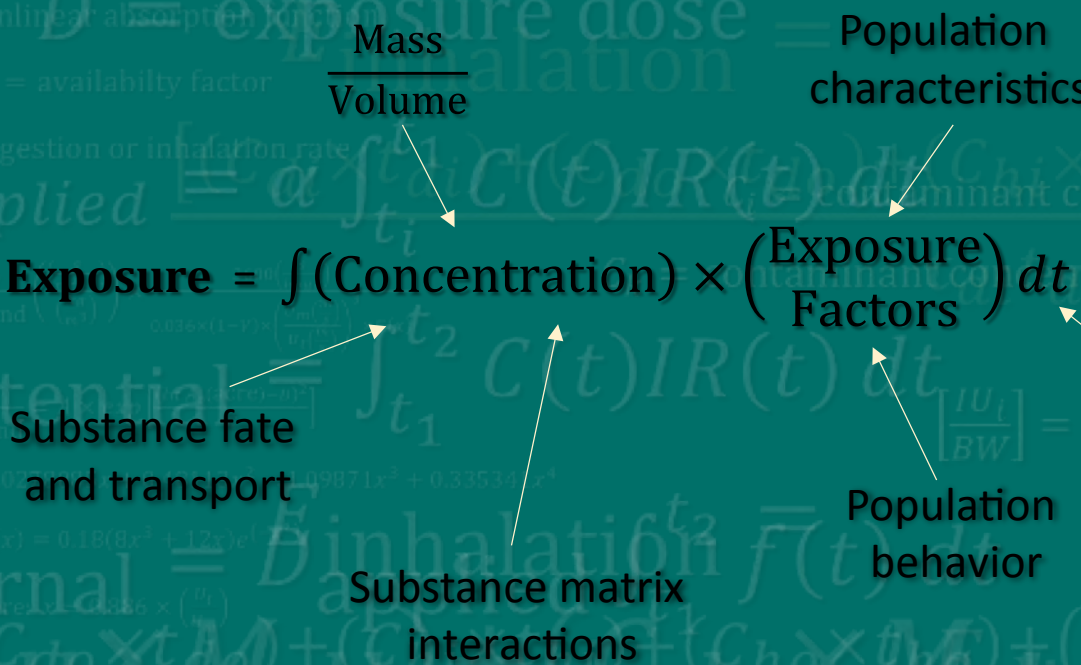
Quantifying Exposure to Engineered Nanomaterials (QEEN) from Manufactured Products

Addressing Environmental, Health, and Safety Implications

Workshop Proceedings
July 7–8, 2015

Sponsored by the
Consumer Product Safety Commission
in collaboration with the
National Nanotechnology Initiative



About the National Nanotechnology Initiative

The National Nanotechnology Initiative (NNI) is a U.S. Government research and development (R&D) initiative involving 20 Federal departments, independent agencies, and independent commissions working together toward the shared and challenging vision of a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry that benefits society. The combined, coordinated efforts of these agencies have accelerated discovery, development, and deployment of nanotechnology to benefit agency missions in service of the broader national interest.

About the Nanoscale Science, Engineering, and Technology Subcommittee

The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee is the interagency body responsible for coordinating, planning, implementing, and reviewing the NNI. NSET is a subcommittee of the Committee on Technology (CoT) of the National Science and Technology Council (NSTC), which is one of the principal means by which the President coordinates science and technology policies across the Federal Government. The National Nanotechnology Coordination Office (NNCO) provides technical and administrative support to the NSET Subcommittee and supports the Subcommittee in the preparation of multiagency planning, budget, and assessment documents, including this report. More information about the NSET Subcommittee, the NNI, and the NNCO can be found at nano.gov.

About the Nanotechnology Environmental and Health Implications Working Group

The NSET Subcommittee and its Nanotechnology Environmental and Health Implications (NEHI) Working Group provide leadership in establishing the NNI environmental, health, and safety (EHS) research agenda and in communicating data and information related to the EHS aspects of nanotechnology between NNI agencies and the public. Through the coordinated activities of the NSET and NEHI participating agencies, the NNI actively supports the development of the new tools and methods required for research that will enable risk analysis and assist in regulatory decision making.

About This Report

This document is the report from a workshop sponsored by the Consumer Product Safety Commission and co-hosted by the NNI that was held on July 7 and 8, 2015. The technical workshop was designed to bring together experts from Federal, regional, State, and local governmental and nongovernmental organizations to provide an assessment of the state of understanding in nanotechnology-related exposure science. The goal of this report is to provide an impactful document that will be useful in planning the future direction of exposure science and nanomaterials environmental, health, and safety research. This workshop is one of a series of technical workshops sponsored by the NSET Subcommittee to inform long-range planning efforts for the NNI and its EHS Research Strategy. This report is not a consensus document but rather a technical report with an aim to assess the state of exposure science and the tools and methods available to characterize and quantify exposure of people and the environment to engineered nanomaterials from manufactured products.

About the Report Cover and Book Design

Book layout design is by NNCO staff. Report cover design is by Kristin Roy and Shelah Morita of NNCO staff.

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Acknowledgements

Thanks are due to all workshop participants (see Appendix C) for sharing their experiences and insights at the *Quantifying Exposure to Engineered Nanomaterials from Manufactured Products* Workshop—the "QEEN Workshop" for short. Particular thanks are due to the plenary speakers and session co-chairs (listed on the workshop agenda, Appendix B), whose remarks are summarized in this report, to the members of the Workshop Planning Team, and to those that judged the travel and poster awards (listed below).

Workshop Planning Team

Workshop Planning Team: William K. Boyes (Environmental Protection Agency), Brendan Casey (Food and Drug Administration), Timothy Duncan (Food and Drug Administration), Cathy Fehrenbacher (Environmental Protection Agency), Charles Geraci (National Institute for Occupational Safety and Health), Elaine Cohen Hubal (Environmental Protection Agency), Debra Kaiser (National Institute of Standards and Technology), Dragan Momcilovic (Food and Drug Administration), Vladimir Murashov (National Institute for Occupational Safety and Health), Elijah Petersen (National Institute of Standards and Technology), Jeffery Steevens (U.S. Army), Treye Thomas (Consumer Product Safety Commission), and Katherine Tyner (Food and Drug Administration).

QEEN Conference Travel Awards and QEEN New Investigator Award Judges: Deborah Burgin (Agency for Toxic Substances and Disease Registry), Custodio Muianga (Agency for Toxic Substances and Disease Registry), Mary K. Schubauer-Berigan (National Institute for Occupational Safety and Health), Jeffery Steevens (U.S. Army), and Lipiin Sung (National Institute of Standards and Technology).

National Nanotechnology Coordination Office (NNCO) Contract Staff: Jewel Beamon (Events Manager), Shelah Morita (NEHI Executive Secretary and QEEN Workshop Project Manager), Diana Petreski (Financial Manager), and Kristin Roy (IT Director).

Note-Takers

Special thanks are also due to the NNCO staff members and AAAS Fellows who took notes at the workshop breakout sessions and throughout the workshop:

NNCO Contract Staff: Tarek Fadel, Geoff Holdridge, Mike Kiley, Stephen Lehrman, Shelah Morita, Marlowe Newman, and Stacey Standridge

AAAS Fellow: Quinn Spadola (NNCO)

Report Writing and Editing

The report was prepared by Shelah Morita (NNCO Contract Staff). The manuscript was edited by Pat Johnson (NNCO contract staff) and Geoff Holdridge (NNCO Contract Staff Director).

Dedication

This workshop report is dedicated to Paul J. Lioy, PhD, an internationally renowned exposure scientist who died while returning home from the QEEN Workshop. Dr. Lioy was most widely known for his work studying exposure to dust during and after the September 11, 2001, attacks on the World Trade Center. Professor and Vice Chair for the Department of Environmental and Occupational Medicine at the Rutgers Robert Wood Johnson Medical School (RWJMS), Dr. Lioy was a New Jersey native, born on May 27, 1947, in Passaic, NJ. He was also Deputy Director for Government Relations at the Rutgers Environmental and Occupational Health Sciences Institute and served as Director of the institute's program in exposure science. Since 2002, he has been identified by *Reuters* as one of the most cited scientists in the category of environment and ecology.

Paul Lioy was a driving force in exposure science; he served on various U.S. Environmental Protection Agency (EPA) and National Research Council (NRC) committees as a tireless champion for the field. A major focus of his research was defining the fundamental principles of human exposure science and their application to state, national, and international environmental health problems. This emphasis included research on the Toms River Cancer Cluster, chromium exposure and health effects in Jersey City, NJ, ozone and asthma, air pollution in China, and nanoparticles in consumer products. During the QEEN workshop, he expressed to his colleagues that, of all the research work he has done, he was most proud of his work in connection with exposure of first responders and others after the September 11 attacks.

Dr. Lioy was involved in exposure science at many levels. In New Jersey, he was Chair of New Jersey Clean Air Council, member of the Science Advisory Board for the NJ Department of Environmental Protection, and on the Executive Committee of the University Center on Disaster Preparedness and Emergency Response of RWJMS Hospital. Nationally, he served on the Science Advisory Board of the U.S. EPA and as the Co-Chairman of the U.S. Consumer Product Safety Commission's Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. He was a member of the National Academy of Sciences Board on Environmental Studies and Toxicology, was Chair of the NRC's first committee on exposure assessment, and was Vice Chair of the NRC Committee on Exposure Science in the 21st Century. Internationally, Dr. Lioy founded the International Society for Exposure Science and was its president from 1993–1994. He participated in the U.S.–Canada International Joint Commission Air Quality Advisory Board (1992–2007) and was a fellow of the Collegium Ramazzini, Carpi, Italy.

Dr. Lioy was an editor for seven journals that deal with environmental science, human exposure, and air pollution. Most recently, he was Associate Editor of the journal *Environmental Health Perspectives* and Deputy Editor in Chief of the *Journal of Exposure Science and Environmental Epidemiology*. He published over 290 peer-reviewed papers, including reviews and vision on science and science policy and ethics. He also contributed book chapters and editorials, and published five books, including *Dust: The Inside Story of its Role in the September 11th Aftermath* and *Exposure Science*.

Preface

This report on *Quantifying Exposure to Engineered Nanomaterials (QEEN) from Manufactured Products – Addressing Environmental, Health, and Safety Implication*s is the result of a technical workshop sponsored by the Consumer Product Safety Commission (CPSC) and co-hosted by the National Nanotechnology Initiative (NNI) on July 7 and 8, 2015, in Arlington, VA. The main goals for the workshop were to (1) assess progress in developing tools and methods for quantifying exposure to engineered nanomaterials (ENMs) across the product life cycle, and (2) to identify new research needed to advance nanotechnology environmental, health, and safety exposure assessment for nanotechnology-enabled products. The workshop included an overview of the field by exposure science experts as well as technical sessions highlighting current research on quantifying exposure at different stages of the product life cycle and in different product media and environments. It also included a poster session and several roundtable discussions organized to help participants better understand the challenges and accomplishments thus far in exposure science.

This report summarizes the presentations and discussions of over 200 participants from the exposure science community regarding progress during the last decade in quantifying ENM exposures. Current gaps in characterization tools and techniques are identified and discussed, along with exposure assessment methodologies, and simulation and modeling tools. Finally, the report suggests a path forward that will help bridge exposure science with toxicology and ultimately benefit data-based risk assessment and risk-based decision making for nanotechnology-enabled products.

On behalf of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council, we thank Treye Thomas, Chuck Geraci, Elijah Petersen, and Elaine Cohen Hubal for taking the lead in organizing this workshop. Thanks are also due to the Nanotechnology Environmental and Health Implications (NEHI) Working Group of the NSET Subcommittee for leading the planning effort on behalf of NSET, and to the other members of the workshop planning team (listed on the previous page). We also thank all the speakers, session co-chairs, poster judges, and participants for their contributions to the workshop. We trust that you will find this report to be a valuable resource for the NNI, the nanotechnology environment, health, and safety (EHS) research community, and other stakeholders as we work together to promote the responsible development of nanotechnology.

Lori Henderson	Lloyd Whitman	Michael Meador
Co-Chair	Co-Chair	Director
NSET Subcommittee	NSET Subcommittee	NNCO

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Executive Summary

The successful commercialization of nanotechnology requires adequately addressing its potential environmental, health, and safety (EHS) implications. Using the best available science in this risk-based approach includes understanding both exposure and hazard across the product life cycle. This report is a summary of presentations and discussions that occurred during the *Quantifying Exposure to Engineered Nanomaterials (QEEN) from Manufactured Products* Workshop, sponsored by the Consumer Product Safety Commission and co-hosted by the National Nanotechnology Initiative. The workshop assembled more than 150 international experts from government (both regulatory and research), academia, industry, and nongovernmental organizations, all part of the nanotechnology EHS (nanoEHS) research community. The goals were (1) to assess progress in developing tools and methods for quantifying exposure to engineered nanomaterials (ENMs) across the product life cycle, and (2) to identify new research needed to advance nanoEHS exposure assessment for nanotechnology-enabled products (NEPs).

Among the overall conclusions is that significant progress has been made, especially over the past decade, in the development of characterization tools and techniques, exposure assessment methodologies, and simulation and modeling tools, to quantify ENM exposures. Current methods can detect nanoparticles well below known toxicity levels and beneath the threshold of economical and reasonable regulatory action. Assessment methods and tool needs have moved beyond those necessary for fundamental laboratory studies on pristine, as-manufactured ENMs towards those needed to evaluate exposure risk under conditions that more closely mimic actual exposure scenarios. Therefore, a science-based estimate of risk to human or environmental health requires knowledge of realistic exposure scenarios and the actual released materials to which exposure may occur. This approach includes understanding transformation products and interactions with environmental constituents. A method that rapidly models exposure estimates can enable timely decisions about the safe and sustainable design of NEPs. As a next step, the community could focus on is the complex issue of determining biomarkers of exposure linked to disease, which will require substantive private–public collaboration, partnership, and knowledge-sharing.

The following summary contains some of the important findings and recommendations arising from each of the topical themes of the workshop.

Life Cycle Considerations for Quantifying Exposure

- The highest volume production ENMs in commerce now have data in the peer-reviewed literature related to use, release rates, and analytical methods for nanomaterial (NM) characterization through the entire life cycle. However, data is lacking on NM biodistribution, bioavailability, biotransformation, and bioaccumulation in humans exposed to these ENMs and more exposure research beyond the occupational arena is needed.
- Linking life cycle stage-specific release and exposure scenarios for categories of NEPs can be achieved by generating released particles and their concentrations under “real-world” conditions and using those particles and concentrations to evaluate transformations that occur *in vivo* and the subsequent toxicological effects.

- Those life cycle stages that result in ENM release to the environment can be identified using material flow analysis (MFA) and environmental fate modeling (EFM). However, limited data on the production amounts of ENMs and their distribution in different product categories can lead to modeling results with high uncertainty values.
- Consumer exposure assessment requires characterization of ENMs in the context of consumer use, and health effects of ENMs depend on their bioavailability to the receptor. This context must be considered to assess accurately the potential health risks associated with particulate matter containing ENMs released across an NEP life cycle.
- An effective nanoEHS approach in the workplace that can link toxicology, risk assessment, and epidemiology requires biological indicators such as molecular biomarkers. While mass is currently the primary metric in toxicology, work is still needed to identify the most relevant metrics indicative of exposure risk.

Exposure Quantification Studies by Receptor Population along the Product Life Cycle

- **Occupational:** Although the most studied receptor population along the NEP life cycle, potential worker exposure to ENMs remains poorly understood, and data from studies are difficult to compare. To improve the utility of research, test materials for these studies should be commercially viable nanocomposites, not as-manufactured, "pristine" materials.
- **Consumer:** Research shows that consumers are unlikely to be exposed to pristine ENMs, because what is released from NEPs is often a mixture of ENMs and other product ingredients. For food, food contact, and personal care products, systemic consumer exposure to ENMs is dependent on the ability of ENMs to cross barriers (translocation). Workshop presentations implied that translocation is so slow that exposure is anticipated to be low over the lifetime that a given product is used by consumers.
- **Environment:** Actual environmental exposures are often quite low, and artifacts can occur for some NMs due to their dissolution over the course of sampling. Current methods can detect these low levels, which are often well below known toxicity levels and beneath the threshold of sensible regulatory action.
- Overall, evaluating an instrument's signal-to-noise ratio and the method's limit of quantification is important when assessing analytical measurements. Quantification methods need to be validated and measurements compared among several methods or lines of evidence.

Measuring and Modeling Exposure in Various Media and Pathways

- Throughout the ENM life cycle, human biological intake has been shown to occur mainly though inhalation, ingestion, dermal contact, puncture wounds, and eye contact. Along a product's life cycle, this exposure could occur during: (1) material production, (2) product formulation and manufacture, (3) consumer use and misuse, and (4) product end-of-life disposal.
- While there are many analytical tools available to measure the physico-chemical properties of ENMs that affect fate and exposure potential, sample preparation remains a challenge, and many methods currently in use can modify the ENMs and alter these properties. Work is needed to develop more benign sample preparation methods as well as *in situ* methods to characterize physico-chemical properties and without altering the sample.

- Distinguishing between naturally occurring or incidental NMs and ENMs of interest remains a challenge. One method of doing so involves identifying unique chemical signatures, e.g., trace impurities, which can be used to track a NM. More work is needed in this area.
- When empirical data is scarce or difficult to generalize, computational modeling is needed to determine the predicted environmental concentrations of ENMs used for risk assessment. Available models of chemical exposure are not directly applicable to ENMs since nanoparticles act differently than the gaseous and dissolved chemicals for which the models were designed.

Exposure Quantification Studies by Medium or Pathway

- **Gaseous Media:** Quantification of airborne ENMs should consider the characterization, source, and physical and chemical stability of an aerosol with time and account for background exposure levels. Equipment is available for both real-time and time-integrated area sampling. Sampling in the personal breathing zone (PBZ) is the most relevant location for sampling, and portable PBZ samplers are under development.
- **Aqueous Media:** For aqueous systems, current research shows that more studies are needed on complex, realistic matrices and exposure scenarios (e.g., milk vs. deionized water). Significant advances in analytical methods have helped illuminate how NMs agglomerate, settle, and transform in aqueous media.
- **Biological Media:** Factors unique to biological media complicate the measurement and characterization of NMs, including difficulty distinguishing exogenous NMs from normal tissues and the localization of sparsely distributed materials in organisms. Increased availability, operability, and affordability are needed for many techniques, but accurate quantitative measurement of NMs in biological media is increasingly possible.
- **Exposure-Health Interface:** To link an ENM to actual disease, epidemiologists must first verify that exposure is likely, then use toxicology to prioritize which ENMs to investigate with cohort and cross-sectional studies. Many candidates are chosen by analogy based on data that links known respirable pollutants with health effects. One area the community could focus on is the complex issue of determining biomarkers of exposure linked to disease.

1. Introduction

Treye A. Thomas, PhD
Chemical Hazards Program Lead, U.S. Consumer Product Safety Commission (CPSC)

The successful commercialization of nanotechnology involves adequately addressing the potential environmental, health, and safety (EHS) implications of this rapidly growing and evolving technology. The 2011 White House *Memorandum for the Heads of Executive Departments and Agencies: Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials* [*1*] outlined the responsibilities of Federal agencies to use the best available science in a risk-based approach to understanding the potential EHS implications of nanomaterials. This risk-based approach includes understanding exposure along with potential hazards across the life cycle of nanotechnology-enabled products (NEPs) (Figure 1.1 [*2*]). In the 2011 NNI EHS Research Strategy [*2*], the U.S. Federal agencies participating in the National Nanotechnology Initiative (NNI), with significant input from the stakeholder community, identified key research areas and data gaps that must be addressed to understand and manage the potential implications of nanomaterials across the life cycle. Exposure assessment was identified as one of the core research needs, and the data developed from exposure science studies are critical for informed risk analysis and risk management decisions.

Over the past several years, Federal agencies involved in the development and regulation of engineered nanomaterials have supported a wide range of EHS research activities including *in vivo* and *in vitro* toxicity studies, analytical methods development (metrology), and exposure assessment studies across the life cycle of engineered nanomaterials (ENMs). The NNI 2014 EHS strategy progress review [*3*] outlines some of the research efforts conducted and supported by Federal agencies, including hazard and exposure assessment, and shows how Federal agencies and researchers are addressing identified research gaps. Now, it is vital to understand the state of exposure science and assess what is understood because of these research activities. Specifically, it is important to know how far the nanotechnology EHS research community has progressed in developing the tools and methods needed to understand nanomaterial releases into the environment, and to characterize and quantify exposures to receptors across the ENM life cycle, including workers and the general public. Additionally, is it important to assess how well

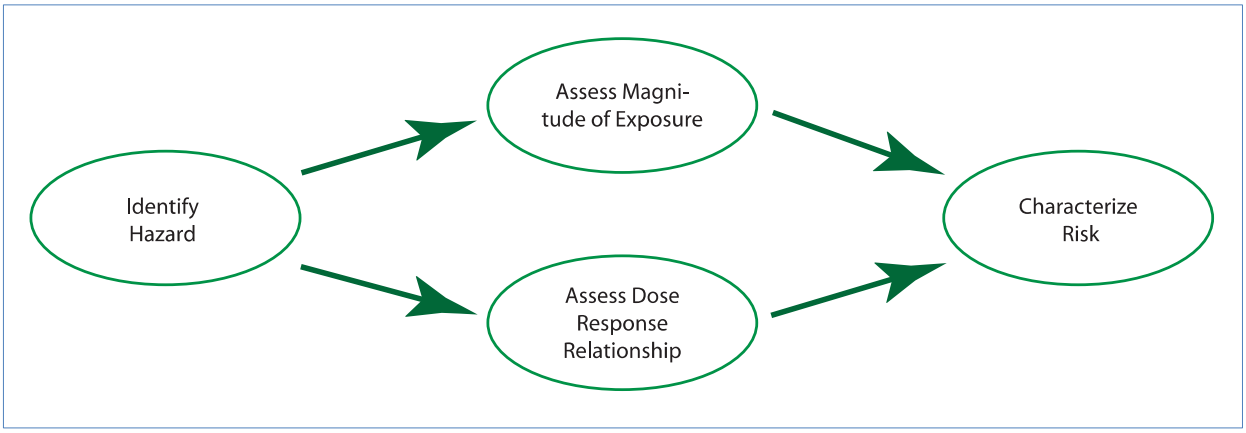

Figure 1.1. Risk assessment process. The risk assessment process is often defined as a mathematical equation, Risk equals Hazard times Exposure, or R = H x E, and indicates that the magnitude of the risk is equal to the magnitude of the hazard measurement (dose-response) made for a material multiplied by the magnitude of the exposure. (Source: U.S. EPA.)

understood the relationship is between exposure to an engineered nanomaterial, the available toxicological data on that material, the uptake by a receptor, and the resulting potential health impacts.

The Federal agencies participating in the NNI, including the CPSC, recognized the need for a workshop to facilitate interaction and dialog between researchers and stakeholders, and collaborated to provide planning and support for an exposure science workshop. The *Quantifying Exposure to Engineered Nanomaterials from Manufactured Products – Addressing Environmental, Health, and Safety Implications* Workshop ("QEEN Workshop"), was a two-day event that brought together a wide range of stakeholders including manufacturers, regulators, academic researchers, nongovernmental organizations, and graduate students to share information on the "state of the science" for exposure research across the ENM life cycle. In the morning session of both days of the conference, over 150 attendees, in addition to nearly 100 webcast participants, were addressed by some of the top researchers in this field from the United States and the European Union. The morning plenary session speakers provided a broad understanding of exposure science, its importance in nanotechnology EHS work, specific research studies conducted across the ENM life cycle, and their results and conclusions. The afternoon concurrent sessions on day one focused on research in a particular phase of the life cycle and addressed occupational, consumer, and environmental exposure assessment studies. The concurrent sessions on day 2 were organized by medium, including gaseous and aqueous media, biological fluids and tissues, and a session on epidemiology. Day one included a roundtable that provided an overview of exposure science in the 21st century and the implications for nanotechnology EHS research. The afternoon plenary sessions on both days provided dialogues among representatives from each concurrent session, and questions and input from the audience. Finally, a poster session allowed young scientists to display their important research to the broader exposure science community.

The following chapters in this report provide an overview of the tremendous amount of information shared at the QEEN workshop. The participants succeeded in providing excellent presentations and robust dialogues that identified the key researchers in the area and the tools and data available to be used to address the implications for nanomaterials used in manufactured products. Exposure science in the 21st century will continue to grow and evolve along with the entire field of nanotechnology. The U.S. Government agencies participating in the NNI, along with their partners in the stakeholder community, will continue to collaborate and share resources to move this important field forward, thus contributing to improving the responsible development of nanotechnology.

2. Life Cycle Considerations for Quantifying Exposure

The Application of Exposure Science to the Life Cycle of Consumer Products

Paul Westerhoff, PhD
Professor, School of Sustainable Engineering and the Built Environment, Arizona State University

Research tools and data related to assessing nanomaterial toxicity (hazard) have advanced more rapidly compared to those in the field of exposure assessment for nanomaterials (NMs). Three central questions each provide the opportunity to show the state of science: (1) who is collecting what types of data? (2) using which methods? and (3) where are gaps that the exposure community should address to assure safe development of nanotechnology-enabled products (NEPs)? Imagine two men: One is a worker claiming to be exposed to nanomaterials, feeling sick and unable to work. The other is a lawyer asking, *what diseases do nanoparticles cause in workers*? As a field, we really do not know how to help either of these men, or a potential industrial defendant, because—despite over a decade of research—it appears that nanomaterials continue to be viewed as a chemical in risk assessment paradigms such that precautions against exposure are largely not specific to nanotechnology.

This section summarizes what the existing exposure science is saying about where data gaps and research needs exist. A major conclusion is that human NM exposure models and scenarios have been developed and validated, and—whereas we have reams of *in vitro* toxicity data—we need better data on NM biodistribution, bioavailability, and bioaccumulation in humans exposed to NMs via different routes.

What is the State of the Science in Exposure to Nanomaterials?

Analysis of publications in the Web of Science since 1995 shows a rising trend in publication titles containing the term "nano," but fewer publication titles with "exposure" (n=1375) than with "toxic*" (n=5,270), and far fewer containing the terms "risk" (n=576) or "epidem*" (n=16). The lack of epidemiological studies is important, especially since the studies found in this search were focused on workers, with none on consumers. Considerable uncertainty exists around workplace and/or consumer exposure because NEPs only began to be commercialized in the 1990s. This young market results in varying projections of the marketplace direction with insufficient information about which types of products may cause potential workplace or consumer exposure to "free" nanomaterials.

This author provides an assessment (i.e., letter grades[1]) for progress made on the five research needs for Human Exposure Assessment research category in the 2008 NNI EHS Research Strategy [*4*] and the four stated requirements to achieve progress in this research category from the 2011 update of those research needs [*2*]. *Research needs from the 2008 NNI report*: Characterize exposure among workers (grade C-); Identify population groups and environments exposed to engineered nanomaterials (ENMs) (grade C); Characterize exposure to the general population from industrial processes and industrial and consumer products containing ENMs (grade D); Characterize health of exposed populations and environments (grade D); Understand workplace processes and factors that can determine exposure to ENMs (grade A). *Requirements for progress from the 2011 NNI update*: Develop methods or approaches to identify sources,

[1] These grades are based upon the author's preliminary review of the literature, primarily the number of publications in a given area, and are not the result of an extensive analysis of research progress in each of these areas.

characterize exposure scenarios, and measure actual exposure to NMs (grade B-); Collect data and information on the life cycle and variables affecting exposure to NMs (grade C+); Collect data and develop databases for health surveillance and exposure to NMs (grade D); Develop models to estimate exposures to specific NMs (grade D). These grades were assigned, mostly related to definitions, dosimetry, measurement methods, and type of nanomaterials selected for research focus.

What Data and Methods are Available for Releases from Products across the Life Cycle?

Concerning global trends in nanomaterial production, the "Big 10"—the ten highest volume production nanomaterials used in commerce—are important for both workplace and consumer exposures. In order of production volumes taken from peer-reviewed papers, these materials are silicon dioxide (SiO_2), titanium dioxide (TiO_2), iron (Fe), aluminum oxide (Al_2O_3), zinc oxide (ZnO), silver (Ag), copper (Cu), ceria (CeO_2), carbon nanotubes (CNTs), and nanoclays [*5*]. These materials have data related to use, release rates, and analytical methods for nanomaterials from the point of synthesis through incorporation into products in the workplace, consumer product use, and end of life (landfills, incineration, recycling). A proposed framework for binning nanomaterials for categorization spans two dimensions, as listed below. Examples of four groups of products that fit into this binning approach are presented in Figure 2.1.

1. **"Freely dispersed" versus "embedded" nanomaterials:** "Freely dispersed" nanomaterials include those used in polishing agents or foods, compared to nanomaterials "embedded" in substrates such as NMs on fabrics or NMs in polymeric coatings or objects.
2. **"Reactive" versus "passive" nanomaterials:** Nanomaterials that are more "reactive" are those that undergo dissolution or are photosensitive, versus those that are generally more passive or nonreactive (e.g., silica).

