of nanomaterials and to gain a better understanding of the intrinsic properties of the nanomaterials. Addressing this foundation data should ensure consistency between the various tests to be carried out on specific ENMs and the data sets developed. It should also lead to the timely development of a dossier on a nanomaterial describing basic characterization, fate, ecotoxicity and mammalian toxicity information.

List of Endpoints

Nanomaterial Information/Identification

Nanomaterial name (from list)
CAS number
Structural formula/molecular structure
Composition of nanomaterial being tested (including degree of purity, known impurities or additives)
Basic morphology
Description of surface chemistry (e.g., coating or modification)
Major commercial uses
Known catalytic activity
Method of production (e.g., precipitation, gas phase)

Physical-Chemical Properties and Material Characterization

Agglomeration/aggregation
Water solubility
Crystalline phase
Dustiness
Crystallite size
Representative TEM picture(s)
Particle size distribution
Specific surface area
Zeta potential (surface charge)
Surface chemistry (where appropriate)

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* Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Safety of Manufactured Nanomaterials: Plans for Testing of a Representative Set of Manufactured Nanomaterials. 42nd Joint Meeting. December 13, 2007. ENV/JM(2008)13.

Photocatalytic activity
Pour density
Porosity
Octanol-water partition coefficient, where relevant
Redox potential
Radical formation potential
Other relevant information (where available)

Environmental Fate

Dispersion stability in water
Biotic degradability
Ready biodegradability
Simulation testing on ultimate degradation in surface water
Soil simulation testing
Sediment simulation testing
Sewage treatment simulation testing
Identification of degradation product(s)
Further testing of degradation product(s) as required
Abiotic degradability and fate
Hydrolysis, for surface modified nanomaterials
Adsorption-desorption
Adsorption to soil or sediment
Bioaccumulation potential
Other relevant information (when available)

Environmental Toxicology

Effects on pelagic species (short term/long term)
Effects on sediment species (short term/long term)
Effects on soil species (short term/long term)
Effects on terrestrial species
Effects on microorganisms
Other relevant information (when available)

Mammalian Toxicology

Pharmacokinetics (ADME)
Acute toxicity
Repeated dose toxicity
If available:
Chronic toxicity

Reproductive toxicity
Developmental toxicity
Genetic toxicity
Experience with human exposure
Other relevant test data

Material Safety

Where available:
Flammability
Explosivity
Incompatibility

Endnotes

1. Product Chemistry Data Requirements for Registration/Reregistration of Pesticides. EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) Harmonized Test Guidelines. Part 830 contains Product Identity, Composition, and Analysis Test Guidelines (40 CFR 161.155, 161.160, 161.162, 161.167, 161.170, 161.178, 161.180). See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/830_Product_Properties_Test_Guidelines/index.html (last accessed March 24, 2008).

2. EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) Harmonized Test Guidelines. Part 830 contains Physical and Chemical Properties (40 CFR 161.190). See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/830_Product_Properties_Test_Guidelines/index.html (last accessed March 24, 2008). See Attachment 4 for additional EPA data requirement information related to physical and chemical properties.

3. Guidance for Industry, Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations FINAL GUIDANCE, December 2007. See http://www.cfsan.fda.gov/~dms/opa3pmnc.html (last accessed March 24, 2008).

4. EPA OPPTS Exposure Guidelines: Indoor Inhalation Exposure (875.1400), Indoor Dermal Exposure (875.1200), Description of Human Activity (875.2800). See http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/875_Occupational_and_Residential_Exposure_Test_Guidelines/index.html (last accessed March 24, 2008).

5. EPA current practice for low-exposure food contact antimicrobial pesticides. See Attachment 1.

6. EPA Environmental Fate and Nontarget Organism Effects Data requirements for industrial discharges are presented in Attachment 3.