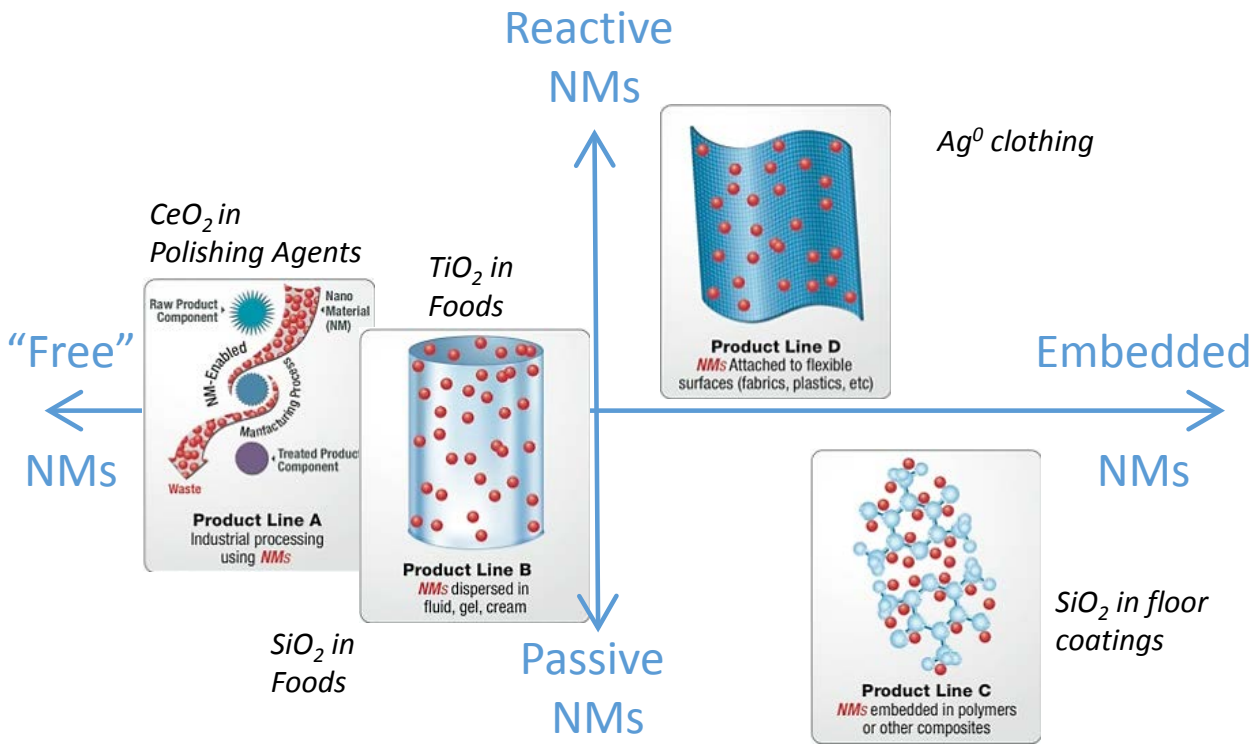

Figure 2.1. A proposed framework for binning nanomaterials. The framework organizes nanomaterials along two dimensions: (1) whether they are active or passive, and (2) whether they are freely dispersed or embedded. (Source: P. Westerhoff.)

What Tools are Being Used to Detect and Quantify Nanomaterial Exposures?

Both analytical and modeling tools are being used to estimate and assess nanomaterial exposures across the product life cycle. The complexity of nanomaterial detection and quantification increases across the life cycle of products and after human contact. This increase is because nanomaterials in stock solutions are fairly homogeneous, free of interferents, and at relatively high concentrations compared to finalized products. As nanomaterials are incorporated into products they may be from 0.1 to 5 % by weight of a product (e.g., CNTs in polymers [*6*]) down to as low as < 0.01% by weight (e.g., TiO_2 in foods [*7*]), and even lower in some consumer products (e.g., 1.5 mg of quantum dots per television [*8*]). Not only do low concentrations hinder detection, but also, the nanomaterials are often enmeshed in heterogeneous and complex matrices of similar elemental composition (e.g., carbon nanotubes in carbon-based polymers).

A number of adaptations to available, non-nanotechnology-specific techniques hold promise for nanoparticles. In pure solutions, simple light scattering detection systems are appropriate at > 1 mg/L in liquids. Advancements to inductively coupled plasma mass spectroscopy (ICP-MS) or time-of-flight mass spectrometry (TOF-MS) software, while using the same equipment hardware, are allowing collection of data for some nanomaterials containing metals when processed in "single-particle" mode. This adaptation allows for counting and sizing of nanomaterials at very low concentrations on the order of parts per trillion. However, this sensitivity is highly dependent upon the element (well-detected elements are silver, gold, cerium, and indium, but not titanium or silicon), and more elegant data processing holds some promise. Even minute quantities of rare earth elements (e.g., yttrium or cobalt in CNTs) hold promise for advancing these detection methods. Other methods developed for monitoring soot in the air have been adapted for CNTs.

Methods to extract, separate, and/or concentrate nanomaterials from complex matrices are under development and hold promise to separate various forms of nanomaterials (e.g., to separate ionic and nanoscale forms of metals). While electron microscopy remains the "gold standard," there are really no methods to answer the simple question, "How many nanomaterials are in a product?" (for example, a computer), especially when information from the manufacturer is not available.

A potential strategy is to combine the availability of the analytical techniques with a tiered sampling approach, but this approach hinges upon having acceptable detection limits. Detecting ENMs among natural and/or incidental NMs with many times higher relative concentrations is challenging. It is also very difficult, and usually extremely expensive due to required access to specialized equipment, to track transformations in nanomaterial properties effectively over time or through the life cycle of a product. This challenge includes tracking transformations during human exposure (dermal, oral, or inhalation). Outside of biomedical drug delivery systems, few human studies track NM biodistribution, bioavailability, or bioaccumulation, or adverse outcomes from nanomaterials released from consumer products.

Occupational Exposure: Current State, Challenges, and Future Research

Charles L. Geraci, PhD, CIH
Associate Director for Nanotechnology, National Institute for Occupational Safety and Health

The introduction of engineered nanomaterials into commercial material applications continues at a rapid pace, despite the overall evolution of the technology now having moved from the initial "excitement stage" to a phase driven by more realistic market forces. High-volume manufacture and formulation of "first-generation" nanomaterials, such as nanoscale titania and ceria, continues globally. Refinement and improvement of manufacturing processes for more sophisticated and promise-filled nanomaterials, such as carbon nanotubes and graphene, are being reported almost daily. All of these indicators point to increasing

volumes of engineered nanomaterials being manufactured and an even greater number of product applications for these materials. The petrochemical industry, for instance, will be using increasing quantities of nanoscale catalysts. One of the natural outcomes of this continued rise in volumes and product applications is concern for human health and environmental damage. Whether in a research laboratory, a manufacturing facility, as part of a commercial task, or in the reuse or recycling of these materials, there are workers involved. At nearly every step along the life cycle of an engineered nanomaterial and the products that contain them, there is potential for workers to be exposed. Evaluating worker exposure, characterizing potential risks, and implementing effective controls to eliminate or minimize risk are all critical to ensuring responsible development of the technology because workers represent the first opportunity for human exposure to any new technology or the materials it produces. Often, the materials may not be completely characterized and their potential hazards not fully understood. In many ways, creating an effective worker health and safety program for a new technology or material is the first step in building a legacy of success for responsible development, sustainability, and stewardship.

To evaluate the potential risk of engineered nanomaterials in any occupational setting, it is extremely important to develop effective exposure assessment science that focuses on properties that are characteristic, if not unique, to this class of materials. Such an approach links toxicology, risk assessment, and epidemiology to create a complete picture of the potential risks and impacts. Hazard information is being generated at a rapid pace for many nanomaterials from toxicological studies. The rise of hazard data and efforts to derive occupational exposure limits (OELs) has accelerated efforts to evaluate occupational exposures. Despite progress in recent years in measurement techniques for nanomaterials, there remains much uncertainty as to the appropriate exposure metrics to use. The growing number of dose metrics proposed for toxicology evaluations, especially for inhalation studies with inhalation being the primary workplace exposure pathway, compounds this uncertainty. While metrics such as particle number, surface area, and surface charge are being explored as more advanced approaches to measure dose and exposure, mass continues to be the primary metric used in reporting results from toxicology studies. The heterogeneity of nanomaterials also complicates formulating exposure assessment strategies. Using multiple sampling, analytical, and instrumental approaches has become widespread among industrial hygiene practitioners, but methods that are more rugged are still needed. This need is particularly important for complex exposure scenarios such as mixed manufacturing facilities and construction sites. The importance of occupational exposure levels, like the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits for titanium dioxide and carbon nanotubes, cannot be overstated as benchmarks for evaluating exposure assessment results.

Several groups around the globe have proposed various workplace-exposure assessment strategies. Employing a multi-metric and tiered or phased approach has become one of the more effective approaches. A basic challenge continues to be potential differences between materials as measured in the workplace compared to the seemingly same materials when evaluated in toxicology studies. Efforts are underway in several research institutes to close the gap between nanomaterials encountered in the workplace or the environment and those that are evaluated in their pure (pristine) or as-manufactured state. These efforts are aimed at making the toxicology evaluations more representative of what is encountered in an actual exposure scenario. This area of research will improve workplace exposure science by linking the efforts of toxicology, exposure measurement, and epidemiology. By creating a feedback process from exposure measurements to toxicology studies, dose metrics and test materials will become more representative and risk characterizations more realistic. Combining health outcome studies into the overall strategy will

incorporate the use of biological indicators such as biomarkers for a more complete picture of the actual exposure experience. The critical challenge is to identify meaningful biomarkers.

Finally, the potential release of engineered nanomaterials from intermediate or finished products has become a growing concern. Research is underway by several groups to evaluate the overall potential for exposure to engineered nanomaterials along their complete life cycle. While the biological significance of these materials in any sort of release in not known, a prudent approach is to characterize the potential for release and explore methods to minimize or control releases. NIOSH has demonstrated that engineering controls are effective in reducing exposure to nanomaterials [*9*–*11*]. Older, proven control technologies must be considered, but new thinking is critical as well.

Health Risk Driven Exposure Assessment for Consumers during the Life Cycle of Nanomaterial-Containing Products

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The number of consumer products containing engineered nanomaterials has increased 5–10 times over the last 5 years, among which titanium, silver, and carbon-based ENMs are the predominant materials employed [*12*]. This increase may affect consumers' exposure to ENMs and associated chemicals along the life cycle of these consumer products. ENMs can be found in sporting goods, appliances, home and garden wares, medicinal products, electronics and computers, food and beverages, children's toys, clothing, and personal care products [*12*], thereby implying potential exposures via all of the three major exposure routes of inhalation, ingestion, and dermal contact. Studies have been reported in the literature that use multiple approaches to assess consumer exposure within the context of human health risk assessment.

Deriving Exposure from Consumer Product Data and Exposure Scenarios

A key component of this approach to exposure assessment is characterization of the consumer product for ENM contents. For example, a tiered approach has been used to characterize silver nanoparticles in selected consumer products relevant to children's potential exposure [*13*]. The approach first identifies all consumer products relevant to the defined exposure. Second, a select subset of the products is identified as having high exposure potential. The final step is to measure the content and form of silver in this subset of products. The analytical method commonly used to determine metal content in consumer products has been ICP-MS; the methods for determining physical forms of ENMs are scanning electron microscopy (SEM) and transmission electron microscopy (TEM). New technologies like surface-enhanced Roman spectroscopy (SERS) have also been explored for the characterization of nanoparticles in consumer products [*14*]. Since exposure is more closely related to the level of ENMs released from consumer products than the ENM's content, studies have been conducted to determine ENM release to the ambient air or to a relevant body organ (e.g., skin surface). Among these studies, experiments using a chamber with a well-controlled ventilation system in which spraying actions mimic consumer practices provide both release rate and physico-chemical properties of ENMs [*15*, *16*]. For example, through characterizing the materials released during spraying of cosmetic powders, Nazarenko *et al.* found that a user would be exposed to nanomaterials predominantly through nanoparticle-containing agglomerates larger than the 1–100 nm size fraction of aerosols [*17*]. These agglomerated particles are different in size compared to the nanomaterials originally added to the products, resulting in deposition in a different region of the respiratory tract.

Estimating Population Exposures to ENMs

Data on ENM exposure distribution across the general population and subpopulations are important for estimating health risks at the population level. A recent study estimated population exposures to silver nanoparticles present in consumer products and found that among the different age groups, children have higher exposures per unit body mass [*18*]. Similarly, another recent study has found that in the United States, children have a higher body-weight-adjusted exposure to titanium dioxide nanoparticles from food and personal care products than adults [*7*].

Assessing Bioavailability of ENMs

Health effects of ENMs largely depend on the bioavailability of ENMs to the receptor. Therefore, the amount of ENM that can be released and become available to consumers is an important determinant for potential health effects. Since the amount and the rate of release depends on the biological media via which people have contact with consumer products, a recent study investigated the release of silver from nanotechnology-based consumer products for children into urine, sweat, saliva, and dermal wipes. The study found that silver release from the interior of a plush toy (compared to a baby blanket and the exterior of the plush toy) is the highest in sweat or urine [*19*]. This study points to the importance of understanding the details associated with human contact with consumer products (e.g., how urine and other biological media can get into certain baby products). Another recent study examined the bioavailability of silver from a medical garment intended for use in the treatment of atopic dermatitis on the skin. In this study a new technique was developed to assess "in use" exposure to silver concentrations at different depths of the skin (stratum corneum), and found silver concentrations were a function of exposure duration and stratum corneum depth [*20*]. Because a large variety of consumer products are intended for various applications, use-specific bioavailability studies are needed to understand the potential for consumer exposure.

Measuring Health-Relevant Exposure

At the point of contact, consumers may be exposed to materials that are different from the as-manufactured ENMs initially added to a product. Exposure to "final" materials determines health effects. A recent study has demonstrated this point by comparing the toxicity of both the whole extract (leachate) from nanosilver-coated socks ("sock-AgNPs") and silver nanoparticles removed from that leachate by centrifugation ("spun-AgNPs") to ionic silver (0.80 g mL^{-1} $AgNO_3$) [*21*]. Results suggest that both the whole extract and the extracted silver nanoparticles are more toxic to zebrafish embryos compared to ionic silver. These results are in disagreement with previous studies that have consistently shown that silver nanoparticles are less toxic compared to silver ions [*22*–*28*]. This difference may be because earlier studies have tested as-manufactured silver nanoparticles versus the silver nanoparticles derived from a commercial textile product in the sock study. This study exemplifies how silver nanoparticle toxicity may be enhanced by other elements or compounds added during the manufacturing process of the socks, rather than the AgNPs alone [*21*]. Hence, it is critical to measure consumer exposures to what they are actually exposed to in the product context. Evaluating potential health effects within the context of the actual exposure scenario is necessary to assess accurately any health risks associated with nanomaterial-containing products.

Ecological Exposure: Review of the State of the Science

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As a starting point for an environmental exposure assessment, exploring sources and pathways of release helps to identify relevant applications and situations where the environment may face exposure to ENMs. By tracking stages along the life cycle of products, it is possible to explore whether and in which situations a release of ENMs from applications may occur. There are currently a number of uncertainties with respect to the behavior, the chemical and biological interactions, and the toxicological properties of ENMs. Investigators should consider the whole life cycle of NEPs to ensure that possible impacts can be systematically discovered [*29*]. The life cycles of ENMs are determined by their application within NEPs. Therefore, the exposure scenarios and potential adverse effects—as well as opportunities for novel applications—are strongly dependent on the life cycle of NEPs that contain ENMs. Depending on the aim of the study, an appropriate life cycle method and scope have to be chosen. Most of the methods either consider all stages of an NEP life cycle or focus on specific parts of the life cycle. Some methods focus on the environmental health effects of ENMs only, whereas some methods, like Life Cycle Assessment (LCA), focus on environmental health impacts of all other materials in an NEP, as well as on environmental sustainability effects such as energy and material consumption.

Material Flow Modeling

Using material flow analysis (MFA) and environmental fate modeling (EFM) as a basis, we can quantitatively identify the determining steps in the life cycle of NEPs that result in release to the environment [*30*, *31*]. With MFA, it is possible to quantify the flow of ENMs from production to manufacturing to use, through the end of life. Within this assessment, two critical points with currently limited data are knowledge about (1) the production amounts of ENMs and (2) the distribution of ENMs into different product categories. Using simple box models, it is possible to transform the material flows into environmental concentrations assuming well-mixed compartments (soil, sediment, suspended matter) according to established procedures [*32*]. The first EFM approaches have been developed for ENMs that take the input flows from an MFA and model with a mechanistic description the fate and behavior of the ENMs in the environment (e.g., agglomeration, heteroagglomeration, or dissolution) [*33*, *34*].

Release to the Environment

A crucial step in the flow assessment of ENMs is to examine their release from actual products to the environment. This process has only been studied to a limited extent, often not in a way that quantitative data for release modeling can be obtained. Release studies not only need to quantify the amount released, but also characterize the released materials. Depending on the starting materials, only a certain fraction of the released materials may actually be in their original form or remain within the nanoscale size range [*35*]. In addition, transformation reactions during use and weathering can significantly alter the form and identity of the ENMs [*36*]. In present MFA models, the limited, currently available release data form the basis for the parameterization of release, resulting in transfer factors from products to environmental or technical compartments with a high degree of uncertainty.

Environmental Exposure

Presently, about a dozen modeling studies provide environmental concentrations for ENMs [*31*]. There are still major knowledge gaps (e.g., on ENM production, application, and release) that affect the modeled values, but overall, an agreement can be reached on the order of magnitude of the environmental concentrations. True validation of the modeled values is difficult because analytical methods appropriate for trace amounts and that are specific for ENM detection and quantification are not available. Additionally, the modeled and measured results are not always comparable due to the different forms and sizes of particles that these two approaches target. The most comprehensive data about environmental exposure have been published by Sun *et al.* [*37*] using a probabilistic MFA model that is able to fully consider the uncertainty and variability in many model parameters. Other recent studies include an exposure assessment for ten nanomaterials performed by Keller and coworkers [*5*, *38*].

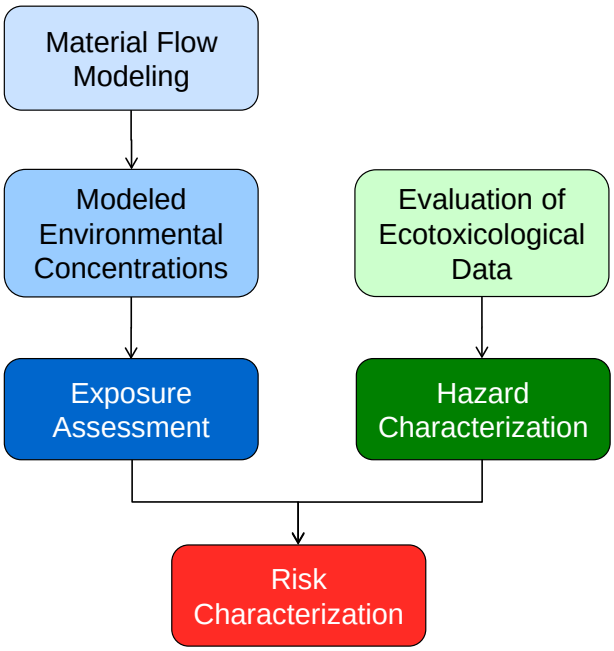

Figure 2.2. Risk characterization of engineered nanomaterials. Characterization of risk can be achieved with a combination of exposure assessment from modeling and the evaluation of ecotoxicological data. (Source: B. Nowack.)

Environmental Risk Assessment

The results from modeling of exposures (predicted environmental concentrations, PECs) can be linked to modeling of the environmental effects of ENMs (predicted no-effect concentrations, PNECs) to derive the first environmental risk assessments for ENMs (Figure 2.2). The probabilistic MFA is very well suited for this task because it can be combined with a probabilistic effect assessment based on species sensitivity distributions [*39*]. A first such probabilistic risk assessment was published for five ENMs by Gottschalk *et al.* in 2013 [*40*], followed by an update in 2015 by Coll *et al.* [*41*]. For most materials and environmental compartments, exposure and effect concentrations were separated by several orders of magnitude. Nano-ZnO in freshwaters and nano-TiO_2 in soils were the two combinations of factors where the risk characterization ratio was closest to one. This result means that these ENM/compartment combinations should be studied in more depth with the highest priority. The probabilistic risk quantification allows considering the large variability of observed effects in different ecotoxicological studies along with the uncertainty in modeled exposure concentrations. These first risk characterization results for ENMs allow for a more focused investigation of environmental risks of nanomaterials by consideration of material/compartment combinations where the highest probability for effects with predicted environmental concentrations is likely.

Linking Life Cycle-Specific Exposures to Biological Impact of Nanomaterials

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Recent evidence and historic data demonstrate the potential for ENMs to elicit adverse biological and environmental effects [*42–44*]. The potential of engineered nanoparticles and nanofibers to translocate across biological barriers to reach pulmonary connective tissues, lymphatics, or the circulatory system to reach other organs is of concern [*45*]. Nanoparticles may enter cells and be more biologically active than their larger counterparts due to their small size and large surface-to-volume ratio [*46–50*]. A nanotechnology environmental, health, and safety (nanoEHS) strategy that focuses only on as-manufactured ENMs may address health implications in occupational settings but is not appropriate to address potential adverse health effects associated with possible particulate matter (PM) released across the life cycle of NEPs (such released particles are called LCPM). Evidence indicates that the physico-chemical properties and toxicological profiles of LCPM may differ greatly from those of as-manufactured ENMs [*51–53*]. This important point has been emphasized in both a National Research Council report [*54*], as well as in the National Nanotechnology Initiative's strategy on nanoEHS [*2*]. This life cycle-specific exposure and toxicological data gap constitutes a major roadblock for risk assessors and regulators and presents a challenge to the sustainable development of nanotechnology-based industries.

Understanding both the life cycle stage-specific release and the exposure scenarios for categories of NEPs is needed for relevant science-based risk assessment. Therefore, developing new standard methodologies and tools at the interface of exposure science and toxicology will assist in assessing potential LCPM risks. For example, the sampling, extraction, dispersion, and dosimetry (SEDD) methodology developed by Pal *et al.* (Figure 2.3, [*55*]) can be employed across the exposure–toxicological characterization continuum of NEPs for risk assessment of LCPMs released in the air across the life cycle. In Step 1 of the SEDD methodology, exposure generation systems are developed suitable to generate "real-world" LCPM exposure atmospheres. LCPM properties are monitored using both real-time and time-integrated instrumentation. Physico-chemical and morphological characterization of size-fractionated sampled LCPMs can be determined to understand inherent properties, which may influence biological activity. The size-fractionated LCPMs can then be extracted and recovered in Step 2. Proper colloidal characterization of the LCPMs is essential; thus, Step 3 involves dispersion and evaluation of LCPM behavior, such as size distribution, along with crucial parameters such as the effective density of formed agglomerates in physiological media. *In vivo* and *in vitro* dosimetric considerations of the LCPM are also considered using recently developed computational tools such as multiple-path particle dosimetry (MPPD) and the Harvard volumetric centrifugation method *in vitro* sedimentation, diffusion, and dosimetry models (VCM-ISDD) (Step 4). Toxicological outcomes of exposure to the generated LCPMs, determination of dose response, and investigation of mechanistic pathways can be explored in Step 5.

Overall, such an integrated methodology needs to include (1) development of standard exposure platforms to assess release dynamics and characterization of LCPM for families of NEPs, and (2) development of multi-tiered toxicological screening methods suitable for the complexity of LCPM to include dosimetric considerations. It is worth noting that current cellular methods used in screening of as-manufactured ENMs may not be appropriate to be used for complex mixtures of particles and gaseous co-pollutants. The toxicology of a complex mixture is complicated, and apportioning the nanofiller effect will bring an extra layer of complexity. However, there are tools developed for ambient particle toxicology research that can be adopted and utilized to address those issues.

Revisiting the current risk assessment paradigm to include comprehensive life cycle stage-specific toxicological and exposure characterization, and developing all necessary tools and approaches to enable comprehensive risk assessment are of paramount importance for the nanoEHS field. These advances will help in reducing the uncertainty surrounding ENMs.

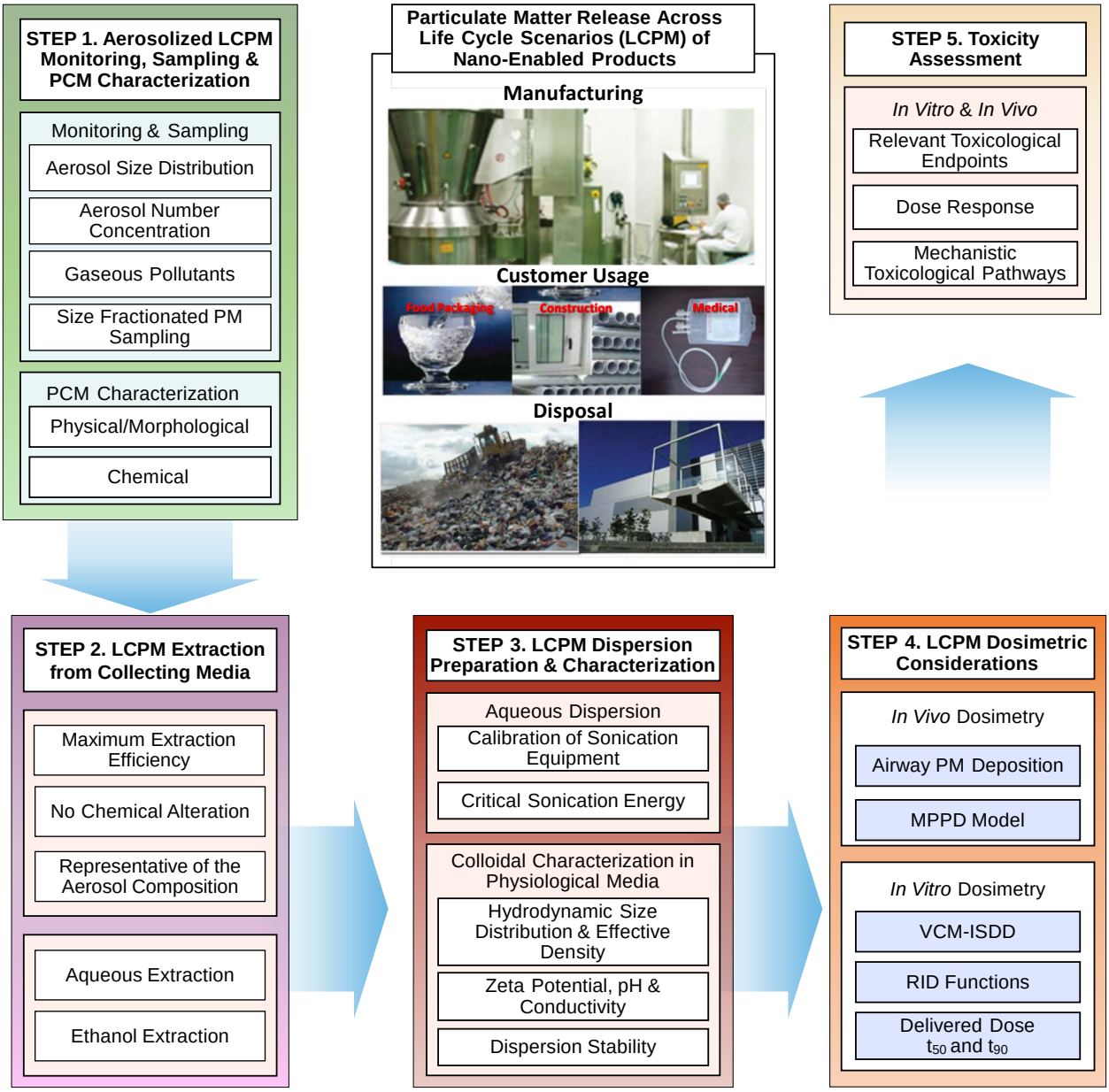

Figure 2.3. Sampling, extraction, dispersion, and dosimetry (SEDD) methodology for toxicity assessment of particulate matter released across the life cycle of NEPs (LCPM). PM: particulate matter; PCM: physico-chemical and morphological; MPPD: multiple-path particle dosimetry; VCM-ISDD: Harvard volumetric centrifugation method *in vitro* sedimentation, diffusion, and dosimetry models; RID: relevant *in vitro* dose. (Source: Pal *et al.*, Linking exposures of particles released from nano-enabled products to toxicology: An integrated methodology for particle sampling, extraction, dispersion and dosing. *Toxicol. Sci.* 146, 321–333 (2015) [*53*], by permission of Oxford University Press.)

3. Exposure Quantification Studies by Receptor Population along the Product Life Cycle

Worker Exposure Studies

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The literature on worker exposure is limited but growing in size and pertinence. Initially, the focus of research was on exposures to workers handling raw, as-manufactured nanomaterials in laboratories and small production facilities. Research in Europe and the United States has more recently been focused on potential exposures to workers handling products after the nanomaterials are incorporated into matrices such as polymers, coatings, and cementitious products [*56*]. A major review of 54 studies on release of nanomaterials from solid nanocomposites along the life cycle from drilling and sanding to eventual shredding, incineration, and composting provided a broad foundation for this workshop session [*57*, *35*]. There are several methods for measuring releases from nanocomposites [*58*]. For carbon nanotubes (CNTs) and carbon nanofibers (CNFs), new NIOSH findings from a range of workplaces add important exposure data [*59*]. There is an innovative thermophoretic personal sampler for collecting airborne nanoparticles on a grid for direct analysis by transmission electron microscopy [*60*]. The technology promises to reduce the number of overloaded filters during sampling, which has meant voided samples in the past.