APPENDIX E Industry Product Stewardship Considerations for Engineered Nanoscale Materials

PREFACE

Although nanoscale materials have probably existed in nature since the creation of the Earth and there is a history of human and environmental exposures to them, new concerns have been raised about the health and environmental impacts of engineered nanoscale materials (ENMs) as well as concerns about familiar substances that are reduced to the nanoscale. Nanosized particles of a substance may have unusual physical, chemical and biological properties compared to larger-sized particles of the same substance. These unique properties allow the development of novel applications in engineering and materials science, electronics, computer science, medicine, agriculture, food and consumer products. At the same time, these unique properties mean that a substance in nanoparticle form may act differently in biological systems—animals, human, plants and the environment— than does the same substance in bulk form. Thus, current safety testing and information, based on bulk forms of materials, may not predict the safety of the same material in nano form. Around the globe, governments and industries are allocating billions of dollars into basic research and development of materials at the nanoscale. Governments are also considering the appropriate levels of oversight for these ENMs. Industry is taking a proactive stance by developing and implementing stewardship programs to address issues that relate to environmental, health and safety concerns.

The members of the Stewardship Working Group, a volunteer group associated with the PEN/GMA case study effort, have attempted to capture their ideas on the structure and value of an industry product stewardship effort. Working Group members believe that product stewardship is an important component of responsible development and commercialization of ENMs and that product stewardship complements the existing role of governments in working toward the common goal of environmental and human health and safety. Many of the product stewardship concepts presented here are derived from practices that have already been adopted by many companies dealing with chemicals in their research and manufacturing operations. The hope is that this effort will inform companies incorporating ENMs in the area of foods and food packaging about how to proceed in a responsible manner. The following is not an attempt to create industry standards but rather a collection of points to consider.

SECTION 1: INTRODUCTION

Nanotechnology offers tremendous potential benefits for innovation, product safety and product quality enhancement. Because knowledge about ENMs is evolving rapidly, regulators are challenged to ensure that regulatory oversight of nanotechnology keeps pace with commercialization activities. Policy that is current, with regard to technology develo-

pments, is important to maintain consumer confidence while research and development proceed. As governments enhance their regulatory approaches and as research expands, it is important that industry demonstrate a responsible approach to commercialization. In that light, the PEN/GMA Nanotechnology Project developed a series of plausible but hypothetical food-packaging case studies to illustrate the regulatory challenges expected to be encountered on the path to commercialization of several nanomaterial applications. To accompany this analysis and the review of current regulatory oversight anticipated for the case studies, the Stewardship Working Group has defined some common product stewardship considerations for companies involved in research or production of ENMs to think about as they move forward.

SECTION 2: SCOPE AND DEFINITIONS

Scope

The purpose of this document is to provide high-level guidance for companies to consider as they begin development and application of ENMs directed toward food and food packaging. These product stewardship considerations do not address the ethical and socioeconomic aspects of developing these products, and they do not make recommendations as to the policy issues associated with ENMs. They should not be considered industry standards. They do, however, present insights into good product stewardship practices.

Definitions

Engineered Nanoscale Materials (ENMs)

Several definitions for the words "nanotechnology," "nanoscale," "nanoparticle," and "nanomaterial" currently exist. For example, the BSI (British Standards Institution) PS71:2005 defines a nanomaterial as:

Material with one or more external dimensions, or an internal structure, on the nanoscale, which could exhibit novel characteristics compared to the same material without nanoscale features.

The Stewardship Working Group recognizes the diversity of definitions for nanotechnology and nanoscale materials. It is not the intent of this project to develop or adopt a standard definition of ENMs. The purpose of this dialogue on definitions is simply to assist readers in considering the scope of their ENM product stewardship program and what products may be covered in them. We also refer readers to the section of the report entitled "Defining Nanoscale," which proposes that the issue of what constitutes "nanoscale" is more likely to arise in the context of defining chemistry, toxicology and environmental data requirements than in attempting to restrict ENMs to any particular size or dimension.