Potential worker exposure during manufacture of nanotechnology-enabled products (NEPs) remains poorly understood. The overwhelming majority of peer-reviewed papers deal with hazards, not exposures. The data from 54 studies investigating release from manufactured nanocomposites containing a variety of nanomaterials (primarily CNTs, TiO_2, and SiO_2) were difficult to interpret and compare. There was a dearth of experimental studies; across the remaining studies, methods and materials diverged widely. The review revealed a major research need for rigorous validation of methods used to induce release from nanocomposites. Additionally, the test materials need to be commercially viable nanocomposites, not the novel, lab-made materials used in many of the studies. Given these caveats, the review showed that ultrafine particles of the matrix were released under all of the release scenarios, but only occasionally did researchers actually see nanomaterials fully dissociated from the matrix.

Currently available data suggest that when manufacturers follow good industrial practices, worker exposure to carbon-based nanomaterials can be minimized to safe exposure levels. NIOSH has set a recommended exposure level (REL) for CNTs and CNFs of 1 $\mu g/m^3$ as an 8-hour time-weighted average (TWA) of elemental carbon (EC) for the respirable size fraction. Recently, the NIOSH Nanotechnology Field Studies team published an industry-wide exposure assessment among U.S. CNT and CNF manufacturers and users [*61*]. They concluded that elemental carbon mass exposures are detectable and reliable, and

the background-corrected data showed that 96% of respirable samples were below the REL. Inhalable samples have had a higher percentage that exceeded the REL, but NIOSH does not presently have an occupational exposure level for the inhalable portion. A life cycle analysis of CNT composites [*62*] came to the same conclusion as the meta-analysis that, in general, individual CNTs rarely come out of the matrix material when subjected to a variety of processes that could cause release (i.e., sawing, cutting, drilling, or weatherization). The researchers did report generation of airborne clusters of CNTs not observed during saw-cutting of similar composites. Even though individual CNTs were not being released from the composites, aggressive mechanical actions were generating high exposures to nanoparticles of the matrix. Thermal degradation of the composite similarly generated ultrafine aerosols of less than 5 nanometers.

Common Themes from the Concurrent Session Presentations and Discussions

Exposure controls should be initiated during synthesis and processing of CNT nanocomposites. The nanotoxicology community should focus on actual exposures along the nanomaterial life cycle, mixtures of chemistries, and exposures of nanomaterials at doses relevant to human health. Most of the worker exposure occurs when CNTs are harvested from the reactor and then processed into the nanocomposite. However, the NIOSH Field Team's experience suggests that CNTs and CNFs can migrate from the production floor throughout the facility by hand or glove contact with doors and surfaces. This transmission could indirectly expose workers to CNTs and CNFs. Because of the variety of nanomaterials and matrices, it would be good to develop several standard reference materials for the most common realistic nanocomposites and perform a standard series of tests to develop release data that can be used for comparisons. There have not been any exposure studies of nanocellulosic structures.

We are in a new paradigm about rolling out an innovative technology, and we want to do it right, including for workers, who are the first to experience exposure. Will we be able to make predictions from worker exposure data? Have we chosen the proper metrics? If so, is there an issue with the sampling and analytical technology catching up with new materials to provide better measurements? Do we know enough about the potency of materials to set a baseline or floor or even to take some nanoparticles out of consideration from a toxicological basis? The next horizon in toxicological measurements may involve simultaneously collecting materials for the toxicological studies while conducting exposure studies.

Clearly, more work is needed to relate test scenarios to real-world conditions and to establish what, if any, differences exist in the release dynamics between nanocomposites and conventional composites. Research is also needed to better characterize the relationship between released nanomaterial detection and dosage of toxicological significance.

Consumer Exposure Studies I: General Products

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Although it is relatively straightforward to assess release from consumer products for the worst-case scenario (in which all engineered nanomaterials [ENMs] contained in the product are released) and for the best-case scenario (in which none of the ENMs are released), a realistic and environmentally relevant exposure assessment is much more challenging. This challenge arises because it requires scientists to consider the entire life cycle of products and their individual expected usage scenarios. A comprehensive

consumer exposure assessment should consider realistic use scenarios, including the reasonable worst case scenarios, along with other factors such as potential matrix effects as well as the length of exposure time and environmentally dependent material transformations [*63*]. The complexity of a product life cycle-based assessment demands a tiered approach where qualitative evaluation of the associated material hazards, exposure potential, and toxicity are used to determine the initial risk, which can be subsequently refined.

When dealing with consumer products, the first step in quantifying the exposure to ENMs should be to characterize the intact products to confirm that ENMs are indeed present, and to characterize the ENMs within the product in terms of the following:

- Composition.
- Size and shape.
- Where they are located.
- How much ENM is present (mass and, if possible, number concentration).
- How they are dispersed or attached to the product matrix.

It should be noted that characterization of the material surrounding the ENM (the product matrix) is also needed at this stage because the properties of both the ENM and the matrix will influence overall product robustness and the probability of subsequent nanomaterial release. Mass spectrometry (MS) methods (inductively coupled plasma [ICP]-MS, affinity purification [AP]-MS), infrared (IR) spectroscopy methods (Fourier transform [FT]-IR, attenuated total reflectance [ATR]-IR), and optical imaging methods (Raman spectroscopy, laser scanning confocal microscopy [LSCM]) are some of the common bulk analysis techniques for detecting and analyzing nanomaterials in consumer product matrices [*64*, *65*]. These techniques are used to confirm the presence of bulk ENMs and can provide information on the physico-chemical properties of the product matrix material and supporting components of the product (e.g., protective surface coatings, or outer cover materials) that can influence overall exposure probability. Higher-resolution analytical methods are needed for the characterization of the nanomaterials themselves. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) combined with elemental analysis (energy-dispersive x-ray spectroscopy, EDXS) or chemical analysis (electron energy-loss spectroscopy, EELS) can provide individual nanoparticle properties. However, it is often difficult to determine bulk-level concentration and dispersion information based on SEM and TEM micrographs because the volume of material that can be analyzed using these techniques is extremely small. Careful statistical and uncertainty analyses should be performed before applying high-resolution analytical data for predicting bulk properties or product-level material characterization.

After the product characterization step, realistic scenarios for release and subsequent exposure must be considered for individual product types based on their intended real-world use, while also considering situations of foreseeable misuse and overuse [*13*]. Some common release mechanisms are the following [*6*]:

- Ultraviolet (UV) degradation of indoor and outdoor use products exposed to UV light such as composites, textiles, paints, and coatings.
- Leaching from food-contact materials.
- Temperature extremes in cookware.
- Mechanical stresses in sporting equipment and safety products.
- Aerosolization of personal care products and cleaning products.

The techniques most commonly used to assess ENMs after release from consumer products include all the methods discussed above for in-product characterization, in addition to single-particle detection methods such as single particle inductively coupled plasma mass spectroscopy (spICP-MS) for release into liquid media. A variety of aerosol characterization techniques are used to evaluate ENM release into air, including size-distribution (using scanning mobility particle sizers [SMPS] and aerodynamic particle sizers [APS]), surface area (using corona discharge methods), and real-time chemical analysis with aerosol mass spectrometry (AMS) instrumentation. Additionally, aerosols can be size-segregated and collected onto filters, TEM grids, or SEM stubs, which can then be used for subsequent physico-chemical characterization (using ICP-MS, Raman, TEM, SEM, etc.).

Multiple studies performed on the release of ENMs (specifically silver nanoparticles) from consumer products into biologically or environmentally relevant liquid media have shown that the chemical characteristics of the liquid media (pH, ionic strength, etc.) are very important in determining the release or dissolution of ENMs. The method used for attaching or embedding ENMs onto the surface or within the matrix of products such as fabrics and plastics also affects the extent of ENM release throughout the product life cycle [*19*, *66–68*].

UV degradation, mechanical stress, temperature extremes, and aerosolization are all possible mechanisms of ENM release into air during the use of consumer products. However, rather than consisting of primary ENMs, dry and wet aerosols released from the use of consumer products are expected to be composed of a mixture of ENMs and other product ingredients. Multiple studies on the release of aerosols from consumer products have demonstrated the release of ultrafine (or nanoscale) dry and wet aerosols [*15*, *17*, *69–73*]. Studies involving UV degradation of polymer nanocomposites and coatings have shown that the UV resistance of the matrix material often dictates the overall integrity of the composite material and the eventual ENM release rate [*74*]. However, in some cases, the accumulation of ENMs on the surface can mitigate further UV-induced degradation [*75*]. Key strategic needs for the future include (1) the development of standard methods for characterizing emissions from groups of consumer products such as sprays, powders, paints, and solid composites, not only in terms of aerosol size distribution, but also in terms of shape, chemical composition, and crystallinity, and (2) studies to determine how these characteristics may relate to potential ENM toxicity and how the product matrix affects aerosol release.

Despite continual and growing research efforts in determining the release of ENMs from consumer products, a data gap persists at the consumer stage of the product life cycle. This gap in knowledge can be addressed by applying life cycle thinking to determine exposure scenarios and prioritizing those in which higher risks to consumers and the environment are expected [*63*]. Key dimensions of ENM exposure to be considered include the material characteristics (both ENM and matrix), expected duration and magnitude of exposure, and receptor characteristics.

The current state of knowledge in ENM release from consumer products is that consumers are unlikely to be exposed to as-manufactured ENMs; therefore, nanotoxicology studies must be performed taking into consideration the physico-chemical characteristics of ENMs as they are released from consumer products under expected usage scenarios [*76*]. Studies presented so far indicate that ENM release levels are expected to be low and exposure scenarios are likely to be chronic. There is a need for a continual conversation between the exposure science and the toxicology communities to determine appropriate ENM doses, purity levels, and matrices for toxicology studies. A closer dialogue and collaboration between these two communities—as well as with the community of life cycle analysis and risk assessment researchers—would also help ensure that the data generated from release studies is transferable and useful to subsequent studies.

There is also a pressing need to establish a set of consumer product-specific quality assurance/quality control (QA/QC) safeguards to minimize errors, losses, and uncertainties. After ENMs are released, collection and analysis introduce opportunities for nanomaterial loss and therefore an inaccurate picture of exposure levels. As a result, performing a mass balance is an important step in exposure experiments.

In this session, several recent studies on the release of ENMs from consumer products were discussed, focusing on the methods and techniques that were used, the challenges associated with different types of nanomaterials and complex matrices, and how these efforts may help facilitate evaluation and adoption of new nanomaterials into both existing and novel products. Key points arising from the discussions at this session of the workshop include the following:

- Consumers are likely to be exposed to low concentrations of ENMs from multiple products.
- Consumers are not exposed to as-manufactured ENMs, because the product matrix is likely to affect ENM emissions.
- Studies should be prioritized on the release of incidental nanomaterials as compared to ENMs.
- Studies should include, when appropriate, a comparison of NEPs with alternative, non-nanotechnology-based applications (e.g., nanosilver applications versus triclosan for antimicrobial protection).
- There is a need to establish generalized release scenarios for product groups in high-throughput frameworks rather than for individual products, and for the collection of released ENMs for the purpose of toxicology studies.
- There is a pressing need for communication between exposure scientists and those working on product life cycle risk assessment and nanotoxicology to establish transferable metrics between those fields.
- Exposure scientists must use realistic release scenarios and consider the expected population(s) of concern in order to determine representative doses to be used in subsequent toxicity and life cycle assessment studies.
- Studying the exposure of consumers to ENMs is inherently challenging because products may not be labeled as containing ENMs and/or have not disclosed the processes by which the ENMs are added to their products. Some participants in this session suggested that increased labeling could significantly assist in exposure, life cycle, and toxicology studies.
- ASTM International is working on consensus methods for release studies, in direct reference to the comments made during the talks at this session of the workshop.

Consumer Exposure Studies II: Food, Food Contact, and Personal Care Products[2]

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Introduction and Scope of the Session

Because engineered nanomaterials are increasingly found in or developed for a variety of consumer products, there is a growing opportunity for consumers and the broader environment to be exposed to ENMs or their residuals. For many consumer product categories, the potential exposure is not deliberate, which adds an extra layer of uncertainty regarding the amount and form of ENM exposure. Measuring potential ENM exposure at all stages of a product's life cycle is a critical aspect of environmental, health, and safety (EHS) assessment. Therefore, there is a need to (a) explore the range of nanotechnology-enabled products that are (or may become) a concern and any unique issues associated with those products from an experimental exposure assessment standpoint, and (b) identify the experimental and theoretical toolsets available (including sample handling strategies) to measure exposure and assess their associated strengths and weaknesses. This kind of analysis has the potential to reveal areas of deficiency that should be addressed by research scientists and policymakers as the commercial development of consumer products incorporating ENMs moves forward.

During this session, some of these issues were explored specifically for consumer products involving foods, food contact materials, and personal care products. For foods, both retail and agricultural products (fresh produce) were considered [*77*, *78*]. Food contact materials discussed were primarily packaging-oriented, although other products deemed relevant included items such as cutting boards, storage containers, or flatware. Personal care products consist primarily of cosmetics, soaps/shampoos, and lotions, and may include sunscreens, many toothpastes, antiperspirants, some shampoos [*79*, *80*]. Even though the term "personal care products" has no regulatory definition, they encompass products that are regulated under the 1938 Federal Food Drug and Cosmetic (FD&C) Act [*81*] either as "cosmetics" (FD&C Act 201(i)) or as "drugs" (FD&C Act 201(g)). The distinction is based on the intended use or purpose of the product. In other words, if a product is intended to treat, mitigate, cure, diagnose, or affect the structure or function of the body it would be considered a drug rather than a cosmetic, which is intended to cleanse, beautify or make attractive.

The session's four speakers broadly represented all aspects of the scope defined above. Moreover, the session was designed to cover a breadth of stakeholder viewpoints, including government, academia, and industry.[3] Speakers reported on their efforts to investigate potential routes of exposure (ingestion, skin absorption, etc.); to measure the quantity and morphology of ingested/absorbed particles; to develop methods to ensure that relevant exposure data can be obtained; and to formulate and test predictive exposure models. In some cases, policy and risk implications were discussed.

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[2] *Disclaimer:* The following is an account of information presented and discussed in this session of the Quantifying Exposure to Engineered Nanoparticles from Manufactured Products workshop. This account is based on notes recorded during the session by a neutral party and is intended to summarize points of discussion between session attendees and the invited speakers. As such, it does not necessarily represent the opinions of the session organizers or the U.S. Food and Drug Administration.

[3] Dr. Ebbs was unable to attend the workshop. His colleague and collaborator, Dr. Jason White, from the Connecticut Agricultural Experiment Station, presented Dr. Ebbs's slides in the session.

Summary of Findings

A common thread linking the four presentations in this session was that exposure is dependent on the ability of large (compared to molecules) ENMs to cross barriers. In most cases, the presentations implied that systemic consumer exposure is anticipated to be low on commercially relevant timescales (i.e., considering how commercial products are used by consumers) due to the processes by which the ENMs may cross barriers. The presentation on agricultural food products,[4] for instance, suggested that exposure to ENMs may require translocation of ENMs located in soils through root barriers and into edible plant tissues, but data presented suggested that even for root vegetables, root skins provide an effective barrier to this process [*77*, *82*]. Likewise, the presentations on exposure to ENMs from food packaging[5] and cosmetics[6] suggested that exposure may require diffusion through or across effective barriers—synthetic polymers [*78*] and skin [*80*], respectively. In addition to physical barriers, other rate-limiting processes exist, such as the release of the ENMs from formulations or other complex matrices (in the case of personal care products[7]) [*79*]. Additionally, data and predictive models presented in the session supported the idea that the ENM uptake mechanisms are likely inefficient. Therefore, a frequent finding of the session presentations and subsequent discussion was that exposure to dissolution or degradation products of ENMs in consumer products (e.g., heavy metal ions) may constitute a larger concern in many cases than exposure to the ENMs themselves.

Public policy and consumer acceptance of ENM-enabled consumer products was also discussed at length. Pertinent regulatory topics presented in the context of ENM exposure included harmonization of different regulatory approaches across geopolitical boundaries, the lack of premarket regulatory oversight of some personal care product categories (e.g., cosmetics in the United States), the value of compulsory and voluntary labeling of ENM-enabled food or cosmetic ingredients, and the value of regulatory definitions of ENMs. Along with these policy discussions, several attendees acknowledged that perceived risk and not actual risk would likely determine consumer acceptance of nanotechnology-enabled products. As such, a common thread among the product categories considered in this session was that stakeholders would likely benefit from a proactive communication strategy to respond to consumer concerns about potential ENM exposure from products associated with foods and personal care products. Some session attendees felt that this communication might be particularly challenging because many consumers do not have a science-based understanding about what constitutes nanotechnology.

Quantifying Exposure to Engineered Nanomaterials from Foods

One of the categories that falls within the scope of this session is food. Exposure to ENMs from food could theoretically occur either because of direct incorporation into the food where the ENM has an intended technical effect on the food, or because of use where there is no technical effect on the food, but rather the exposure results from the ENM migrating into the food. In the cases where ENMs are intentionally added to foods to impart a desired property (e.g., an organic nanoencapsulate incorporating flavor or odor molecules) or perform a technical function, the ENMs or their decomposition products would be ingested. In such a case, quantifying exposure could be reasonably straightforward, as the identity and quantity of the additive would be known ahead of time. Theoretical incidental exposure scenarios could

[4] Presentation by Dr. White (Connecticut Agricultural Experiment Station) on behalf of Dr. Ebbs (Southern Illinois University); see [77]

[5] Presentation by Dr. Roland Franz (Fraunhofer Institute for Process Engineering & Packaging); see [*78*]

[6] Presentation by Dr. Linda Katz (U.S. Food and Drug Administration); see [*80*]

[7] Presentation by Dr. Jay Ansell (Personal Care Products Council); see [*79*]

include ENMs released from food packaging or processing equipment or ENMs that end up in the edible portions of agricultural products due to their presence (intentional or otherwise) in soil, irrigation water, or air. The challenges of detecting nanoparticles in food matrices have recently been reviewed [*83*].

Discussion of potential ENM exposure from agricultural food products centered on research from the University of Southern Illinois on the potential exposure to ENMs from root crop-based agricultural food products.[4] For instance, researchers grew carrots in sand substrates modified with metal oxide or noble metal nanoparticles, after which they analyzed internal portions of the edible crops for the presence of ENMs [*77*, *82*]. One of the findings presented during the session was that, while some ENMs traveled across root barriers, a majority of particles accumulated on the root surfaces. The presentation implied that oral exposure could be minimized by peeling the vegetables prior to consumption. In addition, the data presented showed that ionic equivalents (vs. ENMs) more readily passed through semiporous root barriers. Even in the case of unpeeled vegetables, a newly designed consumption model showed that only in the highest treated concentrations and lowest body mass groups did the amount of consumed analyte element exceed published oral reference dose values [*84*, *85*].[8] In most cases, the model predicted that the amount of vegetable that would have to be eaten to exceed this dosage approached absurd levels; for instance, for the high 500 mg/kg ZnO nanoparticle exposure level, children aged 4–8 years old would have to consume almost 35 kg of peeled carrots in a single day to exceed the oral reference doses.

While sand culture experiments are not a realistic depiction of agricultural systems, the presentation claimed they offer an excellent starting point for understanding potential exposure to ENMs from agricultural food products. Subsequent data shown during the session revealed that nuanced differences exist between crop types owing to anatomical variation in root surfaces. For example, presented data indicated that peeling was critical to reduce ENM exposure from carrots; however, peeling was less important for sweet potatoes. One criticism of the oral exposure model that came up during discussion by attendees was that there are no oral reference doses or standardized toxicological data for ENMs; nevertheless, the presenter felt that these models might offer a valuable starting point for putting ENM levels in edible plant tissues into a relevant consumer perspective. Moreover, the presenter indicated that they are easily adapted to estimate exposure from nonagricultural food products. For instance, the exposure model was applied to a few commercially available ENM-enabled food supplements (e.g., MesoSilver[9]), where it was shown that the consumption of ENMs exceeded available oral reference dosages (for dissolved metal ions) by a significant margin for most human age classes, even when the product was consumed at levels below dosages recommended by product labeling. As such, while some data presented in the session suggested that exposure to ENMs from agricultural food products may not be a concern, a number of session participants felt that food supplements should be investigated more closely.

Quantifying Exposure to Engineered Nanomaterials from Food Contact Materials

The discussion of incidental exposure to ENMs from food contact materials was centered around research from the Fraunhofer Institute for Process Engineering and Packaging involving potential release of ENMs from polymers into food simulants [*78*]. In the published literature, quantifying exposure to ENMs from food contact materials typically involves exposing the material to a food or a simulated food substance

[8] The published reference dose (RfD) values were obtained from the U.S. EPA Health Effects Assessment Summary Tables [*84*]. Since there is no established oral RfD for Ce, a surrogate parameter for comparison was used based on the oral RfD values for nine other rare earth elements [*85*]. For more details see [*86*].

[9] Purest Colloids, Inc., Westhampton, New Jersey

and then analyzing the food or substance for the presence of ENMs or dissolved components [*68*]. Several studies from this group utilized this approach (including those that look at plastics containing nanoscale silver [*87*], titanium nitride [*88*], and carbon [*89*]). One of the studies showed that whereas some material was found to move from the plastic into food simulants under the conditions assayed, the transferred material was ionic, and there was no evidence for exposure to whole ENMs [*78*]. In addition to experimental studies, the use of theoretical modeling to predict rates at which ENMs could move through plastics [*78*] was discussed. These models predict that even incredibly small particles will be practically immobile in polymers, suggesting that exposure to whole particles from food packaging would be minimal. For example, these models predict that if a food contact material containing ENMs is coated by a layer of low-density polyethylene (LDPE) a mere ten microns thick, the amount of time it would take 5 nm-diameter particles to diffuse to the external medium would be 25 million years at room temperature.

As described above, a common theme emerged in this session from the discussion of exposure to ENMs from agricultural food products and food packaging: that of the inability of ENMs to cross barriers readily. As such, the discussion highlighted the notion that it may be most sensible to focus future research efforts on exposure to those factors that influence particle dissolution, because ions are more mobile. Another issue brought up during the discussion was whether chemical or mechanical damage to polymers, or strong interactions between foods and packaging that could lead to polymer swelling, could enable physical release of embedded ENMs by weakening the barriers to mass transfer. Finally, although research presented in the session implied that consumer exposure to undissolved ENMs from food packaging via food contact may be inconsequential, many attendees agreed that the entire life cycle of these products should be considered. For instance, a question that arose from the discussion was, *Can composting, recycling, incinerating, or other end-of-life processes present other routes of exposure to humans or the environment?*

Quantifying Exposure to Engineered Nanomaterials from Personal Care Products: Industry Perspective

An industry perspective on the potential for exposure to ENMs from consumer care products was provided by the Personal Care Products Council.[7] Characterization of ENMs in personal care products can play a large role in determining their safety [*79*]. A historical perspective was provided of ongoing efforts to characterize ENMs, including surveys by the International Cooperation on Cosmetics Regulation (ICCR) initiative conducted in 2008 and 2011, and three reports of its Joint Regulator–Industry Ad Hoc Working Group.

The ICCR is a voluntary group of cosmetics regulatory authorities with global representation, established in 2007, that meets annually to discuss cosmetic safety and regulation.[10] In 2008,[7] ICCR invited industry to develop common definitions for nanotechnology in cosmetics and set up an inventory of current applications in the field. The resulting key aspects for defining nanotechnology in cosmetics are that ENMs must be (1) stable and insoluble, (2) manufactured intentionally, (3) include one of several "nanometric" forms (e.g., particles, tubes, sheets), and (4) have size on the order of 1–100 nm. The lack of surprising ingredients on the list of ENMs that could eventually be used in cosmetics was cited, but it was felt that many questions remain unanswered, particularly related to size. An example discussed was that measured size varies based on method of analysis, state of agglomeration, and stage of the life cycle.

[10] iccrnet.org

In 2009, the Joint Regulator–Industry Ad Hoc Working Group and the Joint Research Center of the European Commission[11] organized the International Workshop on Regulatory Issues Regarding the Use of Nanotechnology in Cosmetics to share current approaches and knowledge on nanomaterials in cosmetics. This European Commission workshop recognized that complete characterization for scientific hazard identification and risk assessment is more detailed than what would be needed for regulatory purposes. Considering this result, the current session discussion suggested that, for risk assessment, simpler definition criteria, (such as those discussed in the previous paragraph), would be sufficient. Even so, it was thought that additional efforts are needed to clarify the meaning of words such as "stable" and "insoluble," and criteria for determining particle size need to be refined. Moreover, participants in this session concluded that, while characterization should be done on finished formulations, analysis methodology and characterization should rely on simplified models or on a raw materials basis.

The presentation finished by explaining how ENM characterization methods are also important [*79*]. As a baseline, the International Life Sciences Institute (ILSI) NanoCharacter Workshop in 2013[12] identified 28 separate lists of characterization parameters.[7] It was concluded that many methods could be used to acquire this information, but there is variability in the results, mainly because of differences between what the various methods are measuring. Ultimately, no single method can fully characterize an ENM. In addition, the presentation claimed that any method to isolate, observe, and quantify ENMs, particularly those in complex environments, might change their physico-chemical properties, making analysis susceptible to artifacts. Moreover, many methods require significant sample preparation (extraction, isolation) and so may have little bearing on the ENM as it is used in a personal care product, suggesting it is important to avoid having scientifically precise reports wholly divorced from the exposure-relevant conditions.[7] In addition, it was advised that great care should be taken in reporting and interpreting results to avoid confusion between characterization for regulatory purposes and for assessing the safety of ENMs.

Quantifying Exposure to Engineered Nanomaterials from Personal Care Products: Government Perspective

A presentation from the Office of Cosmetics and Colors at the U.S. Food and Drug Administration provided a Government perspective on the topic of the potential for nanoparticle exposure from cosmetics, including an account of research done in CFSAN/FDA laboratories on this issue. Manufacturers, it was discussed, may include ENMs as ingredients in topical products, like cosmetics, to perform a number of functions, which include improving dispersibility, delivery, stability, and controlling release of ingredients, altering optical properties, improving skin hydration, and absorbing UV radiation.

Some information was provided on FDA's regulatory framework as it applies to cosmetics.[6] FDA regulates products, not technology, and therefore cosmetics manufactured using nanotechnology are subject to the same legal requirements and safety standards as any other cosmetics [*80*, *90*]. While there is no official FDA definition for nanomaterials, the agency has issued a Final Guidance for Industry, "Safety of Nanomaterials in Cosmetic Products" [*91*]. This guidance specifies certain points for industry to consider, such as criteria for determining whether a cosmetic contains an ENM, which is a material that has at least one dimension in the nanoscale range (roughly 1–100 nm) or that exhibits unique properties deriving from its small size. The guidance also describes (1) the importance of characterizing an ENM ingredient, which includes measuring physico-chemical properties (e.g., type/size, aggregation/agglomeration, morphology, surface chemistry); (2) toxicity testing methods; and (3) relevant toxicological endpoints

[11] ec.europa.eu/jrc/

[12] ilsi.org/NanoCharacter/Pages/NanoCharacter.aspx

(e.g., acute toxicity, dermal irritation, skin absorption). Questions that industry should be able to answer when assessing the safety of an ENM ingredient include:

- Can ENMs distribute systemically by migrating through the skin?
- Can ENMs alter structure or function of the body? (This would categorize the product as a drug.)

With respect to research, this presentation explained that CFSAN conducts research on cosmetics safety to support its activities related to communication, policy development, and enforcement strategies and action [*80*]. For ENMs specifically, research is conducted to determine methods to characterize size, stability, solubility, and other properties in different solutions/vehicles; compare properties of nanoparticles versus macroparticles or bulk phase materials; acquire information on absorption into and through skin; and assess potential dermal toxicity, or toxicity through other administration routes, as needed. Regarding exposure, percutaneous absorption studies have been done at CFSAN/FDA to determine skin absorption of different types of ENMs found or potentially found in cosmetic products. Target ENMs of skin absorption studies at FDA include nanosomes, dendrimers, and polymeric ENMs, which are all soft (organic) nanoparticles, and silver nanoparticles (AgNPs), which are metallic. In general, *in vitro* skin absorption/penetration studies are performed by placing split-thickness skin in flow-through diffusion cells and dosing the skin at consumer-relevant exposures [*92*, *93*]. In this way, the extent of passage of ENMs through the skin can be measured.

For most ENM classes that have been studied, there appeared to be a small amount of penetration through human and animal skin. For the flexible liposomes, studies looked at phase behavior, structure, and extent of dermal penetration to understand the mechanism of penetration [*94*]. Cryo-TEM images showed that flexible liposomes adopt several morphologies, which raises the question of whether different morphologies of soft ENMs may have different toxicological endpoints or exposure profiles. Evidence for the penetration of flexible nanoscale liposomes into the epidermis of hairless guinea pig skin and excised human skin was acquired by labeling the ENMs with fluorophores and imaging skin sections with confocal microscopy. A similar strategy was adopted for dendrimers, which are highly branched polymeric ENMs with terminal functional groups that could be used to increase delivery of chemicals into skin. As such, there is concern not only about the potential exposure to dendrimeric ENMs themselves, but also increased skin absorption of ingredients that are currently considered safe in cosmetic products. Results showed that dendrimers penetrated the epidermis of both pig and human skin, but the process was dependent on the vehicle (solution versus emulsion) as well as the particle size and charge [*95*–*97*]. For AgNPs, according to the analysis done by ICP-MS and TEM, silver uptake was dose-dependent, and again, it appeared that surface-coating and charge may determine extent of silver nanoparticle penetration into the skin [*98*].

As in the case of exposure to ENMs from food and food packaging, a general conclusion from the presentation was that skin might be a good but incomplete barrier to mass movement of ENMs. However, data acquired by FDA has revealed that dose, surface-coating, vehicle type, and other factors may influence the process, and so session participants agreed that these factors could be investigated more thoroughly. Another topic of discussion was that research has revealed that pig skin and human skin may not behave identically, and so the suitability of animal models for ENM penetration may need to be further explored. In the end, session participants felt that the safety of cosmetic products using ENMs should be evaluated by emphasizing focus on the effect of well-characterized physico-chemical properties with relevant toxicology endpoints. It was stressed that manufacturers are encouraged to contact FDA early in the product development process.

Ecological and General Population Exposure Studies

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This session focused on emerging methods that address the challenges of characterizing exposure in complex natural and built environments. The challenges include a wide range of matrices that have the potential to transform nanoparticles released into the environment and complicate an accurate characterization of relevant properties. Presentations emphasized how the emerging methods can be used to overcome these challenges to accurately assess availability and exposure. Presentations covered the state-of-the art techniques for quantification of low concentrations of carbon nanomaterials and metal and metal oxide nanoparticles, and trophic transfer in terrestrial food chains.

Common Themes from the Concurrent Session Presentations and Discussions

While significant progress has been made toward the development of measurement tools for ENMs (Nanomaterial Measurement Infrastructure Goal 1, NNI, 2011 [*2*]), quantifying human and ecologically relevant exposures to engineered nanomaterials in the actual environment remains challenging. In order to obtain realistic measures of exposure in context, one of the most repeated requests is for quick, inexpensive, easily repeatable, and validated methods. Different analytical methods are available for quantification of carbonaceous nanomaterials [*99*–*101*] and metal and metal oxide nanoparticles [*102*–*104*]. Some techniques such as liquid nebulization/differential mobility analysis (LN/DMA) measure the number of nanoparticles and are not dependent upon the elemental composition of the nanoparticles [*105*]. There are emerging methods to quantify carbon nanomaterials in complex matrices (Table 3.1, [*106*]). Methods to isolate carbon nanotubes from biological matrices include selective digestion using oxidants, acids, alkaline conditions, and enzymes followed by analysis of the inorganic carbon [*107*]. Thermal optical transmittance/reflectance (TOT/R) can be used to quantify carbon nanotubes and graphene in complex environmental matrices such as water and rat lungs [*101*, *107*]. Single particle inductively coupled plasma mass spectrometry (spICP-MS) can be used to characterize the concentration and size distribution of gold and silver nanoparticles in environmentally relevant matrices [*102*–*104*, *108*]. Additionally, the analytical capabilities of spICP-MS can be used to analyze silver nanoparticles after release from a model textile [*108*].

Method validation is important, and an LN/DMA method can determine the size distribution and number concentration of nanoparticles in aqueous media [*109*]. This validation method includes deionized water, groundwater, and industrial wastewater, as well as growth media used in ecotoxicology tests that utilize *Daphnia* and algae. There have been repeated requests for analytical techniques to provide size distribution and number concentration measurements of nanoparticles in suspension in addition to the total mass concentration; this technique provides one approach for making such measurements.

Overall, current analytical methods developed by leading researchers have the ability to detect the presence of nanomaterials at low concentrations in water. For example, the detection limits for spICP-MS are often well below known toxicity levels and beneath the threshold of economical and reasonable regulatory action. Actual environmental exposures are often quite low, and artifacts can occur for some nanomaterials due to their dissolution over the course of sampling. Analytical methods also suffer from

challenges related to overcoming matrix interferences inherent to environmentally relevant water matrices; for example, natural organic matter, dissolved inorganic materials, and other suspended solid particles are often present at significant levels in natural waters and industrial wastewaters. The evaluations of an analytical instrument's signal-to-noise ratio, and how that ratio relates to the method's limit of quantification, are important when evaluating analytical measurements from such matrices. Moreover, lab matrix spikes (LMS) are a means to evaluate the magnitude of such interferences that can be included within studies to provide information on the accuracy and precision of the analytical measurements. Overall, quantification methods should be validated and measurements compared among several methods or lines of evidence. Ultimately, these validated methods should be transitioned to commercial analytical laboratories for use in environmental, health, and safety assessment.

Table 3.1. Quantification techniques for carbon nanomaterials

FLG: few layer graphene; GO: graphene oxide; SW- & MWCNT: single- & multiwall carbon nanotubes; NIR: near infrared; HPLC: high-performance liquid chromatography; FFF: field flow fractionation; LC: liquid chromatography; TGA: thermogravimetric analysis; ICP-MS: inductively coupled plasma mass spectroscopy. (Source: [*106*])

Technique	C_{60} & nC_{60}	FLG & GO	SW- & MWCNT
Light scattering		✔	✔
Absorbance			
• UV	✔		
• NIR fluorescence			✔
• Gel electrophoresis			✔
HPLC-UV (FFF-UV)	✔		
LC-Mass Spec	✔		
Thermal			
• Combustion/CO/CH_4	✔	✔	✔
• Microwave induced heat			✔
• TGA mass loss		✔	✔
^{14}C			
• Scintillation	✔	✔	✔
• Thermal-mass spectrophotometry	✔		✔
Raman spectrophotometry		✔	✔
Photo-acoustic/thermal			✔
Single particle ICP-MS of catalyst			✔

Assessors of environmental exposure would like a better understanding of the toxicity of engineered nanomaterials as they are actually present in the environment, for example, in the solvent or other matrix in which they are suspended when used on the shop floor. Toxicity of as-produced nanomaterials is often not relevant to actual exposures. Nanoparticles can be taken up into plants and animals in a process called trophic transfer [*110*, *111*]. Uptake of nanoparticles from soils into food crops is one potential exposure route for the general population, yet trophic transfer (from the food crop to the consumer) would also need to occur. Characteristics of the nanoparticle as it is accumulated and excreted are required to better understand the effect of factors such as particle size on the trophic transfer within a food web [*112*]. An

improved understanding of variation, uncertainty, particle shape, and the kinds of data needed by risk assessors and epidemiologists will help exposure scientists to understand fully the important characteristics and properties to measure, and how to measure them.

Exposure Quantification Studies by Receptor Population Roundtable

Moderator: Janet Carter, MS

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Panelists:[13] Dhimiter Bello,[14] Margaret Kraeling,[15] Greg Lowry,[16] Brian Mader,[17] and Marina Vance[18]

Introduction

Janet Carter from OSHA led representatives of each of the concurrent technical sessions from the first day of the workshop in a discussion of the needs and challenges of exposure science in a life cycle context. The idea of the panel was to provide an opportunity for researchers from specific disciplines (consumer exposure, ecological exposure, and population science) and different sectors (academia, industry, and Federal Government) to talk about the commonalities and differences in their fields. Some specific questions posed were whether researchers have enough information to start developing a robust life cycle analysis for specific nanomaterials, and if investigators can reliably use exposure models for nanomaterials that were developed for other chemicals. The resulting dialogue covered the relevance of nanotoxicological results to exposure research, prioritizing nanomaterials for research, standard protocol development, analytical method development, modeling of particles, collaboration between researchers and industry, and future considerations for the field. The following is a brief summary of some of the comments that were offered by panelists during this discussion; it does not represent a consensus of the panel, but rather a sampling of the viewpoints that were expressed.

Relevance of Results

Scientists should be working with realistic materials and realistic exposure scenarios. This approach includes assessing nanoparticles as they are presented in products as opposed to as-manufactured or “pristine” nanomaterials, and measuring the toxicological effect of real-world exposure levels during product use or handling. However, working with realistic exposure levels can be challenging since they involve minute amounts of materials that will not allow meaningful toxicology testing or evaluation of complex conditions such as mixed exposures. Additionally, researchers should be thinking about deliverables that inform two different communities: (1) life cycle assessment scientists and (2) toxicologists. Deliverables should allow these communities to develop their own studies based on data from realistic user scenarios.

Prioritization of Nanomaterials for Research

Grouping nanomaterials into categories can be useful for both prioritizing and assessing nanomaterials in a

[13] Disclaimer: The opinions and conclusions expressed in this article are solely the views of the authors, and do not necessarily reflect those of the Food and Drug Administration.
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[15] U.S. Food and Drug Administration
[16] Carnegie Mellon University
[17] 3M Environmental Laboratory
[18] Virginia Tech Center for Sustainable Nanotechnology

more efficient manner. Prioritizing groups of materials that have the highest potential for exposures as a tiered approach could help focus research efforts. For instance, the U.S. Army Corps of Engineers NanoGRID [*113*] approach asks as an important step, "Do we expect exposure to occur?" Prioritization by potential exposure into "active" or "passive" nanomaterials, as suggested by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) [*114*], is another technique. However, this classification could be difficult unless done within the context of the exposure scenario. The data quality objectives and exposure scenarios need to be considered in framing the exposure question. These considerations include:

- The population of concern.
- The environmental context. For instance, exposure potential to ambient nanoparticles is likely to be high if there is an electronic waste (e-waste) recycling plant nearby.
- The relevant vehicle of delivery or the matrix.

Because the exposure community is now focusing more on product systems than on products, the nanomaterial itself may be the lowest priority with regard to risk. This shift in concern is in contrast to the focus 10 years ago.

Methods

Considering the development of analytical methods for exposure, the field has moved from proof-of-concept methods toward increasingly robust methods; now there is more focus on reducing the detection limits. Needs for tools have moved from high detection capability to being more robust and cheaper to run. Needs for assessment have moved from addressing simple particles towards addressing more realistic and complicated particles and matrices. Methods should be developed with the realistic quality control and detection limit requirements of the end-users. These end-users include toxicologists and epidemiologists conducting field research, but also regulators.

Standardization

The community must decide explicitly what needs to be known about exposure to nanomaterials in order to guide the collection of data. Currently there still exists diversity in the exposure assessment community regarding how to define quantitative exposure assessment. Developing standards and generalized release scenarios will help move the field forward. However, the wide variety of nanomaterials makes generalization a challenge. For specific nanomaterials, developing robust life cycle analyses will also require developing standards for data collection and test methods. One challenge is that end-use scenarios and applications modify the required exposure quantification method, making it difficult to develop standard methods. Another factor often overlooked is that quantifying the errors and the particle loss inherent in each measurement is important for standardization and comparability. In general, data collected or methods developed should be done in a way that makes them usable by other stakeholders. Finally, the production volumes required to create a robust life cycle analysis may be hard to come by, specifically when dealing with consumer products. Many consumer products, particularly cosmetics, cycle through the market very quickly. For instance, the lipstick bought today may not be available in six months, or the same formulation may be marketed as a different product.

Modeling

Unfortunately, the dynamic nature of nanoparticles makes modeling much more difficult than does the absence of standards. One strategy would be to adapt existing models to handle nanoscale processes, or to employ some new computational methods that the aerosol community is working with. Existing models

designed to handle particles will be sufficient for nanoparticles, but those based solely on elemental identity or molecules will fail because particles and molecules may behave differently. Equilibrium conditions do not necessarily apply to nanoparticles. Nanoparticles migrate to interfaces as opposed to going into one or another phase. Particles undergo transformations and may change over time. Chemicals also transform, but nanoparticles can transform in ways that make their properties so different that they change their behavior in the environment. Properly modeling particle behavior, therefore, requires a multivariate model. This requirement makes modeling a particle population a very large calculation that requires more computing power than is currently available. Regardless, it is important to follow the same model validations for nanomaterials as those for classic chemicals.

Collaboration with Industry

In many cases, the biggest challenge to modeling may not be the available models but limitations on the technology to collect data or access to relevant data collection sites to measure real-world exposure scenarios. With this challenge in mind, industry cooperation regarding data collection and sharing needs to be fostered. For occupational exposure assessment, having wearable, portable instruments that allow measuring the relevant metrics for individuals correctly over a full worker shift would be ideal. Progress in occupational safety has been good, especially considering the work that NIOSH has done in the context of using quantitative exposure assessment for exposure prevention. For consumer products, there is some sentiment that labeling of products containing nanomaterials could be helpful. However, research presented in this workshop shows that, with regard to consumer safety, there is essentially no difference between nanoparticles and regular particles that are in cosmetics. Ultimately, sharing of information on nanomaterials for toxicology and exposure studies will benefit both industry and researchers since, in the absence of data, some regulators and consumers may prefer a more precautionary approach to risk management.

Future Considerations

Finally, the community should look to lessons learned over the past decade to guide the responsible development of nanomaterials and other emerging materials. A suggested future research focus is to look at exposure beyond the intended application of products, including the following:

- Off-label use, overuse, or misuse of products.
- Incidental exposure of bystanders.
- Exposure to intermediate transformations of released materials.

Additionally, exposures to unintentionally engineered nanoparticles that exist as part of the normal particle size distribution of materials and products are something the community should consider.

4. Measuring and Modeling Exposure in Various Media and Pathways

Measuring and Modeling Exposures to Nanomaterials in Complex Systems

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Exposure assessment for engineered nanomaterials (ENMs) used in consumer products is an essential part of evaluating their risks to consumers and to the environment. Accurate exposure assessment is confounded by the enormous variation and complexity of nanomaterials, product matrices and uses, environmental conditions, estimates of sources and exposure pathways, and transformations of nanomaterials that change their properties, fate, and therefore exposure potential. Despite this complexity, there are likely a limited number of fundamental processes governing the release of nanomaterials from consumer products and their resulting fate. Once these fundamental processes are identified, they can be incorporated into fate and exposure modeling. This generalized modeling can be achieved using a systematic, integrated, and experimental approach in well-controlled systems, in systems with managed complexity, and in "real" systems, to confirm that the identified processes indeed control the relevant behavior of the nanomaterials. Central to this integrated experimental approach is development of characterization tools, the use of a centralized large-scale "realistic" test facility, and the early adoption of adaptable models. These elements can be used to integrate and focus research efforts towards a common goal of creating accurate exposure models and measurement methods for ENMs.

Key Elements to Exposure Assessment

Exposure science has developed a robust process for exposure assessment and modeling [*115*]. It remained unclear at the time of the workshop how the incorporation of engineered nanomaterials into consumer products affects this process of exposure assessment. However, regardless of the potential need for new measurement tools and models, the basic elements of exposure assessment must be determined, and the following questions must be answered:

- What do you measure?
  - System inputs.
  - Key processes/factors affecting exposure.
- How do you measure it?
  - New methods versus adapting old methods.
  - Transformations.
- How do you get measurements into exposure models?
  - What exposure models do you use?
- How do you parameterize those models?

Each of these questions are discussed here for environmental exposures to nanomaterials, with a primary focus on the experimental approaches, transformations of nanomaterials, and how these transformations

affect the characterization methods needed to accurately assess nanomaterial exposures. Critical gaps in knowledge that hinder these assessments are presented, as is a proposed plan to address those gaps.

What Do You Measure?

Two approaches may be used to predict exposures to engineered nanomaterials in complex systems such as the natural environment. The first is a bottom-up (deductive) approach where the fundamental properties of a nanomaterial are measured and correlated with their releases measured in a highly controlled environment. These results are then used to predict the release behavior of nanomaterials from consumer products under specified conditions of use. This approach has the advantage of potential for "read across" capabilities between nanomaterial types or product types, and in principle, the prediction of the exposure potential for other nanomaterials with similar properties. However, this approach is inherently flawed because the properties of nanomaterials and nanotechnology-enabled products are also highly dependent on the system in which they are placed, e.g., releases of nanomaterials from a product exposed to sunlight or acids will be different than those in the dark or at neutral pH. Therefore, the system properties must also be taken into consideration in any prediction of releases and exposures. The myriad combinations of system properties and nanomaterial properties make this approach seemingly intractable.

A second approach is the top-down approach where exposure measurements are made for selected products and in selected systems. These systems contain a sufficient level of complexity to be representative of "realistic" exposures where the combination of system and material properties manifest into the measured exposures. The challenge of this approach is that it may be limited in its ability to enable "read across," increasing the number of products and nanomaterials that must be measured. However, this approach accounts for the complexity of the exposure scenarios and is more realistic. With a sufficient number of selected conditions and standard testing strategies, a top-down approach could lead to the development of product and/or material classes that exhibit the same behaviors and therefore can be used to group materials into classes of behaviors.

In reality, both approaches are needed initially, in combination, to identify the key processes that most affect ENM fate and exposure potential. Combining approaches enables the selection of systems and appropriate testing strategies. The latter (top-down) approach, using realistic exposure scenarios and real products, also provides a ground truthing of the fundamental processes that will likely be relevant in real systems, and it provides some indication of the rates of those processes under realistic conditions. Determining the rates of selected processes that affect ENM fate, e.g., dissolution or sulfidation, allows for determination of the processes requiring detailed studies and incorporation into models (e.g., environmental fate models; see the next section of this chapter). It may also provide near-term classifications of materials for risk assessment. In contrast, the first (bottom-up) approach assesses fundamental mechanisms for releases and determines mechanistically how a material's properties affect its behavior, but usually at a small scale and in well-defined systems that neglect the complexity of natural systems. There remains a scientific need for bridging the gap between mechanistic knowledge gained in well-controlled systems and the real behaviors observed in complex natural systems. In this combined approach, measurements are made at the fundamental level, the fully complex systems level (e.g., mesocosms), and at intermediate scales of "managed" complexity. This method is the approach currently taken at the Center for Environmental Implications of Nanotechnology (CEINT) for assessing environmental exposures to nanomaterials (Figure 4.1 A), but it can be easily adapted for direct assessment of consumer exposures to nanomaterials in consumer products (Figure 4.1 B).

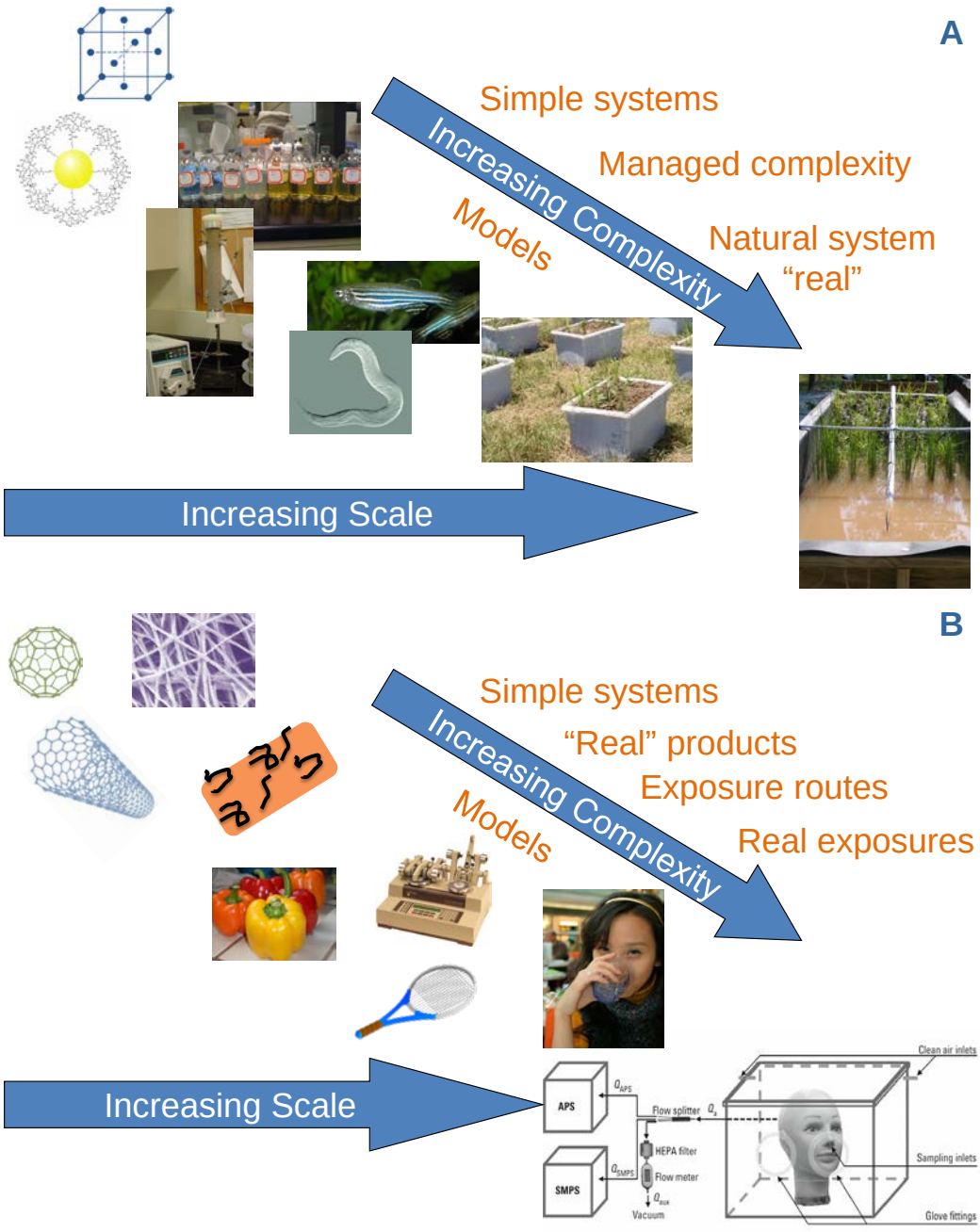

Figure 4.1. Comparison of Experimental Approaches. (A) The experimental approach taken by CEINT to assess the fate of engineered nanomaterials in the environment and resulting exposure potential. This approach includes studies and measurements taken at various scales and levels of complexity in order to determine the linkage between the properties of engineered nanomaterials and their behavior in complex systems. (B) A proposed analogous approach to assess consumer exposures to engineered nanomaterials. (Sources: (A), top left to bottom right): Face-centered Cubic Unit Cell (biochem.co); Gold Nanoparticle (NIST); Zebrafish, *Danio rerio* (Azul/Creative Commons); *Caenorhabditis elegans* (B Goldstein/Creative Commons); all other images courtesy G. Lowry; (B), top left to bottom right): Fullerene and Carbon Nanotube (M. Ströck/Creative Commons); Electrospun PVC and PEO Nanofibrous Membrane (K. Nilsen/Creative Commons); Vegetables (Symphony999/Creative Commons); Taber Abraser (Ajaenecke/Creative Commons). Nanoparticles embedded in a polymer matrix (courtesy H. Fairbrother); tennis racket (Creative Commons); woman drinking (Kristiaan/Creative Commons); experimental setup for simulated cosmetic powder application (reproduced from [*17*]).)

How Do You Measure It?

Measurements of the properties of as-produced ENMs (e.g., size distribution, coating mass, electrophoretic mobility) in standard solutions (e.g., deionized water) are now routine and quite robust [*116*]. However, measurements of ENMs directly in environmental and biological media are more problematic [*117*]. This difficulty is due to a variety of reasons, including their low concentration in these media, the presence of background particles of similar composition, and the fact that they are often in water. For accurate exposure assessment, i.e., determining exactly what an individual receptor is exposed to, the following nanomaterial (NM) properties must be measured *in situ*:

- Distribution and chemical speciation of NMs (*in situ*).
- Distinguishing between individual nanoparticles (NPs) and populations of NPs.
- Distinguishing between ENMs and background nanomaterials.

There are existing tools to measure many of the nanomaterial properties that affect fate and exposure potential. However, sample preparation (e.g., removal of the NPs from the matrix prior to characterization) is often difficult and modifies what is being measured. This alteration prevents good characterization of properties of real particles in a real medium, and prevents accurate determination of the speciation of the nanomaterials. This problem is especially true for materials that readily transform in the medium of interest such as silver- or copper-based nanomaterials [*118*, *119*].

Distribution and chemical speciation *in situ*. Determining exposure potential, i.e., determining which populations are exposed and to what they are exposed, requires good understanding of the distribution of the nanomaterials in the system as well as their chemical speciation. Both spatial distribution and speciation are time-dependent [*120*, *121*], and both must be considered in exposure assessment. There are tools to locate nanomaterials in a complex medium, e.g., sediment, soil, or polymer nanocomposite; in some cases the identity of the nanomaterial can determined [*117*]. For example, transmission electron microscopy (TEM) with energy-dispersive x-ray spectroscopy (EDX) and electron diffraction can indicate where particles are in a sample and provide crystal structure and chemical composition [*122*, *123*]. However, the limited field of view of TEM and the low number of samples that can be analyzed quantitatively makes it difficult to determine if this assessment method is truly representative of the nanomaterials' properties in the entire system. Methods such as x-ray absorption spectroscopy (XAS) can provide detailed information about chemical speciation in a sample. However, bulk XAS measurements represent the average speciation of the metal in the system (e.g., Ag or Cd) and yield no information about spatial distribution of the nanomaterials in the samples, or specific morphological details about the particles. For example, a soil sample containing a mixture of individual Ag and Ag_2S nanoparticles would look similar to Ag/Ag_2S core–shell nanomaterials using bulk XAS. Distinguishing between these would require additional analysis, e.g., through TEM high-angle annular dark field (HAADF) imaging. Some newer techniques, such as synchrotron-based micro-x-ray fluorescence (μ-XRF) mapping with fast x-ray absorption near edge structure (XANES) imaging, can provide both spatial information and chemical speciation information [*124*]. Dark field microscopy with hyperspectral imaging (CytoViva[19]) can provide both spatial distribution and chemical speciation in a laboratory setting [*125*]. However, these techniques are expensive to run, and the limited number and types of samples that can be analyzed currently reduces their utility to scientific discovery rather than to industrial or regulatory use. In general, tools that can differentiate between different nanomaterials in a population of particles would greatly benefit exposure assessment.

[19] CytoViva, Inc., Auburn, Alabama

Distinguishing between individual nanomaterials and populations of ENMs. Single-particle methods will be required to determine accurately the range of properties of nanomaterials in a distribution of those materials, or to identify nanomaterials with a specific composition or size extracted from air or from soil and sediment. A single-particle method is one where the properties of individual particles can be determined. There is a long history of measuring small particles in air and in water, i.e., in colloid science, and this history has led to a number of robust methods to accurately measure particle size and size distributions (e.g., dynamic light scattering or differential mobility analyzers). However, these methods lack an ability to provide chemical information on the particles. Techniques that can measure the chemical composition of individual nanomaterials in air or water or complex matrices like food include aerosol time-of-flight mass spectrometry (aerosol TOF-MS) and single particle inductively coupled plasma mass spectroscopy (spICP-MS), respectively. Further development of these methods will be necessary to determine the composition and size of nanomaterials released from consumer products or ingested in foods, and continued development of these methods could lead to higher sample throughput and routine monitoring of exposures. For now, separation of the nanomaterials from samples (e.g., by dispersion in water followed by successive filtration for spICP-MS, or aerosolization of an NP dispersion for aerosol TOF-MS) is necessary. Methods for these analyses are under development but are relatively immature.

Distinguishing between engineered nanomaterials and background (naturally occurring) NPs. The earth is swimming in naturally occurring nanomaterials [*126*], and distinguishing between these natural nanomaterials and engineered nanomaterials is a challenge. This difficulty is especially true for the most widely used nanomaterials made from SiO_2, TiO_2, and Fe-oxides. These elements are highly abundant in the earth's crust; distinguishing between natural titania and silica structures and engineered ones is a challenge that must be overcome to allow for measurements of nanomaterial concentrations in soil, air, and water. One method to distinguish the natural elements from the ENMs is to determine if there is a unique chemical signature for the naturally occurring nanomaterials relative to the engineered nanomaterials. Such a difference would provide a "fingerprint" of the engineered nanomaterial. For example, engineered CeO_2 NPs are relatively pure and contain no other elements, whereas naturally occurring CeO_2 particles contain a fairly consistent ratio of lanthanum (La) and cerium (Ce). Discrimination between engineered nanomaterials or background nanomaterials recovered from a sample can be achieved with spICP-MS by scanning each particle to determine the La to Ce ratio in the particles. Differences in stable isotopes of elements in ENMs compared to background particles may also prove to be a viable method to distinguish background particles from ENMs. However, this discrimination is only possible if the ENM is somehow enriched or depleted in one isotope relative to the background materials.

Transformations. A factor complicating measurements of ENMs and exposure assessment is that many nanomaterials transform (change properties) once released into the environment. These transformations can greatly affect their fate, exposure potential, and toxicity potential [*127*, *128*]. The types of transformations that nanomaterials undergo in the environment have been discussed in detail elsewhere [*120*, *121*]. What is important to note is that these transformations can change the properties of the nanomaterials that are used to identify them, thereby affecting the ability to detect or to quantify them [*118*]. Transformations are also system-dependent for many nanomaterials, which makes generalizations about transformations across the broad range of possible systems difficult (e.g., oxic water columns versus anoxic sediments). Methods of detection that rely on the coating properties, magnetic properties, optical properties, etc., will be affected by transformations of the nanomaterials in the system.