ENM Product Stewardship Program

An ENM product stewardship program may be defined as a voluntary program that offers insight for responsible development and commercialization of products incorporating ENMs, through programs and practices that help protect people and the environment and that typically involve going beyond applicable governmental requirements.

SECTION 3: PRODUCT STEWARDSHIP CONSIDERATIONS

The following principles should be taken into account when developing a product stewardship program:

- Corporate Responsibility—Product stewardship demonstrates the commitment of industry to act in a voluntary manner to take responsible action.
- Leadership—Participation in product stewardship activities sets an example for others and encourages accessibility and sharing of best practices.
- Sustainability —Adherence to the principles of product stewardship can contribute to a sustainable business model.
- Continuous Improvement—The program must promote achieving environment, health and safety (EHS) goals and minimizing waste.
- Transparency—Transparency entails acknowledging and considering stakeholders' comments and issues, and reporting on progress made on those issues. Transparency will encourage stakeholder and consumer acceptance.
- Education—Educating stakeholders and the public about the technology will increase consumer confidence.
- Global Perspective—Considering broader global impacts of the product (both geographical issues and non-commercial impacts) will facilitate trade.

SECTION 4: PRACTICES AND PROGRAMS

Incentives and Benefits of Product Stewardship Programs

Product stewardship can have a significant positive effect on multiple levels of a product's life cycle, e.g., research, production, handling, use and end of life. By adopting a product stewardship program, companies can promote safety for humans and the environment. Other benefits from incorporating and practicing a stewardship program include:

- Voluntary Actions—The benefits of voluntary actions include flexibility to determine the best solution, innovation, economics, environment protection and improved stakeholder relations.

- Environment, Health and Safety—The impact of following a program can have a positive EHS result for both the company and for others.

- Technology Success—Early successes with products from nanotechnology build future successes of nanotechnology applications.

- Recognized Leadership—Companies providing leadership are recognized by their peers as outstanding corporate citizens.

- Reduced Regulatory Burden—Voluntary programs can demonstrate a cooperative approach to responsible management of essential environmental health and safety criteria in a concerted manner with government.

- Economic Benefits—Following stewardship practices often leads to better management of inputs and reduced output wastes, both of which drive down costs.

- Public Acceptance— Successes with products from nanotechnology can lead to greater public awareness and acceptance of the technology.

- International Harmonization—Global trade can be encouraged when national practices include consideration of regulations and trade issues for other countries.

Industry Product Stewardship Practices: ENM Management

Effective management of ENMs begins by consciously considering all aspects of safe, responsible and economical handling of these materials. This summary of practices is patterned after best practices used in the management of chemicals by the chemical industry. This would include incorporating, among other quality assurance programs, the utilization of the principles of Good Manufacturing Practices (GMPs). The scope of these stewardship practices begins during work planning and continues through research, acquisition, inventory, storage, manufacturing, distribution and end of life. Each step provides an opportunity to improve workplace safety, to reduce workplace accidents while protecting the environment and to minimize the severity of any incidents that might occur.

Responsible management of chemicals within research and manufacturing operations has been the practice of industry for years using established stewardship principles and practices. The Stewardship Group has addressed here the basic considerations for management of potentially hazardous ENMs or ENMs that have unknown hazards associated with them.

ENM Acquisition

ENMs should be ordered in quantities appropriate for the application and within the storage capacity limitations available. Such materials should be managed prudently. Good tracking and records of the purchase, receipt and distribution of the ENMs is important, as is identifying individuals knowledgeable about the potential hazards of the ENM.

Labeling/ Identification

All ENMs, including those produced in the laboratory, should be labeled in accordance with applicable governmental requirements.

ENM Inventory

All work areas, including laboratories, should at all times maintain an inventory of the ENMs present there. The inventory may include the following information: full ENM or product name, container size in measurable units, manufacturer, date of acquisition, expiration date (if any), storage location and any special handling requirements or potential hazards. When ENMs are expended or disposed of, that should be noted in the inventory. The inventory should be examined and updated periodically (at least annually). ENMs that have been kept beyond their appropriate shelf life should be disposed of in a proper manner.