How Do You Get Measurements into Exposure Models?

Environmental fate and toxicity models for ENMs are being constructed [*34*, *129–131*]. These multimedia models are being developed to provide guidance on where we expect to find ENMs in the environment, i.e., "hot spots," and to estimate concentrations expected in different environmental media. These models are described in more detail in the section that follows, Environmental Multimedia Distribution of Nanomaterials. The large body of work and experience on modeling fate and transport of more traditional environmental contaminants is being leveraged to develop these models. Many models are available for consumer exposure to chemicals used in products, e.g., surfactants used in shampoos. The process of exposure modeling is well established. However, it is not known if and how to modify those exposure models for predicting consumer exposures while using nanotechnology-enabled products (NEPs).

What exposure models do you use? Although the exact formulations of nanomaterial-specific exposure models for consumer products is not known, they can at least be postulated based on our understanding of nanomaterial fate in air, water, soil, plastics, etc. The models should be postulated early as a means to identify which model parameters are necessary to determine experimentally and which parameters already have reasonable estimates. An important consideration for nanomaterial exposure models is that the behavior of nanomaterials is very often kinetically controlled rather than by their being in an equilibrium state with the surrounding environment. This aspect means that equilibrium assumptions commonly used in exposure models for chemicals may have to be replaced with rate constants that are not likely to be available.

How Do You Parameterize those Models?

Parameterization of exposure models for nanomaterials will be highly challenging. However, once the key fundamental processes controlling, for example, the rate of release, can be agreed upon, specific tests can be developed to determine the necessary rate constants for the models. This approach has recently been proposed to parameterize environmental fate models [*132*]. Hendren *et al.* propose the development of standard "functional assays" (i.e., measurements) in complex systems to calculate the values of important parameters for fate models such as dissolution rate and attachment efficiency. The measurements are made in key environmental systems where we expect to find nanomaterials after their release, e.g., wastewater treatment plants, subaquatic sediment, and agricultural soils. The systems contain sufficient complexity to mimic the "real" environmental medium. This method does not necessarily provide fundamental mechanistic information on nanomaterial behavior, but it does provide a value or range of values for the parameters that are required by the models.

A similar approach can be taken for modeling consumer exposures to nanomaterials used in products. Assay development would require grouping of nanotechnology-enabled products into types (plastics, creams/ pastes, and fabrics, and so on) based on intended uses. Prior to assay development, the research community must agree on the important scenarios to consider and on the fundamental framework and features of the exposure model such that appropriate assays can be developed and tested for accuracy. While such a framework has yet to be agreed upon, it will likely have to consider aspects of the nanomaterial, the product matrix, the system in which the consumer product is used, and the route of exposure (dermal, ingestion, or inhalation). The framework would ideally include a combination of fundamental scientific discovery assessing how nanomaterial properties impact product performance and exposure potential, but it would also include alignment with product testing for determining product specifications. There could be tremendous benefits in linking product specifications testing with exposure potential because the manufacturers are already measuring product performance properties to ensure that they meet key product specifications.

Environmental Multimedia Distribution of Nanomaterials

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Given the rapid growth of the nanotechnology market, there is a growing concern that ENMs could be released to the environment [*38*, *133–135*] and thus the potential that certain ENMs may pose environmental and human health risks over their life cycles [*136–144*]. Once released to the environment, ENMs can move across environmental boundaries [*145*], thus creating the potential for multimedia exposures [*135*]. Environmental impact (or risk) associated with a given ENM would be expected if it is toxic at the level of existing or potential environmental exposure concentrations. Accordingly, it is critical to assess the potential impact of ENMs and provide the necessary input for decision analysis (Figure 4.2). Information is required regarding both the toxicity of ENMs and expected environmental exposure concentrations throughout their life cycles [*143–146*].

Field monitoring of ENM concentrations and assessment of personal exposure are desirable for arriving at defensible decisions aimed at establishing measures to protect human health and the environment. At present, however, field measurements of ENM exposures are scarce, and various monitoring technologies are in early development stages. In addition, relying solely on field monitoring may be impractical or unfeasible given the rapidly increasing number of ENMs. Moreover, field measurements, while useful and necessary, are insufficient for comprehensive predictions of potential exposures under a wider range of possible scenarios. Therefore, as a complement to field monitoring, computational modeling approaches based on established theories for fate and transport (F&T) of environmental contaminants are needed to predict potential environmental exposure concentrations of ENMs.

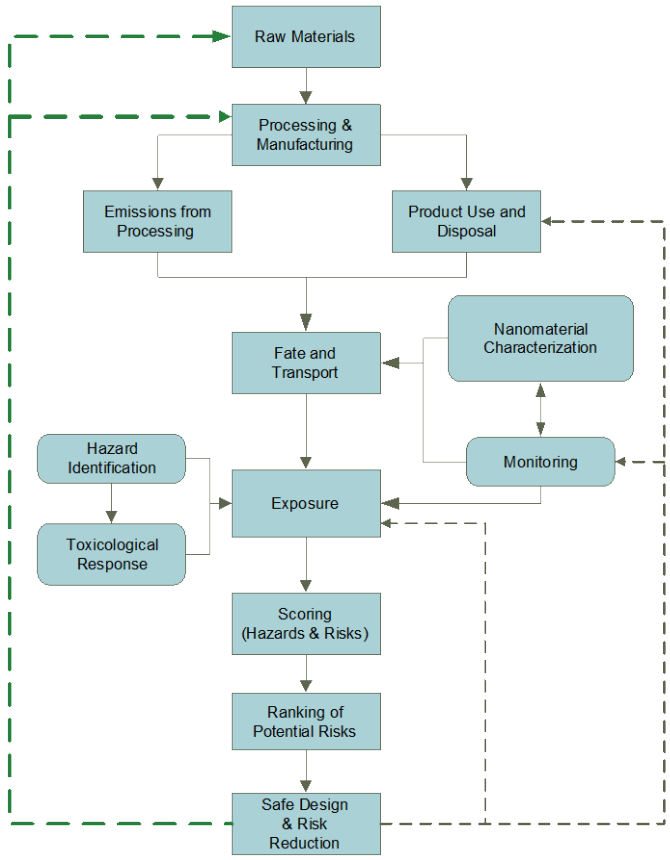

Figure 4.2. Potential process for analysis and identification of risk management options geared throughout the ENM life cycle. In this approach the hazard and risk analyses are direct inputs into the decision process regarding action that may be taken (dashed arrows) to change manufacturing processes, provide guidance or regulatory action with respect to product use and disposal, as well as identify the need for monitoring and material characterization. (Source: Y. Cohen.)

In order to understand the environmental F&T behavior of ENMs, it is necessary to evaluate the effects of various transport and transformation processes, as well as the impacts of geographical and meteorological parameters on the environmental distribution of ENMs. Predictions of ENM environmental exposure levels require information regarding their release rates. Thus, assessing the effect of ENM release kinetics on their temporal environmental distribution (which may be dependent on application) is crucial. The transport behavior of ENMs in the environment is governed by the physical

transport mechanism of particulate matter. Therefore, evaluation of F&T for ENMs of concern in a given environmental medium (e.g., air, water, or soil) or their multimedia environmental distribution requires quantification of intermedia transport rates that are affected by the ENM properties (e.g., particle size distribution, agglomerate geometry, and surface properties). It is important to recognize that such analysis requires reliable data on the physico-chemical properties (e.g., size distribution, shape, composition, surface properties) and understanding of the reactivity of ENMs of concern. However, despite the growing effort to experimentally characterize various ENMs, it is formidable—if not impractical—to experimentally map all the pertinent physico-chemical properties that affect ENM F&T over the wide range of environmental conditions that may be of interest from an exposure viewpoint. Therefore, deterministic or empirical (i.e., data-driven) models will be necessary to enable one to quantify the agglomeration of ENMs in the environment, their association with ambient particulate and dissolved matter (e.g., natural organic matter), as well as their behavior at the bio–nano interface.

F&T Models to Evaluate Potential Environmental Exposures to ENMs

A wide range of analytical and computational models is available to describe the F&T behavior of chemicals in the environment at both the micro- and macroscales. However, such models may not be directly applicable to ENMs since available models are based on the transport rate of gaseous and dissolved chemicals. The dynamics of these chemicals is governed by their chemical potential and chemical driving forces that are constrained by thermodynamic equilibrium. In contrast, transport processes of ENMs are governed primarily by mechanisms that are relevant to particulate matter, which in turn are governed primarily by particle size distribution (PSD) [*147*], geometry, and surface properties. For example, mass diffusivity, sedimentation velocity, deposition velocity, and attachment efficiency of nanoparticles onto solid and biological surfaces are all significantly influenced by particle size [*148*–*151*]. Indeed, it is now accepted that the environmental F&T of ENMs [*152*, *153*], as well as their behavior at the bio–nano interface [*142*, *152*, *154*], is dictated by their physico-chemical properties [*142*], with the particle size being a major factor [*153*, *155*]. In general, environmental transport processes for ENMs can be classified as being due to (1) advective transport processes resulting in dispersion and both short and long-term transport, (2) intermedia (or exchange) transport processes (between adjoining environmental compartments), and (3) transformation (chemical, biochemical, or dissolution).

In the context of integrated multimedia, F&T analysis of the environment can be modeled as a system consisting of both abiotic and biotic media (including the human receptor) with intermedia transport processes leading to chemical mass exchange among the various media. There are four types of multimedia modeling approaches: (1) integrated spatial multimedia models, (2) linked spatial single-medium models, (3) compartmental (“well-mixed” media) models, and (4) integrated spatial-multimedia compartmental models. Integrated spatial multimedia models are those that describe F&T in all pertinent media via spatial models for each medium, including interactions among media, specified through the appropriate boundary conditions. Unfortunately, such models are not yet developed for ENMs, and given their expected complexity and immense data requirements, these models will likely be slow to emerge as practical tools. A more tractable approach for achieving a high level of spatial resolution is to link single-medium models (e.g., for air, water, soil, water, and other media of interest) to describe F&T in the environmental system of interest; however, such an approach requires careful considerations of media interactions in order to assure mass conservation. Simpler compartmental models are essentially mass balance models that consider the environment to be a collection of interacting well-mixed compartments. Such models include the appropriate relationships (or submodels) to quantify the rates of intermedia transport (i.e., exchange of ENMs between adjacent compartments). These types of models are intended

to provide average compartmental exposure concentrations, but they do not provide detailed spatial description of the concentration fields in each environmental medium. However, spatial resolution may be increased by further dividing the environmental media into subcompartments and integrating compartmental with spatial models [*140*].

F&T modeling for exposure assessment is typically a tiered process, which ranges from use of simple models consisting of well-mixed environmental compartments linked by intermedia transport processes [*156*] (first tier), to complex single-medium models at various levels of spatial resolution of predicted contaminant distribution, coupled (where feasible) with field monitoring [*156*]. First-tier screening-level analysis [*140*] can be utilized for order-of-magnitude (or better) estimation of exposure concentrations and mass distribution of chemical pollutants in specific regions [*157–160*]. Such models can serve to identify major exposure pathways and monitoring data gaps, and to assist in the design of monitoring field studies. Subsequent phases, if required, may consist of detailed single-medium models or more extended multimedia analysis coupled with monitoring studies. Higher-tier models can be used for site-specific exposure analyses, but often at the expense of significant parameter inputs that are typically required (e.g., source emissions rates, local geography, and meteorology) for spatial models [*140*, *160*].

Irrespective of F&T model complexity, one must first quantify the release of ENMs to the various environmental media. In order to estimate ENM release rates, life cycle inventory assessment (LCIA)-based approaches have been developed to track the target ENM mass flow throughout its life cycle from production through use to end of life, which could involve disposal and/or release to the environment. LCIA approaches are based on ENM production rates and empirical transfer coefficients that quantify the fraction of mass transferred between compartments that include technical compartments, such as waste processing facilities, as well as environmental compartments, such as air, water, and soil [*5*, *37*, *161–163*]. Although there are uncertainties in LCIA approaches, primarily due to the inherent low reliability of estimated ENM production rates and intercompartmental transfer coefficients [*5*], such methods are considered, at present, as being reasonably suitable for assessing potential ranges of ENM release rates [*5*, *161*]. There have also been attempts to extend LCIA-based methods to estimate ENM media concentrations (e.g., via material flow analysis) [*161–163*], relying on empirically estimated media transfer coefficients. However, with such estimates one is not assured mass balance consistency that adheres to intermedia transport constraints.

Model Selection

The selection of a model or a field monitoring strategy to assess potential exposure levels for specific ENMs has to consider carefully the following:

- The purpose of the analysis (e.g., regulatory compliance, research priority settings, and material design).
- The specific questions that need to be answered to provide the necessary information for decision makers.
- The level of required spatial resolution of model output (e.g., site-specific or regional resolution).
- The required time resolution needed to ensure that the analysis is consistent with the expected level of time variability of exposure (e.g., steady-state, diurnal or seasonal variability, or episodic exposure events).
- The required accuracy of estimated exposure concentrations in relation to the threshold levels for decision-making.

Model Validation

It is critical to establish that a model that is selected for exposure analysis can indeed provide accurate or at least reasonable predictions of exposure concentration for the physical system being modeled. Models that are designed to describe the fate and transport of nanomaterials in the environment are inherently complex. Such models may contain numerous submodules (or submodels) that in turn may contain various components, algorithms, parameters, and parameter prediction units (Figure 4.3). It is acknowledged that validating a complex model based on monitoring field data may be a major challenge or even infeasible given the scarcity of current environmental monitoring data for ENMs. Therefore, it is essential that model components be individually validated prior to their integration into an overall model. For example, one can validate sedimentation and runoff models that are part of a river F&T model. Similarly, one can validate an atmospheric dry deposition model that is incorporated into an atmospheric dispersion model. The process of model validation, irrespective of whether one addresses model components or the entire integrated model itself, requires validation at multiple steps following the type of pyramid structure illustrated in Figure 4.3.

Exposure models must first obey fundamental principles of the basic laws of mass, momentum, and energy transport. The validity of proposed F&T mechanisms of action (i.e., with respect to F&T) have to be established, and model parameter values must be carefully verified as to their fundamental validity. Parameter sensitivity is the next step, which is crucial to assessing the level of accuracy by which model parameters must be obtained. The subsequent step of comparing model predictions with field data, if available, will provide greater confidence in the accuracy of model predictions. This result is particularly true if the model is able to describe episodic events (e.g., response to intermittent releases of ENMs, wind resuspension, and runoff) where significant time variability of transport processes is expected.

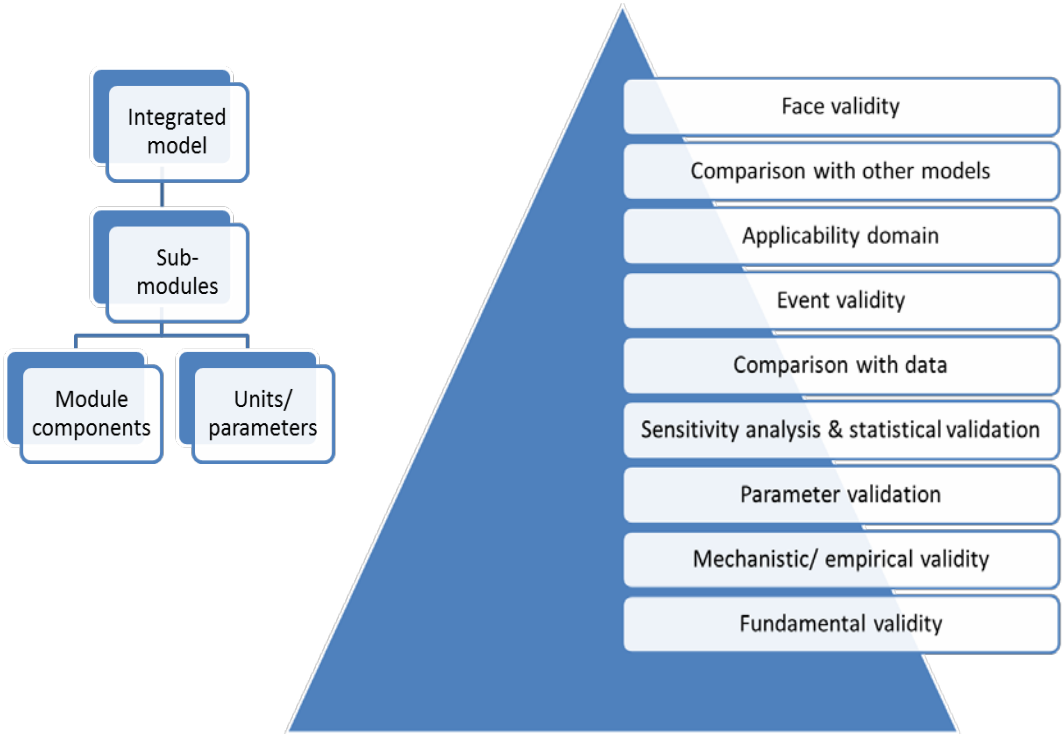

Figure 4.3. Model validation framework. Model validation can be accomplished for various model components (left) and for the different model steps (right) where the steps are progressively more significant toward the base of the model validation pyramid. (Source: Y. Cohen.)

An important but often overlooked element of model application is knowledge of the model applicability domain. This consideration must be part of establishing the usefulness of a model, which should also include comparison with predictions of other models or submodels that may have already been validated. Finally, the often-practiced approach should be avoided of accepting a model at face value (i.e., face validity) simply because it is used by various individuals or groups. Such claims of model validation or acceptance should not be mistaken for scientific validation. However, if all other validation steps have been addressed, then model popularity will clearly add to its acceptability, and likely, to expanded model validation as per the steps described above.

Exposure in Biological Systems: Review of the State of the Science

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Exposure to nanomaterials and nanotechnology-enabled products is possible across the entire life cycle. From research and development (R&D) in workplace facilities to consumer use in homes to disposal processes at end-of-life, biological intake has been shown though five main routes of exposure: inhalation, ingestion, dermal contact, puncture wounds, and eye contact. In this context, aerosol inhalation is described as breathing in vapors, liquid droplets, or small particles. An ingestion exposure occurs when aerosols are swallowed or after hand-to-mouth contact. Dermal exposure usually occurs through abraded skin contact or through puncture wounds from syringe needles or broken glassware. Exposure through the eyes occurs after a sample solution or suspension splashes on the face. A common "Stop-Work" procedure used in many laboratories working with engineered nanomaterials is:

1. Wash exposed area with warm soapy water for 15 minutes.
2. Flush eyes at eye wash station.
3. Call or visit the infirmary.
4. If injury is severe, call 911.
5. Report the incident to your supervisor.
6. File an injury report.

While this procedure is applicable to many different laboratory exposure scenarios, it is not specific to engineered nanomaterials, nor is it useful for people outside the workplace.

The growing body of research on the hazards that follow nanoparticle inhalation exposure demonstrates the potential for unwanted health outcomes. Many studies and guidance documents have focused on inhalation as the primary route of exposure to nanoparticles [*164–166*]. Particles <10,000 nanometers in size are trapped by the mouth and nose, and then are coughed, sneezed, or ingested. Particles >10,000 nanometers in size enter the conductive airways, are caught in the mucociliary escalator, and are then coughed, sneezed, or ingested. Particles >250 nanometers in size are inhaled into the alveolar region of the lung. Recent papers have indicated that nanoparticles may enter the bloodstream and translocate to other systems in the body. Certain metals and metal oxide particles in the nanometer size regime have been shown to travel along the olfactory nerve and deposit in brain tissue. Certain multiwalled carbon nanotubes have been shown to induce fibrosis and mesothelioma-like symptoms in the lungs of exposed rodents [*167–171*]. The effects were divergent among the studies, but in general, adverse effects were more prominent after exposure to long, stiff nanotubes (which resemble the shape of the harmful form of asbestos) and less prominent after exposure to short, tangled nanotubes.

Exposure via ingestion is studied less than exposure via inhalation. However, some studies indicate that various nanoparticles have the potential to damage intestinal cells and, after translocating out of the gut, induce unwanted health effects in other organs. Nanomaterials are proposed for use in the food and food packaging industry, and some nanomedicines are *meant* to be ingested and to translocate; therefore, human exposure via ingestion is expected to be intentional in specific situations [*19*, *172*]. This research area is in its infancy; most papers conclude that more research is needed to better understand the effects of ingested nanoparticles [*171*, *173–175*].

Similar to the inhalation route, the remaining routes of exposure (i.e., ocular, nasal, dermal, and puncture wound) are also dependent on the size of the nanomaterial [*176*]. Methods have been developed to measure the concentration of either solid particles or liquid solvents on the skin, such as the DeRmal Exposure Assessment Method (DREAM), which uses variables like the surface area of the skin and the surface area of the particles and the pseudo-skin method [*174*, *177–179*].

It is important to remember, however, that not all types of nanoparticles have demonstrated hazards, and only a handful of research projects have been performed on commercially relevant nanoparticles or nanotechnology-enabled products. There are four main stages along a product's value chain where biological exposure could occur: (1) as-manufactured material production, (2) product formulation and manufacture, (3) consumer use and misuse, and (4) product end-of-life disposal. In the case of nanomaterials, individuals who may be exposed include researchers or engineers in the production or manufacturing line, staff and custodians in neighboring offices, families (i.e., spouses, children, and pets). Exposures may occur from the clothes of the workers, distributors and transporters of the goods, and waste and recycle management after material disposal. Determining the exposure concentration and the intake fraction is needed in order to quantify exposures to engineered nanomaterials at all stages [*180*, *181*].

As long as nanotechnology continues to provide better-performing and more sustainable next-generation consumer goods, routine exposures to nanomaterials are inevitable, but the hazards associated with engineered nanomaterials exist on a continuum. For the general population, individuals are able to recover from an injury such as an inflammatory response lasting less than a few hours. As the exposure concentration increases, the level of physiological stress also increases [*182*, *183*]. There is striking published evidence that relates the engineered nanomaterial's physico-chemical characteristics to transient (and even sustained) biological/toxicological responses [*184–187*]. For example, Poland *et al.*, among others, reported that high aspect ratio in a particle's shape or structure can lead to frustrated macrophage accumulation and fluid congestion in the lung. Persistent conditions of this kind may lead to chronic fibrosis [*50*]. Single-walled carbon nanotubes and titanium dioxide nanoparticles have been implicated in the formation of arterial plaques [*50*, *188*, *189*]. Particles with high ionic metal content in exposure media often lead to allergies and hypersensitivity. Prolonged exposure may contribute to cancers or infertility [*190*].

Contaminant containment, hazard or health banding, and categorization frameworks can aid in mitigating exposures, but measuring the exposure to biological systems is still an understudied area within the field of nanotechnology environmental, health, and safety. To monitor is to observe and check the quality (of something) over a period of time and keep it under systematic review. Nanomaterial monitoring is often classified in one of three endpoints: area, personal, or biological (Figure 4.4). The most informative material monitoring is performed when both observing the physico-chemical properties and measuring the quality/quantity of engineered materials occurs over a period of time. Biological monitoring measures contaminants, metabolites, or enzymes in an individual's blood,

urine, or exhaled breath. Together with personal and area monitoring, biological monitoring can result in quantifying exposure to engineered nanomaterials.

The tools to detect and measure engineered nanomaterials are different depending on the endpoint. For area, the current methods available to measure nanoscale aerosols include condensation nucleus counters or condensation particle counters (CNCs or CPCs), ion-charged trapping electrometry, Raman and Rayleigh scattering, scanning electron microscopy (SEM) with energy dispersive x-ray spectroscopy (EDS), scanning transmission electron microscopy (STEM), and high-resolution transmission electron microscopy (HRTEM). Most of these tools can be coupled to additional size-selecting instruments, such as differential mobility analyzers (DMA), aerodynamic and scanning mobility particle sizers (APS and SMPS), impactors, or aerosol mass spectrometers, to gain more accurate physico-chemical information.

For personal detection, protective equipment is the current best practice to mitigate exposure to engineered nanoparticles in the workplace. Dermal exposure is reduced using gloves and laboratory coats or suits. Inhalation exposure is reduced using respirators or dust masks and HEPA filtration systems. Eliminating the use of contact lenses and wearing safety glasses or goggles reduces ocular exposure. The traditional tools used to measure personal, localized particle accumulation are personal samples, gravimetric measuring after skin wipe, or photometric measuring via particle fluorescence or luminescence. Not all of these tools are suitable for detecting and measuring all engineered nanoparticles.

For biological monitoring, quantifying exposure can be accomplished by either measuring the nanomaterial itself or by measuring a signature biological marker [*191*, *192*]. Measuring the nanomaterial requires collection of tissue or body fluid for examination of the nanomaterial concentration (parent material or metabolite). Biomatter is dissolved or digested, and the resultant analyte is measured for chemical speciation and concentration in the known volume of body fluid or correlated to the known skin surface area. Measuring biological markers requires correlating the biomarker concentration to the nanomaterial internal dose. The biomarker is collected and measured in an individual's blood, urine, or exhaled breath, while the internal dose is calculated via dosimetry. There is a need to develop new

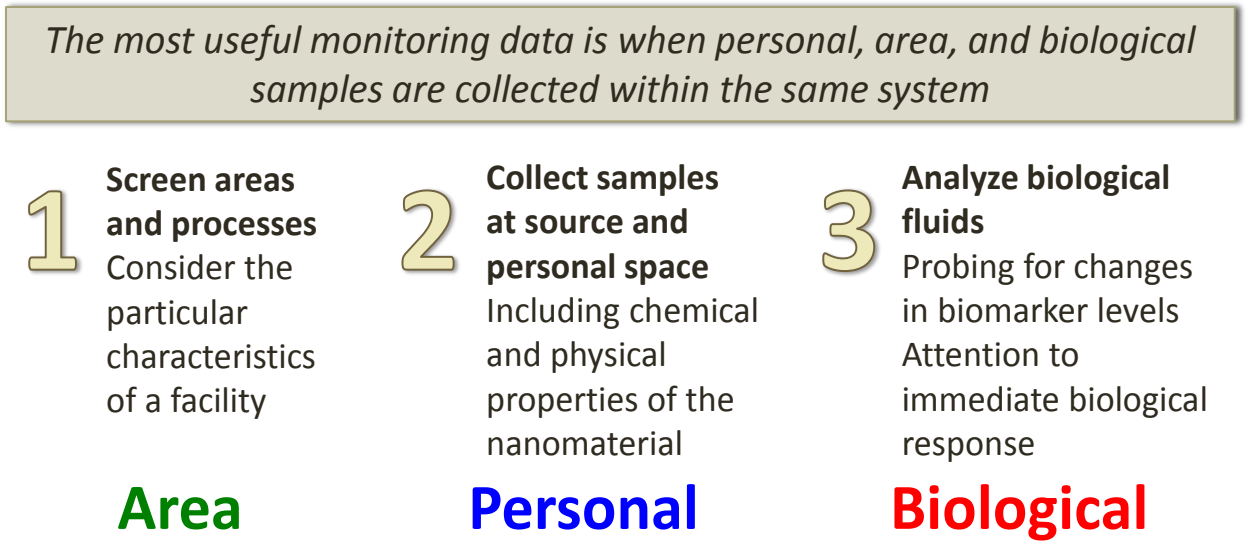

Figure 4.4 Types of monitoring. Nanomaterial monitoring is often classified as area, personal, or biological. Monitoring is defined as observing and checking the quality (of something) over a period of time and keeping that under systematic review. The most useful monitoring data is when personal, area, and biological samples are collected within the same system. (Source: C. Sayes.)

relationships between nanoparticle dose and markers of biological effects such as DNA and protein adducts, chromosomal aberrations, and genetic or proteomic markers [*193–195*]. The most commonly cited challenges related to this effort include (1) no specific biomarker exists (gene, protein, enzyme, or other); (2) the type of exposure could change the biological response (single versus multiple, direct versus indirect); and (3) personal monitoring is still being assessed (efficacy of clothing, personal protective equipment, and skin). The effects of "dose rate" have not been thoroughly investigated in the nanotoxicology literature. It is important to consider particle spread within the body, decay in number concentration, metabolized individual particles, and solubilization in biological fluids.

As a potential path forward, three major research areas are worth exploring with regard to biological monitoring of engineered nanomaterials. First, the community can learn from the polyaromatic hydrocarbon (PAH) community. Studies have shown that a suitable way of estimating PAH exposure is to measure DNA and protein adducts in blood [*196*]. Second, toxicological experimental designs can use mass spectroscopy to better understand biomarkers in fluids. Martel *et al.* have shown that liquid chromatography and tandem mass spectrometry (LC-MS/MS) can be used to characterize proteins bound to the surfaces of either synthetic or natural nanoparticles [*197*]. Third, more published manuscripts can include descriptive mechanisms of action. Recently, a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry signature peak was attributed specifically to nanoporous silica and used to quantify biomolecule absorption on the material's surface [*198*].

It makes sense to control exposure to those nanomaterials for which preliminary hazard data has already shown unwanted health effects or for those nanomaterials where the hazards are unknown. When it comes to human exposure, measuring markers in biological systems is a useful tool in moving exposure science, toxicology, and nanotechnology forward. The already published nanotoxicology literature includes clues about exposure routes, triggered pathways, tissue damage, and ADME (absorption, distribution, metabolism, and excretion) properties after exposure to nanomaterials. These data can serve as a starting point for quantifying exposures to engineered nanomaterials.

5. Exposure Quantification Studies by Medium or Pathway

Exposure Studies in Gaseous Media

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The session addressed critical issues for nanoscale particulate matter released throughout the life cycle (LCPM) of nanotechnology-enabled products. A number of important factors should be addressed when measuring nanoparticles that are aerosolized during synthesis, incorporation into products, product use, and/or incineration at the end of a product's life. These events can happen in workplaces and during use by consumers, and require answering the following considerations [*199*]:

- Characterization of the aerosol generated: composition (single or a mixture of particles, surface coating and functionalization, volatiles generated), concentration (nanoparticles and volatiles), shape of the nanoparticles (sphere, plate, fiber), and size distribution.
- Source of the generated aerosol.
- Physical and chemical stability of the aerosol with time after generation (persistence, transformation).

An important issue in measuring nanoparticles released into air is to distinguish the generated nanoparticles and gases associated with synthesis, use, and disposal of engineered nanomaterials from other preexisting particles and volatiles from sources not related to the process in question. Examples of such sources are combustion sources, diesel vehicles or equipment, and local traffic. Thus, one must incorporate a strategy to monitor background exposures in the absence of nanomaterial-related activities and processes. These background levels can then be subtracted from total exposure levels measured when nanomaterial-related processes are active. Accurate instrumentation for characterization of aerosolized nanomaterial and volatiles exists and includes both real-time instruments and time-integrated samplers that can be used to collect size-fractionated samples (Tables 5.1–5.3). Examples have been reported of use of such instrumentation with great success in plants using multiwalled carbon nanotubes (MWCNTs) and in copier centers using laser printers [*200–202*]. Unfortunately, such procedures to measure size distribution of particle mass or count, chemical composition of particles and gases, and morphology of generated structures require technical expertise and involve large, expensive equipment [*55*]. This prerequisite limits the use of these measurement and characterization techniques for routine day-to-day monitoring. Low-cost, portable, real-time monitors are available, and procedures using such instruments to evaluate workplace exposures have been published [*203*]. However, there is a loss of precision with such procedures. An additional issue with the use of the exposure methods discussed above is that these are area-sampling methods. Personal sampling of nano-aerosols generated in the breathing zones of workers or consumers would give a more realistic picture of human exposure. There has been progress in developing small, lightweight, personal samplers for characterization of nanoparticle mass concentration, number concentration, surface area, size distribution (inhalable, thoracic, or respirable

particle sizes), and loading filters for morphologic evaluation using transmission electron microscopy (TEM) [*199*]. Some of such samplers are presented in Tables 5.1–5.3. Therefore, the state of science for characterization of nanoparticles generated in gaseous media could be considered as reasonably good and improving rapidly.

Table 5.1. Indicative real-time and integrated instrumentation/methods for LCPM characterization: Real-time monitoring of released LCPM.

TNC: total particle number concentrations, RH: relative humidity, PM: particulate matter, VOC: volatile organic compound. (Source: Adapted from [*55*]).

Instruments	Measures	Size Range	Key Features
Fast Mobility Particle Sizer (FMPS) (TSI 3091)	Size distribution; TNC; electrical mobility diameter	0.0056-0.56 µm	Upper limit of 1.0 X 10^9 particles/cm^3
Aerodynamic Particle Sizer (APS) (TSI 3321)	Size distribution; TNC; aerodynamic diameter	0.5-20 µm	Upper limit of 1.0 X 10^4 particles/cm^3
Condensation Particle Counter (CPC) (TSI 3785)	TNC	0.01-1000 µm	Upper limit of 1.0 X 10^5 particles/cm^3
P-track (TSI 8525)	TNC	0.02-1 µm	Upper limit of 5.0 X 10^5 particles/cm^3
Dust Track (TSI 8520)	Mass concentration	0.10-1 µm	No size resolution; Upper limit 100 mg/m^3
Scanning Mobility Particle Sizer (SMPS) (TSI 3080)	Size distribution; TNC	0.0025-2 µm	Upper limit of 5.0 X 10^7 particles/cm^3
Total VOC (Gray Wolf Sensing Solutions)	CO_2, CO, NO_2		Parts per billion (ppb)
Q-track (TSI 8551)	Temperature, RH, and ozone concentration		
Low-Cost Total Active Surface Area Monitor (Dekati)	Surface area	0.01-3 µm	Portable, indicates 3 concentrations at programmable levels
NanoGuard (TSI, iuta)	Number concentration, size distribution, morphology	<20 to 400 nm	Real-time, offline for morphology
MicroPEM (RTI)	Real-Time PM detection ~3 to 15,000 µg/m^3		Integrated referee filter collection; onboard accelerometer to sense movement
Partector (Naneos)	Lung-deposited nanoparticle surface area	10 nm-10 µm	Concentration range 1–20,000 $µm^2/cm^3$

Table 5.2. Indicative real-time and integrated instrumentation/methods for LCPM characterization: Integrated particulate matter (PM) samplers. (Source: Adapted from [*55*]).

Instruments	Measures	Size Range	Key Features
Thermophoretic Precipitator (TP)	For TEM grids analysis	0.001 to >100 µm	Size dependent, highest for nanoparticles
Electrostatic Precipitator (EP)	For TEM grids analysis	0.001 to >100 µm	>80 (at 20nm to 100% (at 400nm)
WRASS (Nano-ID) (Naneum Ltd.)	Mobility diameter based collection	0.002-20 µm	< 0.2% Penetration; Upper stage (0.25–20 µm); Lower stage (2–250 nm)
Harvard Compact Cascade Impactor (HCCI; [*204*])	Aerodynamic diameter based collection	$PM_{2.5-10}$; $PM_{0.1-2.5}$ and $PM_{0.1}$	Size dependent collection, collects up to mg quantities of PM
Thermal Precipitator (RJ Lee Group)	Substrate to be analyzed by TEM		
Nanoparticle Respiratory Dose (NRD) Sampler	Offline analysis for counting, sizing; Personal sampler	<300 nm	

Table 5.3. Indicative real-time and integrated instrumentation/methods for LCPM characterization: Offline physico-chemical and morphological (PCM) characterization. (Source: Adapted from [*55*]).

Instruments	Measures	Size Range	Key Features
Scanning/Transmission Electron Microscopy (SEM/ TEM-EDX)	Size, particle shape and elemental mapping	0.001-10 µm	Particle morphology determination
X-Ray Diffraction (XRD)	Crystallinity and particle size	0.001-10 µm	Inference about structure of material
Fourier Transform Infrared Spectroscopy (FTIR)	Surface chemistry of particles		Chemical identification and mapping of materials
Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	Elemental analysis		Elemental identification and quantitation
Gas Chromatography-Mass Spectrometry (GC/MS)	Semivolatile organic compound (SVOC)		Chemical identification and quantitation
Nuclear Magnetic Resonance (NMR)	Functional groups analysis		Chemical identification and quantitation

One issue is the difficulty of gaining access to nanomaterial-related workplaces for research. Efforts are needed to educate employers about the benefits of exposure assessment for improvement of worker morale and productivity, since if exposures are detected, relatively simple control measures can be employed (containment, ventilation, filtration, and use of personal protective equipment); these are reasonably inexpensive but very effective.

An example of research investigating the implications of nanoparticles in gaseous media are the inhalation studies in rats. Inhalation exposure of rats to nanoscale titanium dioxide or MWCNTs has been shown to result in a defect in the ability of peripheral and coronary arterioles to respond normally to dilatory stimuli [*205–207*]. Microvascular dysfunction of the coronary arterioles would result in decreased oxygen

delivery to the heart muscle, while peripheral microvascular dysfunction would result in increased peripheral resistance and, thus, an increase in workload on the heart. Inhalation exposure of pregnant rats to nano-titanium dioxide also resulted in a decrease in pup weight and litter size, as well as microvascular dysfunction in the delivered pups [*207*]. These abnormalities appear to be due to nanoparticle-induced abnormal uterine and placental blood flow during pregnancy.

It should be emphasized that critical to these or any animal exposure studies is the use of relevant exposure doses that represent feasible human exposures [*207*]. This requirement can be achieved using National Institute for Occupational Safety and Health (NIOSH) recommended exposure levels for nanoscale titanium dioxide (nano-TiO_2) and MWCNTs [*208*, *209*] and calculating the number of days of worker exposure that would result in a similar lung burden in humans (normalized per alveolar epithelial surface area) as in these rat models. This calculation allows risk assessors to more easily relate animal data to human risk. Another take-home message is that hazard assessment of airborne nanoparticles should not be limited to the lung alone. Indeed, cardiovascular, central nervous system, and reproductive effects have been reported after pulmonary exposure to nanoparticles [*207*, *210*, *211*].

One way to study realistic exposure scenarios is to employ the integrated methodology developed by Pirela *et al.* [*212*]. This method is used to enable generation of "real world" exposures of laser printer-emitted engineered particles (PEPs) while simultaneously evaluating the physico-chemical and *in vitro*/*in vivo* toxicological characterization of such an LCPM particle system [*212*]. Various *in vitro* exposure studies of macrophages or lung epithelial cells to size-fractionated PEPs collected by sampling of this generated aerosol indicate that PEPs are bioactive, inducing mediator release from these cells [*213*, *214*]. These mediators activate morphological and functional changes (decreased gap junction integrity, induction of inflammatory cytokines, and adhesion factors) in lung endothelial cells. Such changes could result in lung edema or release of inflammatory signals in the systemic circulation, which could lead to cardiovascular changes. These cellular studies used *in vitro* doses of PEPs (mass/surface area of cultured cells), which directly relate to feasible lung burdens (mass/alveolar epithelial surface area) in workers or consumers during both acute and heavy use of laser printers. Therefore, these studies emphasize the importance of using worker- or consumer-relevant exposures (composition, size distribution, dose) when conducting hazard assessment studies in cell and animal models. More importantly, the presented integrated methodology can be applied to any LCPM system released from nanotechnology-enabled products (NEPs) across their life cycle to assess nanosafety issues. It is worth noting that the Pirela *et al*. PEP case study almost exclusively used methods developed to understand toxicological outcomes associated with ambient particulate matter. The nanotoxicology community can learn, adopt, and utilize approaches and methods successfully implemented from the ambient PM health effects community.

Human exposure to nanoparticles during spray application to a wall of a nanotechnology-enabled antimicrobial product also has been characterized [*215*]. Composition, aerosol concentration, and particle size indicate that short-term levels of nano-TiO_2 in the breathing zone of the user of this product can be as high as 3.4 mg/m^3 [*216*]. A generation system was constructed using an automated finger to spray this product on a surface within a chamber. The aerosol generated in an animal exposure chamber closely mimicked the concentration, composition, and particle size of the aerosol produced during human application of this spray. Inhalation exposure of rats to this generated aerosol resulted in a dose-dependent, transient, inflammatory response [*217*]. Since the physico-chemical characteristics of the human and animal exposure were nearly identical, animal dose and time dependence could be directly related to duration of human spraying by calculating human lung burden from airborne nanoparticle concentration, inhaled volume/time of application, and particle-size-dependent alveolar deposition, and

normalizing the rat lung burden to human lung burden by alveolar epithelial surface area. Risk analysis of the rat data indicates that there is little risk associated with likely consumer use of this product.

In summary, the following conclusions can be drawn from this session:

- Instrumentation and methods are currently available to measure and characterize worker or consumer exposure to nanoparticles during the life cycle of nanotechnology-enabled products.
- Hazard assessment, using *in vitro* and *in vivo* test systems, should use exposure doses and structure sizes (agglomerated versus dispersed nanoparticles) that reflect likely human exposures.
- It is possible to construct generation systems that closely mimic real-world exposures. Use of such exposure systems to generate nanoparticles, capturing the interactions of mixed exposures, makes cell and animal testing more useful for risk assessment.
- Evidence indicates that although inhalation is likely the major route of worker and consumer exposure to aerosolized nanoparticles, evaluation of nanoparticle bioactivity should not be limited to pulmonary responses. Indeed, evidence exists indicating that cardiovascular, central nervous system, and reproductive changes can occur after lung exposure to nanoparticles.

Exposure Studies in Aqueous Media

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In a recent report by the National Academy of Sciences, exposure science is defined as "the study of the contact between receptors (such as humans or ecosystems) and physical, chemical, or biologic stressors… including the roles of space and time" [*218*]. Aqueous systems are an important phase in the release and exposure to one potentially important class of chemical stressors, engineered nanomaterials (ENMs). This section of the workshop report focuses on ascertaining and predicting how ENMs propagate through aqueous systems to reach important ecological and human receptors. Considered here are topics across the continuum of evaluating release from nanomaterial-containing products in aqueous media [*219*], predicting fate and transport in aquatic systems [*220*], using ENM exposure information to properly evaluate and extrapolate hazards derived from toxicity assays [*221*], and characterizing and quantifying aqueous exposure in food contact materials [*222*]. New approaches and techniques were discussed that advance exposure science in this universal medium. Several questions were posed related to the release and subsequent exposure to ENMs in aqueous media, including: (1) What are the challenges with measuring exposure in aqueous media? (2) What new methods are available for analysis of ENMs over the life cycle of the product and related to release of ENMs into aqueous media? and (3) What are the challenges with predicting and modeling exposure?

In aqueous systems there are several questions that need to be addressed related to the fate and toxicity of released particles in order to decrease the uncertainty in characterizing exposure to ENMs released from products. In the example by Fairbrother *et al.* (Figure 5.1, [*219*]), the release of carbon nanotubes (CNTs) can occur through a range of environmental conditions such as the presence of an oxidizer, physical abrasion, and ultraviolet (UV) light, among others. The polymer-containing ENM may release particles in

the form of fragments containing polymer and ENM or the ENM alone. Methods are needed to characterize the material released from a polymer composite, both as a released nanoparticle (e.g., similar to a pristine nanoparticle [NP] used in manufacture) and as a particle bound to a fragment of the polymer. These methods should be able to accurately determine the rate of release from the product, how much is released from the product, and the properties of the fragment released from the product.

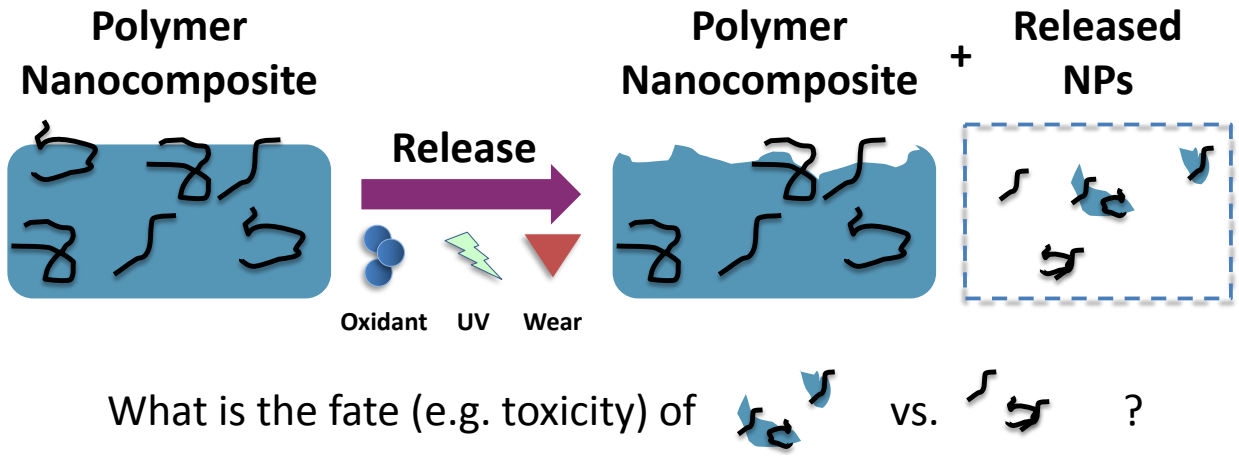

Figure 5.1 Concept of carbon nanotubes released from polymer nanocomposite. (Source: H. Fairbrother.)

New methods, approaches, and understanding in the context of new media have been developing in the last couple of years, but challenges remain. There has been significant progress developing analytical measurement tools for ENMs in relevant products and media throughout the life cycle of NEPs (i.e., Nanomaterial Measurement Infrastructure Goals 1 and 4, see [*2*]). Advances in analytical methods such as inductively coupled plasma mass spectroscopy (ICP-MS), single particle ICP-MS (spICP-MS), field flow fractionation, transmission electron microscopy (TEM), ultraviolet-visible (UV-Vis) spectroscopy, thermal gravimetric methods, and near-infrared fluorescence , have helped enabled a much richer understanding of how quickly nanomaterials agglomerate, settle, and transform in aqueous media. Additionally, these new tools have enabled characterization and quantification of the release of ENMs from polymer composites that are increasingly used in consumer products.

The biggest analytical challenges are detection limits with trace analysis and real-time sampling methods. Due to its extremely high sensitivity, a comparatively new technique, spICP-MS, has been used to measure release of carbon nanotubes from polymer composites. Due to the ambiguities inherent in detecting CNTs by carbon analysis, particularly in complex environmental matrices, spICP-MS has been used to detect trace catalytic metal nanoparticles intercalated in the CNT structure as proxies for the nanotubes. However, further quantitative investigations are needed on more complex, realistic matrices and exposure scenarios. For example, the findings from a study on deionized water will not necessarily apply to a system like milk.

With regard to release characterization, more work is needed on model systems to try to develop and demonstrate the validity of predictive models. Although studies with model polymer-ENM composites synthesized in the laboratory can provide useful insights on the release of the ENMs, it should be kept in mind that commercial products are complex, and simplified systems may not accurately represent what is used in commerce. Systems used in polymer-based products are limitless, and therefore, models are required to be able to predict potential releases. These models will require knowledge of the polymer's properties related to release of ENMs because of the factors that influence release. For example, factors that influence migration processes of ENMs from polymer products into aqueous systems include

agitation, pH, surfactants, and temperature. Where dissolution of metal ENM occurs, these factors include pH, ionic strength, size and shape, and concentration. The migration of ENMs from polymers such as low-density polyethylene and polypropylene has been described by parameters such as a coefficient of diffusion, which can subsequently be used in models to predict release [*223*].

As the ability to detect and measure ENMs in aquatic systems has improved, so has the ability to determine and model their environmental multimedia distributions. Intermedia transport processes will disperse the ENMs throughout aquatic and atmospheric media. Regarding the state of the art in modeling fate and transport of ENMs in aquatic media and multimedia distribution of ENMs, modeling results demonstrate that the transport of sediment particles with adsorbed ENMs can play an important role in ENM transport and deposition in aquatic systems. Various approaches for estimating potential environmental releases of ENMs and associated exposure concentrations include experimental laboratory and mesocosm fate and transport studies, environmental monitoring, and transport models developed at different scales. Environmental transformations of ENMs have important effects on their transport and toxicity. As examples, dissociation of silver nanoparticles produces toxic silver ions, but reduction of ionic silver by natural organic matter leads to formation of silver nanoparticles. Moreover, light-induced transformations of graphene oxide produce much more hydrophobic—and likely more toxic—polycyclic aromatic products. The Water Quality Analysis Simulation Program (WASP) is one numerical, mechanistic fate and transport model that is being modified to assess ENM behavior in the aquatic environment. Process descriptors and data, e.g., for aggregation, deposition, and transformations, and data inputs for conditions prevalent in aquatic environments, are incorporated into WASP to provide improved understanding of the factors that influence exposure to ENMs.

Linking environmental exposures to released ENMs with relevant toxicity data is a significant challenge. Studies using pristine ENMs are challenged with maintaining constant exposures in aqueous media. Challenges include varying mass concentration and agglomerate size as well as the requirement for renewal of exposure media and addition of stabilizers to maintain an ENM dispersion. Methods to describe exposure in aqueous media go beyond traditional mass concentration dose metrics to include particle number, surface area, and dissolved fraction (for metal ENMs) [*224*]. This assessment becomes more challenging for ENMs that are released from a product as a fragment containing the polymer. There are logistical challenges such as obtaining adequate material for fate and toxicity testing. However, approaches are under development such as the development of a factor that is the ratio of the toxicity of the fragment containing the ENMs to the toxicity of pristine ENMs [*225*].

Exposure Studies in Biological Media

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The measurement and characterization of nanomaterials in biological tissues is complicated by a number of factors. These challenges include:

- The sensitivity of an assay to small-sized particles or materials at low concentrations.
- Difficulty differentiating particle phases from ionic phases of nanoparticles that dissolve.

- The ability to distinguish different forms and transformations of materials related to the biological matrix.
- Difficulty distinguishing exogenous nanomaterials from normal biological tissues (since they may be composed of biologically common elements such as carbon).
- Difficulty localizing sparsely distributed materials in a complex substrate (the "needle in the haystack" problem).
- A plethora of potential artifacts of analysis.

In this breakout session, four speakers discussed the current state of the art with regard to quantifying the exposure concentration of nanoparticles in biological tissues and biological media [*226*–*229*]. Importantly, the studies ranged from examining concentrations of NPs in organism tissues using microscopic measurements, to using the mass concentration of NPs in synthetic stomach fluid, a surrogate media to assess changes to nanoparticles after ingestion by humans.

During the session, different NP usage scenarios were described along with the relevant quantitative measurement needs for those scenarios. For CuO nanoparticle-treated wood, issues include the potential for NP release during sanding and drilling, and changes to the NPs that may occur after ingestion by humans of released NP-containing wood fragments [*226*]. In this usage scenario, aging and transformations of NPs during the life cycle of nanotechnology-enabled products are key factors related to determining the relevant exposure concentration by humans. Conversely, understanding the exposure concentration of the NPs as manufactured is the most important factor when NPs are administered to humans as a drug [*228*]. In these scenarios, the literature produced to date on analytical methods for the as-manufactured nanoparticle would be most relevant.

One key theme is the importance of robust control experiments to avoid potential artifacts. For example, the likelihood of "false positive" identifications of nanoparticles is possible when using microscopy approaches [*228*]. Similarly, it is important to fully separate *C. elegans,* the model organism, from suspended gold nanoparticles prior to ICP-MS) and spICP-MS [*227*]. A comprehensive set of control experiments can be used to avoid artifacts prior to assessing the biodistribution of carbon nanotubes in rats using hyperspectral imaging [*229*]. In general, avoiding artifacts and operating a technique accurately requires extensive experience and attention to seemingly minor details that may not be considered by scientists who are new to an analytical technique.

Overall, making quantitative measurements of various nanoparticles in biological tissues or media is becoming increasingly possible as analytical technology improves. However, many of the recent techniques are expensive, not yet standardized, and only have limited availability—at this point primarily for research purposes. Thus, collaborations are often needed with research organizations, institutes, or universities to make these measurements. This necessity poses a significant barrier for commercialization of NPs and related industries, especially when it is necessary to quantify NP exposure concentrations, such as during regulatory approval processes. There is a need to move toward more widely available instruments, which may occur as the costs for the instruments decrease; in addition, there is the need for more sensitive, precise, and quantitative approaches. However, there is a risk that increased access to these instruments could lead to scientists who do not have extensive experience with the techniques acquiring data that is impacted by artifacts. The development of standards and the cataloging of confounding artifacts could help avoid this outcome.

The future outlook for the next five or ten years for making quantitative measurements of nanoparticle exposure concentrations in biological media or tissues is that there will be increased availability and decreased cost and ease of operator use for many techniques. A key need is to develop standard analytical methods and to conduct interlaboratory comparisons to determine their precision and bias. It is important to consult with stakeholders, including companies and regulatory agencies, to determine what measurements or sets of measurements are sufficient for quantifying exposure in these tissues. In other words, what type of precision and limits of detection, for example, are needed for the technique to be "fit for purpose"? It is also important to develop analytical protocols specific for key biological tissues with appropriate controls and standards to minimize the opportunities for measurement artifacts. Lastly, it is important to develop quantitative methods for "as-manufactured" and "weathered/transformed" NPs, given the different NP usage scenarios (e.g., drugs or consumer products) that are relevant for different governmental agencies in the United States and worldwide.

Epidemiology: The Exposure–Health Interface

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This session featured researchers conducting state-of-the-science studies of exposure and associated measures or indicators of possible early health effects among workers and others exposed to engineered nanomaterials. The goal of this session was to raise awareness among other disciplines of the importance of incorporating appropriate physical, chemical, and route-of-exposure metrics to studies of health effects in those exposed to engineered nanomaterials, and to identify research needed to correlate exposure data and health effects.

Epidemiology for nanomaterials is challenging. The population of nanotechnology workers is relatively small [*230*, *231*], and the amounts of engineered nanomaterials handled on a daily basis per worker are also small and difficult to measure [*61*, *232*]. To perform an epidemiological study that can link an ENM to disease, epidemiologists must first verify that exposure is likely. They then will use the degree of hazard indicated by toxicology to prioritize which materials to investigate with cohort and cross-sectional studies [*233*]. Many candidate ENMs are chosen for study by analogy, based on the wealth of information that already exists on the links between respirable pollutants (e.g., carbon, asbestos) and health effects such as pulmonary fibrosis and cancer. Some important characteristics in this regard are particle shape (which is difficult to quantify in a standardized way) and mass (simply because most toxicology data are derived from mass-based air concentrations). Relevant *in vivo* data for long-term exposure to skin remains sparse, while inhalation exposure studies are moving from acute, high-dose to subchronic, lower-dose studies that are more reflective of real-world exposure scenarios. The U.S. Food and Drug Administration has issued a 90-day testing duration recommendation for inhalation but has not yet provided guidance on how long to test these materials for skin [*234*, *235*].

Inferred health concerns about nanomaterials are based on their size and shape. It is thought that cardiovascular disease may result from the inflammatory cascade initiated by the particle, not the particle itself at the site of exposure [*236*]. A long, thin shape may confer asbestos-like properties; a lot is known

about ultrafine material and fibers, so researchers have theorized that CNTs could cause similar effects [*237*]. Toxicological and environmental studies of nanoparticles suggest possible pulmonary effects (from CNTs and carbon nanofibers [CNFs]) and, based on air pollution epidemiology, cardiovascular effects. However, the most relevant exposure assessment metrics are still uncertain [*61*]. Additionally, when evaluating nanomaterial risk, both individual (clinical) and population views are relevant. While assessing the association between occupational exposure and health, confounding by lifestyle factors such as smoking is a potential concern. However, it is important to note that effects of occupational exposure on lung cancer risk can be detected even among smokers [*238*]. Epidemiology attempts to isolate causal factors and to determine how they interrelate to cause disease. Some factors are not actually confounders in a particular study, but are effect modifiers; that is, they are not associated with either exposure or disease (or both), but their presence may amplify or mitigate the effect of exposure. An example is cigarette smoking in uranium miners exposed to radon progeny in the southwestern United States. In this study, smoking was unrelated to radon exposure, but the interaction of smoking and radon in causing lung cancer was found to be less than multiplicative, but more than additive [*238*]. Therefore, attention to effect modifiers can be important in projecting risks from occupational exposure to another population.

Exposure to ENMs for nanotechnology workers is task-dependent, with harvesting, dry powder handling, cleaning operations, and waste disposal posing the greatest exposure potentials among carbon nanotube workers [*179*, *239*]. An industry-wide exposure assessment found both inhalable and respirable elemental carbon (EC) mass. TEM-based structure count concentrations were important and are being used in an epidemiologic study [*61*]. The respirable fraction is often much less than 50% of the inhalable fraction due to agglomeration increasing particle size to 2–5 µm. NIOSH recommended exposure levels (RELs) are based on the respirable fraction, so only measuring the inhalable fraction (and assuming it is all respirable) is misleading.

In a complex real-world industrial environment, other ongoing tasks and processes may influence the results of exposure assessment for a particular job task if it is not separated sufficiently by space and time. When performing occupational exposure assessments along the life cycle of an ENM in an occupational environment, exposures tend to reflect the stage of use of the ENM-containing product; that is, where first used, ENMs captured in worker breathing zones tend to resemble as-manufactured ENMs. Further down the chain of use and along the waste stream, samples captured tend to contain larger aggregates and agglomerates of mixed composition that include both ENMs and other constituents [*240*–*243*]. Often, the overall ENM concentration in the task area and worker's breathing zone is low compared to the background ultrafine particulates. If the target ENM and the particulates are of the same elemental compound, then nonspecific measurement metrics (e.g., gravimetric measures or particle counts) may give misleading results. Actual particles found in the environment or in the workplace are frequently agglomerated or aggregated, on the micrometer scale, and unrespirable.

Additionally, the associated costs, time, and lack of standard and validated methods make it difficult to implement an occupational exposure assessment program or attempt to comply with recommended occupational exposure levels (ROELs) for ENMs. Epidemiologists need validated analytical techniques that consistently, reliably, and accurately identify and characterize ENMs captured in the occupational settings. One wish would be for a single air-sampling instrument that collects data on morphology, composition, agglomeration state, and particle size. Ideally, such an instrument would also provide fine size resolution ranging from nanoscale particles to ultrafine particles. Researchers, employers, and industries that incorporate ENMs into their manufacturing processes and industry requirements and/or consumer products require EHS answers faster than can be provided using currently available tools.

NPs already have a role in cosmetics. Over 1600 products listed in the Wilson Center Project on Emerging Nanotechnologies (PEN) Consumer Products Inventory [*12*] contain nanomaterials; L'Oréal alone has over 200 nanotechnology patents [*235*]. The utilization of nanometals in sunscreens is probably the product application best appreciated by the lay public; its purpose is to minimize the unsightly color of zinc- or titanium-based UV filters in order to enhance consumer use. Ultraviolet radiation is an established carcinogen, and therefore, unprotected exposure is likely a greater risk than potential health effects of ENMs in sunscreens.