Storage

ENMs should be stored in a manner that minimizes any safety and health hazards to personnel, equipment, buildings and the environment.

Distribution

The method of transportation of ENMs should reflect their potential hazards. Persons transporting hazardous ENMs should be familiar with their potential hazards. Persons transporting ENMs should have personal protective equipment consistent with the potential hazards. ENMs should be received by a knowledgeable individual and should not be left in unsecured areas.

Disposal and Waste Minimization

Users of ENMs should be responsible for ensuring that all used or unneeded ENMs, or articles containing them, are disposed of according to applicable government requirements. Every reasonable effort should be made to reduce the generation of waste containing ENMs.

Broadening the Knowledge Base and Management Practices for ENMs

The Environmental Protection Agency (EPA) has launched a Nanoscale Materials Stewardship Program (NMSP) that may be helpful to companies manufacturing, handling and using ENMs.[1] It is intended to encourage development of new data to better characterize health risks and other exposure issues of specific nanoscale materials. Its purposes are to:

- Identify and encourage the use of risk management practices in developing and commercializing ENMs;
- Encourage the development of test data needed to provide a firmer scientific foundation for further work and regulatory and policy decisions concerning ENMs; and
- Encourage responsible development of ENMs..

It is anticipated that participants in the NMSP and EPA will jointly develop a plan of action that could include:

- Characterizing the physical and chemical properties of the ENM.
- Testing ENMs for health and environmental hazards;
- Determining fate and transport characteristics;.
- Monitoring or estimating exposures and releases;
- Evaluating the effectiveness of engineering controls and protective equipment;
- Developing a model worker-education program; and
- Undertaking other evaluations or actions as appropriate.

Even if they do not choose to participate in the NMSP, manufacturers and users of ENMs may wish to refer to the NMSP materials for ideas and practices for development of their own ENM stewardship program.

Implementing a Product Stewardship Program for ENMs

For a product stewardship program for ENMs to succeed within an organization, there must be a clear commitment to the stewardship principles and to the goal of improvement of EHS practices of the company. Success will depend on planning, resources and training and on empowering employees to drive continuous improvement of the program.

The following outlines the needed steps to achieving success of a program:

- Corporate Commitment—Corporate managers must make a commitment to their stewardship program and back it up with adequate resources.
- Life Cycle Analysis (LCA)—A good starting point to determine the EHS aspects of ENMs is to conduct an LCA.

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1. 73 Fed. Reg. 4861 (Jan. 28, 2008). See http://www.epa.gov/oppt/nano/stewardship.htm (last accessed March 24, 2008).

- Major Impacts—From the LCA, both positive and negative impacts can be identified, as well as opportunities for improved operations and increased worker safety.
- Risk Management—Negative impacts require steps to mitigate risk and set safety practices and goals.
- Program Management—This includes program startup, training, ongoing active monitoring and control, review, corrections and improvement.
- Reporting Progress—The company should have a routine mechanism for reporting progress to management and to stakeholders.

Independent Review and Certification Considerations

Companies may consider achieving a higher level of recognition for their ENM stewardship practices and programs by coupling their efforts with a review process or a certification program that documents and validates their activities. No certification programs or auditing specifically for manufacturing or using nanomaterials currently exist. Were such programs to be developed, it might be possible to independently examine a company's level of stewardship competency and achievement. This could be accomplished by conducting an audit for the firm to use for internal purposes or to benchmark their activities against those of other companies and/or industry initiatives. Independent reviews and certifications are often done using a third party to audit activities and report on practices and procedures. The audit is used to collect data and information regarding the current status of the company and its ability to comply with its internal policies and programs or its ability to meet industry standards. Multi-year data can be gathered and used to establish trending to help achieve a goal of continuous improvement and to demonstrate a philosophy of corporate commitment and responsibility. Maintaining and publishing information about corporate activities on ENM product stewardship programs can contribute to the transparency of a company's ENM activities and provide the public a perspective about the company's dedication to being a responsible developer or user of nanotechnology.