In terms of cutaneous exposure to ENMs, the outer layer of the epidermis, the stratum corneum, prevents entry of most organisms and nanoparticles greater than 13 nm in diameter. Routes of entry are intercellular (between), transcellular (through), and follicular. The follicular pathway is unique, as it is a natural imperfection in the barrier and can allow micrometer-sized materials passage, thereby facilitating entry and access to deeper aspects of the skin. In general, ENMs, due to their size, exhibit a greater and longer resident time on the skin, which can result in both a higher likelihood of permeation as well as an occlusive or film-like effect preventing transepidermal water loss and improving skin hydration.

The safety of nanomaterials in consumer products has been questioned, and answers are limited due to a lack of diagnostic tools and techniques with respect to following the lifetime of ENMs in skin. *In vitro* studies are limited, and available results are mixed in terms of ENM safety outcomes. Research has shown that commercially available ZnO nanoparticles do not penetrate beyond the stratum corneum. This result is true even when the skin has lesions (an effect modifier), although skin damaged by tape pulls did allow penetration. Nanoparticles can also be used as effect modifiers, protectively. Calcium phosphate nanoparticles can be used to prevent nickel from getting into the skin to cause a reaction.

For research purposes, rats and mice are very poor models for human skin in terms of anatomy and histology. Alternatively, pig skin is very similar to human skin. Multiphoton imaging with confocal microscopy validated with scanning electron microscopy (SEM) can be used to noninvasively image in real time instead of a biopsy and histopathology with hematoxylin and eosin (H&E). This technique makes acquiring a time series of data during an *in vivo* exposure experiment much easier. Finally, when assessing potential exposure, researchers should consider the vehicle as well as the ENM. Just because the as-manufactured ENM is at the nanoscale in the product does not mean it will interact with the skin that way. It may agglomerate, otherwise transform, or bind with something else in the environment.

Exposure Quantification Studies by Medium or Pathway Roundtable

Moderator: Cathy Fehrenbacher, MS, CIH
Chief, Exposure Assessment Branch, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency (EPA)

Panelists: Sara Brenner,[20] Vincent Castranova,[21] Steve Diamond,[22] Adam Friedman,[23] and Elijah Petersen[24]

Introduction

Cathy Fehrenbacher of EPA led representatives of each of the concurrent technical sessions on the second day in a discussion of the needs and challenges of exposure science quantification in different media and pathways. The panelists, who included researchers from specific disciplines (airborne exposure, aqueous exposure, exposure in biological media, and epidemiology) and different sectors (academia, medicine, industry, and Federal Government) were asked to consider what data, tools, and modeling capabilities they envision or desire five to ten years in the future. Their discussion covered data and modeling needs, general research strategy including desired tools and guidance, and future considerations for the field. The following is a brief summary of some of the comments that were offered by the panelists during this discussion; it does not represent a consensus of the panel, but rather a sampling of the various viewpoints that were expressed.

Data and Modeling Needs

Realistic exposure levels and the actual physical properties of the material during exposure are needed to inform toxicology studies and to develop realistic models for exposure. This need includes real-time exposure assessment of consumers to nanoparticles when they use nanotechnology-enabled products. Data from long-term exposure studies are also needed. This information, combined with biodistribution models for nanoparticles within an organism, are needed to inform not only the mass, but also particle number and surface area relevant to exposure. However, a fair amount of empirical data will be necessary to inform and parameterize any realistic model. With this requirement in mind, the minimum characteristic approach advocated a few years ago should be avoided. Additional data may be very useful in terms of broad-spectrum analysis, and having only parsimonious data limits the availability of null data with which to calculate uncertainty factors. A risk is that researchers define a minimal characterization set and find out in 10 years that they missed 20–30% of the characterization needed. Finally, background particle values in any environment must be considered. Natural ultrafines, which are the incidental particles that occur in most environments, should be measured in addition to the engineered nanoparticle of interest.

However, it is still unclear what the relevant metrics are in field exposure scenarios. Although the most common metric is mass per cubic meter, more relevant exposure assessment metrics may be particle count per cubic meter and total surface area of particles per cubic meter. Moreover, for specific exposure scenarios, various other factors must be considered. Exposure studies for cosmetics and drugs should incorporate how consumers actually use products over time. For dermally applied products, better

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[21] West Virginia University
[22] NanoSafe
[23] Einstein College of Medicine, George Washington University
[24] National Institute of Standards and Technology

understanding is needed of the vehicle that contains the nanomaterial and how it is being delivered; this will ultimately affect if the consumer uses it and how or whether it the product penetrates the skin. Tests looking at nanoparticle transfer from food wrappers to simulated food items need to be evaluated to ensure they are done in a comparable, standard, and realistic way. In aquatic systems, determining how environmental factors like sunlight and agitation affect the release potential of nanomaterials in water is important. When considering airborne exposure, determining whether NPs physically or chemically change while in the airstream is essential. For instance, would NPs agglomerate with or attach to other nanoparticles in the air, or would chemicals in the air absorb the NPs? Most hazard testing does not include data on the fate of ENMs, so there is little information concerning the rapid loss or transformation of materials from test systems. Exposure values and toxicity potency values derived from those tests may be questionable. Guidance documents regarding test systems and methods that would make test results more comparable are currently under development under the auspices of the Organisation for Economic Co-operation and Development (OECD).

Research Strategy

Creating a broad network throughout the United States and internationally for sharing of resources and draft texts will allow for rapid movement toward the community's goals. This effort includes collaborative discussion across sectors at least annually to facilitate translation of the community's work into methods. This continued dialogue with all stakeholders is necessary since what and how to measure is dependent on stakeholder perspective. Additionally, exposure scientists need better integration with industry since that is where the technologies are employed and where workers are handling the materials.

Studies should transition from simple to complex, more realistic model systems, as well as move beyond the dose–response relationship and focus on the mode and mechanism of action. An adverse outcome pathway (AOP) model will help the field move forward with rapid throughput and analysis using genomics and proteomics data to look at population-level outcomes by way of biomarkers. From a research perspective, it would be interesting not to limit research to 100 nanometers since important nanophenomena may not adhere to such limits.

Future Considerations

The exposure science community needs less expensive and easier-to-use techniques. Innovating new technologies aimed at rapid and high-throughput screening for environmental and occupational samples would be extremely useful. Lowering the cost of these technologies will make them more available for regulatory testing to facilitate compliance and good stewardship in industry, particularly in smaller companies. Developing high-throughput *in vitro* screening testing methods will support data-driven, predictive risk assessment and help circumvent the impracticality of testing every possible exposure scenario using chronic inhalation exposure studies. Categorization of nanoparticles by physical properties, mechanism of action, and mode of action is still needed to actualize such predictive tests. Some type of read-across or categorization supported by standard and reproducible methods would be helpful. One method for collecting this information may be for reviewers and journal editors to request such data during the publication process. Ultimately, the community should begin addressing the more complex NEPs that are now under development, so that in five to ten years the tools and the ability to evaluate them will be available.

6. Conclusions and Next Steps

Roundtable—Exposure Science in the 21st Century: How its Principles Can Transform Safe and Sustainable Innovation and the Development of Nanomaterial Products

Moderator: Treye Thomas, PhD
Chemical Hazards Program Lead, U.S. Consumer Product Safety Commission

Panelists: Paul Lioy,[25] Tina Bahadori,[26] Shaun Clancy,[27] Chuck Geraci,[28] and Greg V. Lowry[29]

This panel included a variety of stakeholders from both the public and private sectors with the goal of discussing how furthering exposure science will be a key driver for nanotechnology safety assessments. The webcast of this panel is archived online.[30] The entire edited transcript is also being submitted for publication as a special feature in the *Journal of Exposure Science and Environmental Epidemiology*.

Some questions asked of the panel were as follows:

- What is exposure science in a nanomaterial context?
- How can progress in the nanomaterial-exposure science community be compared to that in the nanotoxicology community?
- How does the development of nanotechnology-based consumer products benefit from answering exposure science-based questions?
- How do you understand the risk for nanomaterials that may be used in unknown ways by producers of consumer products?
- What types of data collection and management are needed along the value chain of nanotechnology-enabled products to assess or predict potential exposures to nanomaterials in those products? Can we integrate that data across sources to get a sum total exposure potential?
- What do we need to move exposure science forward? Do we need more methods?

In discussing these questions, the energetic discussion among the panelists and the engagement from the audience highlighted both the complexity of the issues and the opportunities that the current state of the science is providing to address them. Observations that were offered by the various participants included the following:

- Exposure scientists have been measuring ultrafine particulates for a long time; it is not new (John Aitken measured ultrafine particulates in 1888 [*244*]). To move forward, the community should focus on the complex issue of correlating the biological activity of an engineered

[25] Rutgers Environmental and Occupational Health Sciences Institute
[26] U.S. Environmental Protection Agency
[27] Evonik Corporation
[28] National Institute for Occupational Safety and Health
[29] Carnegie Mellon University
[30] www.tvworldwide.com/events/nnco/150707/

nanomaterial (ENM) to a specific property of that material, and, subsequently, determining if that property is a feasible measure (metric) of exposure.

- Successful commercialization of nanotechnology requires assessment of the health implications of materials incorporated into manufactured products; robust exposure assessments play an important role in this assessment.
- It is necessary to develop approaches that rapidly estimate/predict exposures and enable timely decisions about the safe and sustainable design and use of nanomaterials in products. This need is particularly true for ubiquitous consumer products.
- Exposure science specific to ENMs considers the real-world continuum of exposure and, therefore, risk. Engineered nanomaterials will change over time, and their availability to a receptor, human, or the environment is different at various stages of the life cycle. Evaluation of exposure to most ENMs should move beyond analyzing the properties of pristine, as-manufactured ENMs and instead consider the products of (bio)transformation and other interactions with environmental contaminants.
- Obtaining exposure information to improve risk-based decisions is difficult; the effort required should not be underestimated. When possible, the community should leverage the knowledge of multiple stakeholders. This leveraging was done in the NanoRelease Project,[31] not only to obtain solid information but also to come to a common understanding on how to collect, analyze, and use the information.
- A significant knowledge gap exists in knowing where and how large volumes of ENMs are actually processed and incorporated into products. Absent that knowledge, it is difficult to conduct valid, science-based estimates of risk to human or environmental health.
- The most constructive path to ensuring safe and sustainable innovation in nanotechnology development is one that is founded on substantive private–public collaboration, partnership, and knowledge sharing.

U.S.–EU Collaboration on Exposure: The *Exposure Through Product Life* Community of Research

Martie van Tongeren, PhD
Research Director, Institute of Occupational Medicine (Scotland, UK)

Rick Canady, PhD
Director, NeutralScience L3C (USA)

Exposure assessment is a critical part of health and environmental risk assessment, without which it is difficult, if not impossible, to study the determinants of risk or to control and manage these risks. It is widely recognized that exposure assessment in the field of nanotechnology is extremely complicated, specifically when carried out in complex exposure scenarios. Hence, it is essential that resources are allocated to develop/adapt tools and methodologies that can be applied in a cost-effective way, without nonessential duplication of effort. Considering that resources are limited, collaboration and coordination between scientists is vital. Within the European Union, the number of nanotechnology-related safety projects that focus on or include exposure assessment elements has grown considerably over the years. Several projects

[31] www.ilsi.org/ResearchFoundation/RSIA/Pages/NanoRelease1.aspx

have been funded that focus predominantly on exposure assessment (e.g., NANODEVICE,[32] NANEX,[33] nanoIndEx,[34] and most recently, NanoFASE[35]). Within the European NanoSafety Cluster,[36] Working Group 3 focuses on exposure assessment and aims to promote improvement and harmonization of methods through sharing of project methods, techniques, results, and data, and to coordinate relevant cross-project activities.

The EU-U.S. Community of Research (CoR)[37] working groups were set up several years ago to promote, facilitate, and coordinate collaboration between EU and North American researchers in the field of nanotechnology environmental, health, and safety research. One of these CoRs, The *Exposure Through Product Life* Community of Research, is focused on exposure assessment. The group has met during various workshops over the last few years and is developing a coherent program of work. The CoR is seeking to establish a core group of 4–8 people covering the various exposure disciplines who will develop an active work plan in areas such as methods and tools, databases, and data sharing. This CoR will work closely with other CoRs (e.g., the database, modeling, and risk assessment CoRs). Providing incentives to encourage participation in the CoRs is important; the group is seeking opportunities for joint funding, papers, and workshops or conferences.

Common Themes and Next Steps

Treye A. Thomas, PhD
Chemical Hazards Program Lead, U.S. Consumer Product Safety Commission

The successful commercialization of nanotechnology requires assessment of the health implications of materials incorporated into manufactured products. Robust exposure assessments play an important role in this evaluation, and reliable, inexpensive methods must be developed and improved to meet current and future exposure science needs. Evaluation of exposure to ENMs should move beyond analyzing the properties of pristine, as-manufactured ENMs and instead consider the products of transformation and other interactions with environmental constituents.

The community cannot afford to evaluate exposures to ENMs one material at time. It is necessary to develop approaches that rapidly estimate and predict exposures and enable timely decisions about the safe and sustainable design and use of nanomaterials in products. A significant knowledge gap exists in knowing where and how large volumes of ENMs are actually processed and incorporated into products. Absent that knowledge, it is difficult to conduct valid, science-based estimates of risk to human or environmental health.

The most constructive path to ensuring safe and sustainable innovation in nanotechnology development is one that is founded on substantive private–public collaboration, partnership, and knowledge sharing. In the future, lessons learned over the past decade should guide the responsible development of ENMs and other emerging materials. To move forward, the community should focus on the complex issue of correlating the biological activity of an ENM to a specific property of that material, and subsequently, determining if that property is a feasible measure (metric) of exposure.

[32] cordis.europa.eu/project/rcn/90995_en.html
[33] cordis.europa.eu/project/rcn/94285_en.html
[34] cordis.europa.eu/project/rcn/63053_en.html
[35] cordis.europa.eu/project/rcn/197194_en.html
[36] www.nanosafetycluster.eu/
[37] us-eu.org/

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Appendix A. Posters Presented

Posters from Recipients of the QEEN Conference Travel Award for Graduate Students and Postdoctoral Associates

During the first evening of the Quantifying Exposure to Engineered Nanomaterials from Manufactured Products (QEEN) Workshop, there was a poster session featuring 18 academic posters. As an important part of the meeting, workshop organizers were able to award travel grants to seven graduate students and postdoctoral associates to present posters during this session. QEEN funding allowed nascent researchers studying exposure science an opportunity to interact with scientists from all over the world and to share their work. The posters of each recipient of the Conference Travel Award were entered into the *QEEN New Investigator Award* Poster Contest. A panel of judges evaluated each poster based on (1) knowledge and clarity of the presentation (40%), (2) poster appearance (20%), (3) quality of the work (20%), and (4) quality of the abstract (20%). Overall, the judges were delighted by the experience, saying that all of the research was excellent and that it was invigorating to see the great work being done by these enthusiastic new investigators. To see interviews with some of these new investigators, including the winner of the *QEEN New Investigator Award*, please visit the webcast archive for the conference.[38]

Below are abstracts of all the posters presented by QEEN Conference Travel Award recipients, with the travel award winners for each contribution marked with an asterisk (*).

Winner of the QEEN New Investigator Award: Dilpreet Singh

108.12 Nano-waste: Environmental health and safety implications during thermal degradation/ incineration of nanotechnology-enabled products at their end-of-life

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Engineered nanomaterials (ENMs) are increasingly being incorporated into consumer products such as car tires, paints, toners for printing equipment, building materials, and cosmetics, to name a few. This exponential proliferation of nanotechnology-enabled products (NEPs) in the consumer market has rendered human exposure to ENMs released across the life cycle of NEPs inevitable. Over the past decade, the risk assessment paradigm for nanomaterials has focused primarily on potential adverse effects of as-manufactured (raw) ENMs. However, the physico-chemical properties of ENMs may be drastically altered across their life cycle, especially when they are embedded in various NEP matrices. There is limited understanding on the release mechanisms and properties of released particles throughout the NEP life span, which may or may not contain the ENMs used in its synthesis.

The end-of-life scenario of NEPs through thermal decomposition is of particular interest and raises concerns of a possible emerging nano-waste problem from the resulting byproducts of such a process. Recent studies on the material flows of ENMs through society indicate that 60–80% of all ENMs end up in landfills and approximately 9,000 metric tons/year end up in incineration facilities. Additionally, the use of ENMs in building materials and furnishings raises concerns about the implications of incidental fires in the built environment.

[38] www.tvworldwide.com/events/nnco/150707/

Here, we systematically investigate the thermal decomposition of one of the most widely used industry-relevant family of NEPs, namely, thermoplastic polymer nanocomposites enabled with a variety of organic and inorganic nanofillers using a recently developed standardized, versatile, and reproducible integrated exposure generation system (INEXS) that allows for the systematic physico-chemical and toxicological characterization of the thermal decomposition of NEPs. The target of the study is to establish a fundamental understanding of the parameters that govern the thermal decomposition of NEPs and affect the physico-chemical properties of the byproducts (released aerosol and residual ash).

Our results indicate that thermoplastic polymer matrix strongly influences the size and morphology of the released aerosol, while there is minimal but detectable nano-release, especially when inorganic nanofillers are used. The chemical composition of the released aerosol was found not to be strongly influenced by the presence of nanofiller at least for the low, industry-relevant loadings assessed here. Furthermore, the morphology and composition of residual ash was found to be strongly influenced by the nanofiller presence. Upon thermal degradation of the NEP, the nanofillers surfaced with the brittle degraded thermoplastic matrix of the residual ash holding them together, thereby making them prone to release under mechanical or weathering conditions. The mass concentration of the nanofillers was significantly enhanced in the residual ash as compared to that in the original NEP.

The findings so far raise important questions and concerns regarding exposure to released engineered nanomaterials in byproducts to professionals (incineration facility employees, fire fighters) or consumers (incidental fires in buildings). Disposal of residual ash in landfills raises environmental, health, and safety (EHS) concerns regarding possible release of ENMs in environmental media as a result of the thermal degradation of the polymer and under weathering conditions. Thus, the generated data and developed methodology are of crucial importance in addressing the life cycle EHS implications of NEPs and will facilitate the development of safer-by-design NEP approaches, exposure control practices, and a risk assessment framework that is based not on “raw” ENM properties but on real-life exposures and toxicological properties of associated byproducts.

Honorable Mention for the QEEN New Investigator Award: Jacelyn Rice

108.09 Release of silver nanoparticles from nanotechnology-enabled water treatment membranes across the product’s life cycle

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Duke University’s Center for the Environmental Implications of Nanotechnology

In recent years progress has been made in the development of nanotechnology-enabled polymer membranes for water treatment, giving way to the design of next-generation membranes with high performance and antifouling properties. Many studies note the potential added benefit of incorporating nanosilver into water purification applications, and point-of-use products are currently available for purchase. The potential effects of leached nanomaterials to the environment illuminate the need to forecast exposures in support of future risk assessments. Here we aim to help address this research need by quantifying release under varying use and disposal scenarios. This research explores the roles of polymer type, membrane pore size, and dissolution matrix in the release and dissolution of silver nanoparticles from nanotechnology-enabled membranes. In doing so we (1) synthesize and characterize several types of polymer membranes impregnated with Tween-20 nanoparticles, (2) perform passive release experiments designed to mimic the potential material and chemical stresses subjected to the product during the use and disposal phases of its life cycle, and (3) assess efficacy by testing the antibacterial properties of the membranes.

Other winners of the QEEN New Investigator Travel Award

108.03 Quantifying toxicity levels of engineered silica nanoparticles used in semiconductor manufacturing

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With rapid developments in the use of engineered nanoparticles (ENPs) in various fields such as in consumer goods, medicine, energy, information technology, and packaging, the impact of workplace and environmental exposure has not been thoroughly understood. In particular, the ENPs of silica, ceria, and alumina are used in large quantities in polishing slurries for a semiconductor manufacturing process called chemical mechanical planarization (CMP) of silicon wafers. For example, about 2.4 million metric tons of silica nanoparticles were used in 2014 by the semiconductor industry (Holden *et al.*, 2014). However, the regulations for use and toxic levels for these engineered nanoparticle slurries are yet to be established. Therefore, it is very important to study the EHS impact of silica nanoparticles and subsequently establish safe threshold limits. The objective of this work is to quantity and correlate worker exposure/ environmental discharge levels and threshold limits of toxicity for silica nanoparticle slurries to their physico-chemical properties before and after the CMP process. The threshold limit of toxicity is formulated by calculating the half maximal inhibitory concentration (IC_{50}). The IC_{50} value is a measure that represents the effectiveness of a substance in inhibiting 50% of specific biological/biochemical function. In the current study, we present a time-dependent toxicity and threshold limit comparison between pre- and post-CMP slurries containing colloidal silica ENPs after polishing semiconductor-patterned test wafers of high-density plasma (HDP) oxide (MIT 864) on a high-volume manufacturing IPEC Avanti 472 CMP tool. In addition, we also present comprehensive characterization of pre-CMP slurries and post-CMP waste using a host of physico-chemical techniques such as DLS, zeta potential, BET, XRD, FT-IR, Raman, SEM, and TEM. Lastly, we studied time- and dose-dependent impact of preslurries and post-waste on lung epithelial cells (A549 lung epithetical cell lines) for 6–48 hours to determine IC50 for cytotoxicity (cell viability and membrane integrity). It was clearly observed that colloidal and fumed silica ENPs in slurries exhibited dose- and time-dependent IC50 for cytotoxicity.

108.04 A nano-architectured electrode for a high-performance supercapacitor

Yiyang Liu [a], Alex Aboagye [b], Lifeng Zhang [b]*, and Jianjun Wei [a]

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There is an emerging need for improved electrical energy storage devices. This project aims to develop a robust electrochemical capacitor (supercapacitor) electrode with high energy density, long life cycles, and a wide range of operational temperature. We take advantage of a low-cost, high-conductivity, mechanically flexible mat consisting of electrospun carbon nanofibers (ECNFs), coupled with skills for a high dielectric uniform coating to produce a state-of-the-art supercapacitor electrode with superior performance. Preliminary results represented by the cyclic voltammograms (CVs) obtained from the MnO_2-coated ECNF electrodes in 6 M KOH aqueous electrolyte gave a capacitance of 1247 F/g at current density 117 A/g. Furthermore, the ECNF mats electrode presents excellent cyclic stability. The planned major work will be the introduction of uniform nano-architectured high-k materials to the ECNF electrode via various techniques to enhance the energy storage density and power density.

108.05 Silver nanoparticle release from commercial plastic articles

Aiga Mackevica,* Mikael Emil Olsson, and Steffen Foss Hansen
Department of Environmental Engineering, Technical University of Denmark

Silver nanoparticles (AgNPs) are used for a wide range of applications due to their antimicrobial activity, including in personal care products, appliances, and various household items. In recent years, the number of consumer products containing AgNPs has increased. While there is a lot of research focusing on effects exerted by nanoparticles, the knowledge concerning release and exposure to nanoparticles is very limited.

To investigate whether AgNPs can be released from plastic articles and consequently lead to consumer exposure, we tested four brands of commercially available plastic food containers and two brands of toothbrushes that advertised the presence of AgNPs. The release rates from food storage containers were performed following European Commission Directive 97/48/EC for articles intended to be in contact with food. Experimental setup involved incubating products for 10 days at 40°C with three different food simulants (Milli-Q water, 10% ethanol, and 3% acetic acid). The release of silver from toothbrushes was assessed by mixing toothbrushes in tap water for 24 hours at room temperature. The total amount of silver in selected products and migration solutions was quantified by ICP-MS analysis, and the size of the migrated particles was investigated by single-particle ICP-MS (spICP-MS) and TEM imaging coupled with EDS.

The results showed that AgNPs were indeed present in the plastic articles and had the potential to migrate from the food storage containers as well as from the toothbrushes. The highest release rates from food storage containers were measured in 3% acetic acid. The size of released particles ranged from around 10 to more than 200 nm in diameter (by TEM-EDS). AgNPs released from toothbrushes were mostly in the size range of 40–60 nm in diameter (by spICP-MS), but no Ag particles were found by TEM imaging.

This work emphasizes that consumers can be exposed to AgNPs by using commercially available AgNP-containing products. This kind of data can assist in consumer exposure assessment, which could subsequently aid appropriate human risk assessment and labeling of products containing NPs.

108.08 Development of a sensitive assay to detect and characterize the effects of nanomaterials on aquatic ecosystems using an *ex vivo* preparation of crustacean olfactory receptor neurons

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As the use of nanomaterials in all industries increases, the impact of nanomaterials on the environment must be understood. While much progress has been made in determining end-point toxicity (e.g., EC_{50}'s), very little effort has been made to understand the myriad other interactions of nanomaterials with animals in the environment. While overall toxicity is important, there is a paucity of information about the effects of nanomaterials on behaviors such as foraging, mate selection, migration, and predator avoidance. Many of these behaviors rely on sensing chemical cues from the environment; however, it is unclear how nanomaterials affect these behaviors. In many ways nanomaterials are desirable because their small size give them unique chemical and physical properties. This small size, however, makes them somewhat problematic to certain ecosystems. In particular, the tendency of colloidal nanomaterials to agglomerate and fall out of solution in aquatic environments means they often aggregate in sedimentary ecosystems.

In order to investigate the possible effects of nanomaterials on sedimentary ecosystems, we have developed an assay to measure the potency of nanomaterials (e.g., carbon nanotubes, fullerenes, or quantum dots, in their natural colloidal state in water) as olfactory stimuli for various commercially and ecologically important crustacean species. Crustacean olfaction relies on groups of olfactory receptor

neurons (ORNs) arranged in clusters and housed in cuticular extensions called aesthetascs found on two, paired antennae. It has been previously shown that the magnitude of stimulation of these neurons in response to stimuli is indicative of the attractive or repulsive nature of the stimulus. We hypothesize that nanomaterials in environmental mediums will stimulate ORN signaling pathways, which will allow for the precise and quantitative assessment of their exposure to crustacean species. To test this hypothesis, primary ORN from antenna are challenged with a wide range of nanomaterials at different concentrations and intracellular release of calcium measured using fluorescent dyes, a flow chamber, and confocal microscopy. This research is of great importance because there are currently no established assays to assess the ability of nanomaterials to stimulate and alter signaling pathways in crustaceans, which may be predictive of detrimental behavioral consequences of exposure.

108.11 Toxicological comparison of *in vitro* exposure techniques of commercial nano products to lung cells

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Engineered nanomaterials are widely claimed as ingredients in various products, including medicines, cosmetics, and cleaners. Historically, this claim has proven false for some nano-labeled products and even harmful to consumers who have been exposed to aerosols generated through proper use. Unlike manufacturers of medicines, manufacturers of consumer products are responsible for ensuring their products are safe, but they are not required to provide documentation. By investigating the specific toxicological effects of ENM-containing consumer products to the lungs using *in vitro* models, we can better screen for potential immediate effects to the human body from commercial use.

Two commercial products, Mesocopper (Purest Colloids, Inc.) and Superior Nanowax (Eagle One), were characterized by dynamic light scattering and transmission electron microscopy and exposed to multiple lung cell lines. Each of these products was chosen from the Woodrow Wilson Center's Consumer Products Inventory list of products with manufacturer claims that the product includes ENMs without documentation providing support of the claim. Mesocopper is a colloidal suspension of copper nanoparticles used as a mineral supplement with claims such as promoting healthy skin, promoting metabolism of specific neurotransmitters, and helping with tendon regeneration. Nano-sized carnauba particles are used to promote shine, reduce dust, and repel water from one's vehicle in the use of Superior Nanowax. Both products are aerosolized during use, and thus inhalation is a concern. The lung cells used were the A549 alveolar adenocarcinomic epithelial, the BEAS-2B immortalized normal bronchial epithelial, and the Calu-3 bronchial adenocarcinomic epithelial cell lines. Suspensions and air–liquid interface exposures, where the cells are grown on a membrane exposing one side to air, were used to expose the cells to the product aerosols and compare the cytotoxic and oxidative stress responses.

Other Posters

108.02 SERENADE An 8-year French funded safe(r) by design project: Introducing consumer exposure case studies

J. Rose, J.-Y. Bottero, A. Masion, S. Pekar-Bonifay, and C. de Garidel-Thoron

Nanotechnology appears as one of the most promising fields of science and technology. The improvement and modification of these new nanoscale material properties can appear disruptive and strongly challenges existing products and technologies. In most cases nanotechnologies will bring beneficial effects in our lives (e.g., in medicine, environment, or electronics). Nanotechnology therefore appears as strategic

and a key to success in the globalized economy. However, the fast development of nanomaterials and the estimated production volumes for next few years has triggered many debates concerning their safe development and use.

To reach the forecasted level of economic development, the public acceptance of nanotechnology is essential, not only in terms of human health and safety, but also concerning the environmental impact. Nanotechnology faces a big challenge that requires the development of a new paradigm in the concepts of design and production of nanomaterials.