SECTION 6. RESOURCES

Although the field of food nanotechnology is still relatively new, there are some programs, best practices, guidelines and frameworks that could assist a company in adopting a stewardship program or in developing its own program. Readers may find the following resources helpful in learning more about the voluntary initiatives associated with nanotechnology.

- Environmental Defense and DuPont Nano Risk Framework. (2007). www.nanoriskframework.com (last accessed March 24, 2008).

- American Chemical Council: Responsible Care Program. www.americanchemistry.com/responsiblecare (last accessed March 24, 2008).

- Personal Care Products Council (formerly CTFA). Chemical Management— CIR. www.cir-safety.org (last accessed March 24, 2008).

- ORC Worldwide. Nanotechnology Consensus Workplace Safety Guidelines. www.orc-dc.com/Nano.Guidelines.Matrix.htm (last accessed March 24, 2008).

- National Institute for Occupational Safety and Health (NIOSH). Approaches to Safe Nanotechnology: An Information Exchange with NIOSH. (2006). www.cdc.gov/niosh/topics/nanotech/about.html (last accessed March 24, 2008).

- Occupational Safety and Health Administration (OSHA) Hazard Communication Standard. Designed to ensure that information about hazards and associated protective measures is disseminated. www.osha.gov/SLTC/hazardcommunications/index.html (last accessed March 24, 2008).

- ASTM E2537-07, Standard Guide for Handling Unbound Engineered Nanoparticles in Occupational Settings. (2007). http://www.astm.org (last accessed March 24, 2008).

- EPA's Nanoscale Materials Stewardship Program. http://epa.gov/oppt/nano/stewardship.htm (last accessed March 24, 2008).

- British Standards Institution. Nanotechnologies Part 2: Guide to Safe Handling and Disposal of Manufactured Nanomaterials. (2007). www.bsigroup.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/PD-6699-2/Download-PD6699-2-2007 (last accessed March 24, 2008).

- Commission Recommendation of 07/02/2008 on a Code of Conduct for Responsible Nanosciences and Nanotechnologies Research. (2008). http://ec.europa.eu/research/science-society/document_library/pdf_06/nanocode-recommendation-pe0894c08424_en.pdf (last accessed March 24, 2008).

- German Chemical Industry Association. Responsible Production and Use of Nanomaterials. http://www.vci.de/default~cmd~shd~docnr~122306~lastDokNr~-1.htm (last accessed March 24, 2008).

The **Project on Emerging Nanotechnologies** was launched in 2005 by the Wilson Center and The Pew Charitable Trusts. It is dedicated to helping business, governments, and the public anticipate and manage the possible human and environmental implications of nanotechnology.

The Pew Charitable Trusts serves the public interest by providing information, advancing policy solutions and supporting civic life. Based in Philadelphia, with an office in Washington, D.C., the Trusts will invest $248 million in fiscal year 2007 to provide organizations and citizens with fact-based research and practical solutions for challenging issues.

The **Woodrow Wilson International Center for Scholars** is the living, national memorial to President Wilson established by Congress in 1968 and headquartered in Washington, D.C. The Center establishes and maintains a neutral forum for free, open and informed dialogue. It is a nonpartisan institution, supported by public and private funds and engaged in the study of national and international affairs.

The **Grocery Manufacturers Association** (GMA) represents the world's leading food, beverage and consumer products companies. The Association promotes sound public policy, champion's initiatives that increase productivity and growth and helps to protect the safety and security of the food supply through scientific excellence. The GMA board of directors is comprised of chief executive officers from the Association's member companies. The $2.1 trillion food, beverage and consumer packaged goods industry employs 14 million workers, and contributes over $1 trillion in added value to the nation's economy. For more information, visit the GMA Web site at www.gmaonline.org

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