The Safe(r) and Ecodesign Research and Education applied to NAnomaterial DEvelopment project (SERENADE; funded by the French National research Agency's (ANR) LABEX call[39]) proposes an integrated scientific and educational approach to develop new concepts and tools for the safer and ecological design in nanomanufacturing processes and products. It is supported by a French, multi-disciplinary network of 14 academic partners including most of the French pioneering groups in the field from fundamental to applied research (including Aix-Marseille University, CNRS, CEA, INSERM, INERIS, and INRA) and education (including Higher Education Pole [PRES] Aix-Marseille University, University Joseph Fourier, Montpellier University, University Paris-Est-Creteil, and Novancia Business School) and 2 industrial partners (Suez-Environment and ALLIOS).

To reach this ambitious objective, the core of the project will be structured around the three stages of the nanomaterials life cycle: (1) production, (2) usage, and (3) end-of-life and consumer case studies. The aim of this presentation is to introduce the different cases studies from cosmetics, paints, food packaging, nanowire based products, with a specific focus on the determination of consumer exposure.

108.06 Testing strategy to measure exposure throughout the life cycle
A. Masion, M. van Tongeren, and J. Rose

To address concerns about the risks associated with nanotechnologies, regulatory agencies are seeking tools for reliable and efficient decision making. While considerable efforts are undertaken to characterize possible hazards, the exposure to nanomaterials over the entire life cycle still remains a somewhat neglected research domain. However, meaningful risk assessment requires a reliable high-quality characterization of the exposure.

The EU project NANoREG addresses this issue in a regulatory approach. The work package "Exposure through Life Cycle Analysis"[40] aims at:

- Characterizing real exposures (intensity and frequency) to humans (workers and consumers) and the environment during the entire life cycle of nanomaterials.
- Providing companies and legislators with a set of tools for risk assessment and decision making for the short to medium-term, by gathering data and performing pilot risk assessment, including exposure monitoring and control, for a selected number of manufactured nanomaterials (MNMs) used in products.
- Developing, for the long-term, new testing strategies adapted to a high number of ENMs for many factors likely to affect their environmental and health impact.

[39] www.agence-nationale-recherche.fr/investissements-d-avenir/appels-a-projets/2011/laboratoires-d-excellence/
[40] www.iomnanoreg.org/IOMinNANoREG/WorkPackage3.aspx

The various tasks in this work include identifying high release scenarios and data gaps; characterize nanomaterial release qualitatively and quantitatively with harmonized testing procedures relevant to all stages of the life cycle; develop predictive exposure models; and assess risk management measures.

This poster shows how the work developed within the NANoREG project addresses major knowledge gaps in the exposure assessment.

108.07 Release of copper nanoparticles from pressure-treated lumber through simulated dermal contact

W. Platten, III, N. Sylvest, C. Warren, M. Arambewela, S. Harmon, K. Bradham, K. Rogers , T. Thomas, and T. P. Luxton

Micronized copper pressure-treated lumber has become the dominant product of the consumer lumber treatment industry. The micronized treatment formulation contains copper carbonate ($Cu_2CO_3(OH)_2$) particles ranging in size from a few nanometers to several microns. The present research investigated the release of copper from consumer lumber products during simulated dermal contact and if the copper released was in a particulate form. Treated lumber was purchased from retailers and left to weather outdoors for approximately one year. Wipe samples were collected at time 0, 14, 34, 70, 97, 140, 260, and 399 days. The two, as-purchased, micronized copper materials were analyzed via XAFS and SEM and determined to contain copper carbonate particles with sizes of, on average, 121 x 56 and 244 x 105 nm (L x W), respectively, with a large fraction of the particles below 100 nm in at least one dimension. Surface wipe samples were analyzed for total copper and revealed a high initial release of copper that became constant (~1.5 mg m^{-2}) after one month. Copper particles were identified on the sampling cloths during the first two months of the experiment, after which the levels of copper were insufficient to collect data. The XAFS and SEM data showed that particles were always associated with cellulose material, indicating that they were released with dislodged wood material and not as free particles.

108.10 Physical-chemical state and mechanisms of nanomaterial release from products during their life cycle: Self-cleaning cement and acrylic wood coating case studies

L. Scifo, N. Bossa, A. Avellan, P. Chaurand, C. Levard, O. Aguerre-Chariol, J. Vicente, C. Geantet, M. Auffan, D. Borschneck, J. Labille, J.-Y. Bottero, and J. Rose

The industrial scale production and wide variety of applications of engineered nanomaterials (ENMs) and their possible release into the natural aquatic environment have produced an increasing concern among the nanotechnology and environmental science community. Even though there is much data dedicated to address hazards of ENMs, few data exist on exposure, the second essential aspect of risk assessment. Environmental and consumer exposures will be based on many possible abiotic and biotic processes affecting stability (bio-degradation), fate, transport, and transformation of released nanomaterials. Moreover, as a function of different stages of the life cycle of products incorporating ENMs, the structure, shape, and properties of released ENMs will vary. The study of nanomaterial releases from solid matrices (in which ENMs are incorporated) is therefore an emerging field of research. Until now, most efforts have focused on quantifying and identifying the released objects, providing valuable inputs to risk assessment models. However, the mechanisms lying behind release are still largely unknown and rarely investigated. Nanomaterials are used in construction to improve the properties and functions of commonly used building materials like cements, glasses, and paints. A part of this production concerns a new type of cement, called self-cleaning cement, which maintains clean and white wall fronts. Such building materials may also provide interesting pollution-reducing properties. Nanomaterials also have wide applications in

the paint and coating industry. They can improve the rheological and mechanical properties of products, confer self-cleaning or antimicrobial capacity, or act as a UV-absorber, stabilizing agents, or pigments.

Along their life cycle, cements and, especially at the use stage, paints and wood coatings, will experience processes that may lead to release of nano-objects, and their aggregates and agglomerates greater than 100 nm (NOAA) . This phenomenon is especially true for outdoor products as sunlight and rain can induce very strong degradations. The aim of this study is to determine the mechanisms of NOAA release for two case studies: self-cleaning cement, and wood coating, incorporating TiO_2-based and CeO_2-based NMs respectively, during aging process and to identify parameters controlling it. Specific aging and weathering protocols were developed at the CEREGE to mimic at best products uses and environmental and consumer exposures. The elements released (particulate and soluble fractions) and their kinetics were quantified using separation techniques and chemical analysis (ICP-OES/MS) and characterized with DLS and TEM. We thoroughly analyzed the aged solid matrices (from the unaltered core to the surface altered layer) using laser-ablation-ICP-MS and several X-ray based techniques (XRD [X-Ray Diffraction], µ-XRF [micro X-Ray Spectroscopy], and an unprecedented combination of nano- and micro-X-ray computed tomography) to perform a complete altered matrix characterization, including pore structure. Original results concerning the low-stability of the matrices while NOAA are released in fresh water will be detailed with regards to the size and surface properties of nanomaterials (nano-TiO_2 in cements and nano-CeO_2 in wood coatings). Moreover, a deep investigation of the alteration mechanisms of cement and wood coatings will help in deciphering which physical and chemical properties control NOAA release. Based on our results, a predictive strategy will be proposed.

108.13 Case study on risk evaluation of silver nanoparticle exposure from antibacterial sprays containing silver nanoparticles [*245*]

E. Kim, J.-H. Lee, J.-K. Kim, G.-H. Lee, K. Ahn, J.-D. Park, and I.-J. Yu

With the recent widespread application of nanotechnology to consumer products, consumer exposure to nanomaterials released from these products has also increased. As a result, there is a growing concern about the risks this increase may have on human health and the environment. Many of the available products containing silver nanoparticles (AgNPs) are household products, along with machinery used in workplaces. While many studies have already investigated the levels of AgNPs contained in consumer products, this study investigates the release of AgNPs from sprays that contain these particles. Using an exposure simulation chamber as the setting for the experiment, various instruments, including a scanning mobility particle sizer (SMPS), a condensation particle counter (CPC), a dust monitor, and mixed cellulose esters (MCE) filters, are connected to the chamber to measure the exposure levels of AgNPs when using the sprays. When evaluating the risk of inhalation exposure using the margin of exposure (MOE), spraying a whole can and spraying an air conditioner both resulted in a high-risk concern level with a MOE ranging from 59-132 that was much lower than the no-risk concern level of 1000. Plus, the dermal exposure levels with a single layer of clothing were estimated at 2-50 mg/kg. However, when considering the results of another acute dermal toxicity study at concentrations up to 2,000 mg/kg/day and recent 28-day dermal toxicity data up to 1,000 mg/kg, neither of which showed any significant toxicity or systemic absorption in the blood or urine, the current dermal exposure levels were negligible when compared with the MOE no-risk concern level of 1000. Therefore, the current results showed the possibility of high-risk inhalation exposure to AgNPs released when using antibacterial sprays.

108.14 A case study on risk evaluation of printed electronics using nanosilver ink
E. Kim, J.-H. Lee, J.-K. Kim, G.-H. Lee, K. Ahn, J.-D. Park, and I.-J. Yu

With the ever-increasing development of nanotechnology, our society is being surrounded by possible risks related to exposure to manufactured nanomaterials. The consumer market already includes many products that contain silver nanoparticles (AgNPs), including various household products, such as yoga mats, cutting boards, running shirts, and socks. Plus, there is a growing concern over the release of AgNPs in workplaces related to the manufacture and application of nanomaterials. Therefore, this study investigated the release of AgNPs during the operation of a printed electronics printer. Using an exposure simulation chamber, a nanoparticle collector, SMPS (scanning mobility particle sizer), CPC (condensation particle counter), dust monitor, and MCE (mixed cellulose esters) filters are all connected to measure the AgNP exposure levels when operating a printed electronics printer. As a result, a very small amount of AgNPs was released during the operation of the printed electronics printer, plus the number of AgNPs inside the exposure simulation chamber was lower than that outside. Plus, when evaluating the potential risks for consumers and workers using a margin of exposure (MOE) approach and target MOE of 1000, the operational results far exceeded the target MOE in this simulation study and in a previous workplace exposure study. Therefore, the overall results indicate a no-risk concern level in the case of printed electronics using nanosilver ink.

108.15 Evaluation of darkfield microscopy and hyperspectral imaging for analysis of airborne carbon nanotubes captured from occupational settings
N. M. Neu-Baker, A. Eastlake, S. A. Brenner, and C. L. Geraci

Current best-known methods for engineered nanomaterial (ENM) exposure assessment in occupational environments include the capture of airborne ENMs onto filter media. The standard method for the detection of ENMs captured onto filter media is direct visualization via transmission electron microscopy (TEM) for particle sizing, count, and morphology, coupled with compositional analysis, typically by energy-dispersive spectroscopy (EDS). This method is low-throughput, expensive, and time- and resource-intensive. Enhanced darkfield microscopy (EDFM) with hyperspectral imaging (HSI) analysis is being evaluated as a high-throughput screening technique to rapidly identify filter media samples that contain ENMs of interest that may then move on for further, more intensive TEM/EDS analysis. Building upon a preliminary study lead by NIOSH, we are further exploring the use of EDFM/HSI for the rapid visualization and identification of carbon nanotubes (CNTs) captured on mixed cellulose ester (MCE) filter media. We will compare the protocol we develop for EDFM/HSI of CNTs on MCE filter media to conventional TEM methods for accuracy, reliability, and precision of this new screening method. Future directions include expanding the EDFM/HSI protocol to other ENMs and to polycarbonate (PC) filter media samples.

108.16 Information resources for exposure assessment of engineered nanomaterials
M. D. Hoover

Nanoinformatics is the science and practice of determining which information is relevant to meeting the objectives of the nanoscale science and engineering community; and then developing and implementing effective mechanisms for collecting, validating, storing, sharing, analyzing, modeling, and applying that information; and then confirming that appropriate decisions were made and that desired mission outcomes were achieved as a result of that information; and finally conveying experience to the broader community, contributing to generalized knowledge, and updating standards and training. In our roles as information customers, creators, curators, and analysts, this definition should guide our collaborations to effectively assess and manage exposures to engineered nanomaterials. Key questions include: Is a hazard

present? Is there exposure to that hazard? What is the resulting risk? How can that risk be managed? and Is the risk management approach achieving the desired protection?

The development of information resources such as the Nanomaterial Registry[41] has required our community to identify nanomaterial characteristics that are both meaningful and measurable and to validate reproducible protocols and practices for collecting information about those characteristics. The identification of key nanomaterial characteristics for exposure assessment is benefiting from a combination of field measurements[42] to determine what is actually present across the nanomaterial life cycle, as well as laboratory investigations of how materials with those characteristics behave under environmentally, biologically, or industrially relevant conditions.

Collaborations such as the National Nanotechnology Initiative signature initiative on Nanotechnology Knowledge Infrastructure—Enabling National Leadership in Sustainable Design[43] are developing unifying concepts such as data-readiness levels and approaches for sharing and ensuring the reproducibility of data and experimental results. Community-based resources such as the GoodNanoGuide[44] are helping to share information in a manner that is relevant, reliable, and actionable. New generations of sensors will undoubtedly be needed to characterize nanomaterials efficiently and affordably and collaborations on that front are available through the signature initiative on Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment.[43]

The extensive list of links to information on the environmental health and toxicology of nanotechnology and human health at sis.nlm.nih.gov/enviro/nanotechnology.html illustrates both our current resources and our opportunities to improve our identification, creation, curation, analysis, and meaningful application of exposure assessment information in support of safe nanomaterial applications.

(The findings and conclusions in this abstract are those of the author and do not necessarily represent those of the National Institute for Occupational Safety and Health.)

108.17 Nanotechnology Knowledge Infrastructure (NKI): Enabling national leadership in sustainable design—Nanotechnology Signature Initiative [*246*]

S. Lehrman

The knowledge infrastructure has been identified by the Federal agencies participating in the National Nanotechnology Initiative as a focus area that may be more rapidly advanced through enhanced coordination and collaboration as a Nanotechnology Signature Initiative (NSI). The goal of the Nanotechnology Knowledge Infrastructure (NKI) Signature Initiative is to provide a community-based, solutions-oriented knowledge infrastructure to accelerate nanotechnology discovery and innovation. The NKI has four thrust areas that focus efforts on cooperative interdependent development of: (1) a diverse collaborative community; (2) an agile modeling network for multidisciplinary intellectual collaboration that effectively couples experimental basic research, modeling, and applications development; (3) a sustainable cyber-toolbox to enable effective application of models and knowledge to the design of nanomaterials; and (4) a robust digital nanotechnology data and information infrastructure to support effective data sharing, collaboration, and innovation across disciplines and applications. Agencies involved include Consumer Product Safety Commission, Department of Commerce (National Institute of Standards

[41] nanomaterialregistry.org
[42] e.g., cdc.gov/niosh/topics/nanotech/
[43] nano.gov/signatureinitiatives
[44] nanohub.org/groups/gng

and Technology), Department of Defense, Department of Health and Human Services (Food and Drug Administration, National Institutes of Health, National Institute for Occupational Safety and Health), Department of Labor (Occupational Safety and Health Administration), Environmental Protection Agency, National Aeronautics and Space Administration, and National Science Foundation.

108.18 Nanotechnology for sensors and sensors for nanotechnology: Improving and protecting health, safety, and the environment—Nanotechnology Signature Initiative [*247*]

S. Lehrman

Sensors have been identified by the Federal agencies participating in the National Nanotechnology Initiative as a focus area that may be more rapidly advanced through enhanced coordination and collaboration as a Nanotechnology Signature Initiative (NSI). The goals of this NSI are to support research on nanomaterial properties and development of supporting technologies that enable next-generation sensing of biological, chemical, and nanoscale materials. This interagency effort coordinates and stimulates creation of the knowledge, tools, and methods necessary to develop and test nanosensors and to track the fate of nanomaterials. The current thrust areas for this NSI are to: (1) develop and promote adoption of new technologies that employ nanoscale materials and features to overcome technical barriers associated with conventional sensors; and (2) develop methods and devices to detect and identify nanomaterials across their lifecycles. Agencies involved include Consumer Product Safety Commission, Department of Commerce (National Institute of Standards and Technology), Department of Defense, Department of Health and Human Services (Food and Drug Administration, National Institutes of Health, National Institute for Occupational Safety and Health), Environmental Protection Agency, National Aeronautics and Space Administration, National Science Foundation and the U.S. Department of Agriculture (National Institute of Food and Agriculture).

Appendix B. Workshop Agenda

Day One Plenary: Quantifying Exposure Across the Life Cycle

Morning Plenary Moderator: Treye Thomas (CPSC)

- **Welcoming Remarks** **Treye Thomas** Leader, Chemical Hazards Program (CPSC); **Lloyd Whitman,** Assistant Director, Nanotechnology (OSTP); **George Borlase,** Assistant Executive Director, Hazard Identification and Reduction (CPSC)
- **Introduction:** The application of exposure science to the consumer product life cycle
  Paul Westerhoff, Arizona State University
- **Occupational Exposure:** Review of the state of the science
  Chuck Geraci, NIOSH
- **Consumer Exposure:** Health risk driven exposure assessment for consumers during the life cycle of nanomaterial-containing products
  Jim Zhang, Duke University
- **Ecological Exposure:** Review of the state of the science
  Bernd Nowack, Empa

Concurrent Sessions

106A Worker Exposure Studies

Co-Chairs: Kevin L. Dunn[1] and Bruce Lippy[2]
[1]NIOSH, [2]CPWR

106A.3 Do studies of release from manufactured nanocomposites inform potential for worker exposure?
S. Froggett—Froggett & Associates

106A.4 Exposures to nanoparticles and fibers during manufacturing, recycling, and post-processing of carbon nanotube-reinforced composites
D. Bello—UMass Lowell

106A.2 Carbon nanotube exposure assessment: An evaluation of workplace exposures in the U.S.
M. Dahm—NIOSH

106A.1 Development of a nanoparticle sampler for particle speciation using electron microscopy
G. Casuccio—RJ Lee Group, Inc.

106B Consumer Exposure Studies I: General Products

Co-Chairs: Marina Vance[1] and Keana Scott[2]
[1]Virginia Tech, [2]NIST

106B.2 Environmentally relevant exposures to nanomaterials in consumer products
J. Shatkin—Vireo Advisors, LLC

106B.1 Potential inhalation exposures for nanoparticles due to the use of consumer products
G. Mainelis—Rutgers University

106B.4 Quantifying the release of silver from nanotechnology-based consumer products for children
M. Vance[1], N. Tulve[2], R. Willis[2], K. Rogers[2], T. Thomas[3], L. Marr[1]—[1]Virginia Tech, [2]EPA, [3]CPSC

106B.3 Characterization of mechanical and UV-induced nanoparticle release from commercial products
L-P Sung[1], K. Scott[1], and T. Thomas[2]—[1]NIST, [2]CPSC

The webcast of this presentation is archived at www.tvworldwide.com/events/nnco/150707/
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For full abstracts and descriptions, please see nano.gov/sites/default/files/pub_resource/qeen_workshop_draft_agenda.pdf

106C Consumer Exposure Studies II: Food, Food Contact, and Personal Care Products

Co-Chairs: Timothy Duncan and Margaret Kraeling
FDA

160C.2 Challenges in the characterization of nanomaterials relevant to cosmetics and personal care products
J. Ansell—Personal Care Products Council

106C.1 Using dietary intake modeling to project human intake of nanomaterials present in agricultural foods and commercial products
S. Ebbs[1], S. Bradfield[1], P. Kumar[1],W. Zhang[1], J. White[2], and X. Ma[3]—[1]Southern Illinois University, [2] The Connecticut Agricultural Experimental Station, [3]Texas A&M University

106C.3 Studies on the potential of nanoparticles to migrate from polymer nanocomposites for food packaging
R. Franz—Fraunhofer Institute for Process Engineering and Packaging IVV

106C.4 Nanomaterial cosmetic research at the Food and Drug Administration
L. Katz—FDA

106D Ecological and General Population Exposure Studies

Co-Chairs: Elijah Petersen[1] and Jeff Steevens[2]
[1]NIST, [2] USACE

106D.3 Quantification of carbon nano materials in complex matrices
P. Westerhoff[1], K. Doudrick[2], P. Herckes[1], and T. Nosaka[1]—[1]Arizona State University, [2]University of Notre Dame

106D.2 A liquid nebulization / differential mobility analysis (LN/DMA) method for valid sizing and quantification of engineered nanoparticles in environmentally-relevant water matrices
B. Mader, M. Ellefson, and S. Wolf—3M Environmental Laboratory

106D.4 An exploration of some capabilities and limitations of single particle ICP-MS
K. Murphy and A. Montoro Bustos—NIST

106D.1 Accumulation and trophic transfer of engineered nanomaterials by plants
J. White—CT Agricultural Experiment Station

106E Roundtable—Exposure Science in the 21st Century: How its Principles can Transform Safe and Sustainable Innovation and Development of Nanomaterial Products

Paul Lioy, Tina Bahadori, Chuck Geraci, Greg Lowry, and Shaun Clancy
Moderator: Treye Thomas (CPSC)

Afternoon Plenary Moderator: Janet Carter (OSHA)

Concurrent Sessions Roundtable: Comparison of exposure assessment in different receptor populations

U.S.-EU Collaboration on Exposure: The Exposure Through Product Life CoR
Martie van Tongeren—Institute of Occupational Medicine, & Rick Canady—NeutralScience L3C

Evening Poster Session, Featuring the QEEN New Investigator Poster Competition

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Day Two Plenaries: Quantifying Exposure in Various Media and Pathways

Morning Plenary Moderator: Debbie Kaiser (NIST)

QEEN New Investigator Award Announcement: *Treye Thomas (CPSC); Mike Meador (NNCO)*

- **Introduction:** Measuring and modeling exposures to nanomaterials in complex systems
  Greg Lowry, Carnegie Mellon University
- **Airborne Exposure:** Linking life cycle specific exposures to biological impact of nanomaterials
  Phil Demokritou, Harvard School of Public Health
- **Waterborne Exposure:** Environmental multimedia distribution of nanomaterials
  Yoram Cohen, UCLA Center for Environmental Implications of Nanotechnology
- **Exposure in Biological Systems:** Review of the state of the science
  Christie Sayes, Baylor University

Concurrent Sessions

205A Exposure Studies in Gaseous Media

Co-Chairs: Vincent Castranova[1] and Gedi Mainelis[2]
[1] West Virginia University, [2] Rutgers

205A.4 Strategies for Measuring Airborne Nanomaterials
J. Thornburg—RTI International

205A.2 Physico-chemical and toxicological characterization of engineered nanoparticles emitted from laser printers: A case study of consumer exposures across life cycle of nanotechnology-enabled products
P. Demokritou—Harvard University School of Public Health

205A.3 Microvascular outcomes of engineered nanomaterial inhalation
P. Stapleton—West Virginia University

205A.1 Characterization of an aerosol generated during application of a nano-TiO_2 enabled antimicrobial spray product to a surface: Pulmonary and cardiovascular response to inhalation exposure in rats
V. Castranova[1], W. McKinney[2], B. T. Chen[2], D. G. Frazer[2], D. Schwegler-Berry[2], T. M. Sager[2], J. S. Reynolds[2], K. Krajnak[2], R. R. Mercer[2], and T. Thomas[3]—[1]West Virginia University, [2]NIOSH, [3]CPSC

205B Exposure Studies in Aqueous Media

Co-Chairs: Jeff Steevens[1] and Richard Zepp[2]
[1]USACE, [2] EPA

205B.2 Simulating the fate and transport of nanomaterials in surface waters
C. Knightes—EPA

205B.3 Understanding and quantifying nanomaterial exposure and dosimetry in aquatic hazard testing—The link between hazard, exposure, and risk assessment
S. Diamond[1], A. Kennedy[2]—[1]NanoSafe, [2]USACE

205B.4 Assessing nanoparticle migration from commercial food contact materials into aqueous food simulants
G. Noonan[1], S. Addo Ntim[1], T. Thomas[2]—[1]FDA, [2]CPSC

205B.1 Detection and release of carbon nanotubes from polymer nanocomposites
D. H. Fairbrother[1], R. Lakone[1], D. Goodwin[1], R. B. Reed[2], J. J. Wang[2], A. Barber[2], J. F. Ranville[2]—[1]Johns Hopkins University, [2]Colorado School of Mines

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205C Exposure Studies in Biological/Tissue/Serum

Co-Chairs: William K. Boyes[1] and Elijah Petersen[2]
[1] EPA, [2] NIST

205C.1 Assessment of the bioaccessibility of micronized copper wood in synthetic stomach fluid
K. Rogers[1], L. Santiago-Rodríguez[2], J. Griggs[1], K. Bradham[1], C. Nelson[1], T. Luxton[1]—[1]EPA, [2]Formerly EPA

205C.2 Using single particle ICP-MS as a tool for understanding metallonanoparticles transformation during nanotoxicity assays
M. Johnson, S. Hanna, E. Petersen, J. Elliott, B. Nelson, and L. Yu—NIST

205C.3 Measuring exposure levels of drug products containing nanomaterials
K. Tyner—FDA

205C.4 Determination of the fate of inhaled nanoparticles
R. Mercer—NIOSH

205D Epidemiology: The Exposure-Health Interface

Co-Chairs: Mary Schubauer-Berigan[1] and Sara Brenner[2]
[1]NIOSH, [2] SUNY Poly CNSE

205D.2 Epidemiologic studies of U.S. workers handling carbon nanotubes: The interface between exposure and health
M. Schubauer-Berigan—NIOSH

205D.3 Field-based exposure assessment: Tailoring your approach to maximize and obtain key data for each worker
S. Brenner—SUNY Albany CNSE

205D.1 Nanodermatology: Identifying promise and assessing risk
A. Friedman—Einstein College of Medicine, GWU

205E New Investigator Interviews

Featuring the QEEN New Investigator Award winner

Moderator: Chuck Geraci (NIOSH)

Afternoon Plenary Moderator: Cathy Fehrenbacher (EPA)

Concurrent Sessions Roundtable: Comparison of exposure assessment in various media and bridging exposure science with toxicology

Concluding Remarks: Lloyd Whitman (OSTP) and **Treye Thomas** (CPSC)

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Appendix C. List of Workshop Participants

Attendees

Jay Ansell
Personal Care Products Council

Shyam Aravamudhan
North Carolina A&T State University

Tina Bahadori
Environmental Protection Agency

Mark Banash
Nanocomp Technologies

Charles Barton
Oak Ridge Associated Universities

Jewel Beamon
National Nanotechnology Coordination Office

Dhimiter Bello
University of Massachusetts Lowell

Melanie Biggs
Consumer Product Safety Commission

George Borlase
Consumer Product Safety Commission

William Boyes
Environmental Protection Agency

Sara Brenner
SUNY Polytechnic Institute Colleges of Nanoscale Science & Engineering

Kristin Bunker
RJ Lee Group, Inc.

Deborah Burgin
Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry

Richard Canady
NeutralScience L3C

Chris Cannizzaro
U.S. Dept of State

Amber Carlberg
National Institute of Standards and Technology

David Carrillo
Department of Defense, U.S. Air Force Headquarters

Janet Carter
U.S. Department of Labor

Elizabeth Casman
Carnegie Mellon University

Vincent Castranova
West Virginia University

Gary Casuccio
RJ Lee Group, Inc.

Byron Cheatham
CytoViva, Inc.

Dejun Chen
Georgetown University

Hongda Chen
U.S. Department of Agriculture, National Institute of Food and Agriculture

Shaun Clancy
Evonik Industries AG

Yoram Cohen
University of California Los Angeles

Matthew Dahm
LT, U.S. Public Health Service
Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health

Raymond David
BASF Corporation

Camille de Garidel-Thoron
CEREGE—European Centre Research and Teaching in Geosciences

Philip Demokritou
Harvard University

Steve Diamond
NanoSafe, Inc.

Timothy Dole
Environmental Protection Agency

Matthew Dreyfus
Consumer Product Safety Commission

Timothy Duncan
Food and Drug Administration

Franklin Dunmore
Consumer Product Safety Commission

Kevin L. Dunn
LT, U.S. Public Health Service
Centers for Disease Control and Prevention

Victoria Duwve
Betco Corporation

Doyle Edwards
Brewer Science

Heather Evans
National Institute of Standards and Technology

Don Ewert
RJ Lee Group, Inc.

Tarek Fadel
National Nanotechnology Coordination Office

Howard Fairbrother
Johns Hopkins University

Cathy Fehrenbacher
Environmental Protection Agency

Roland Franz
Fraunhofer Institute for Process Engineering and Packaging IVV

Lisa Friedersdorf
National Nanotechnology Coordination Office

Adam Friedman
George Washington School of Medicine and Health Sciences

Stephan Froggett
Froggett & Associates, LLC

Sean Garcia
American Water Works Association

Charles Gause
AxNano, LLC

Chuck Geraci
Centers for Disease Control and Prevention

Steven Gluck
Dow Chemical Company

Ted Gresik
PerkinElmer Inc.

Mark Grossman
Verisk Insurance Solutions

Franklyn Hall
Environmental Protection Agency

Jaydee Hanson
International Center for Technology Assessment

Daniel Harrison
CPT, U.S. Army Environmental Science and Engineering Officer

Laura Hodson
Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health

Geoff Holdridge
National Nanotechnology Coordination Office

Eric Hooker
Consumer Product Safety Commission

Mark D. Hoover
Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health

Matthew Hull
Virginia Tech

Robert Iafolla
Bloomberg BNA

Ashish Jachak
Exxon Mobil Corporation

Monique Johnson
National Institute of Standards and Technology

Kimberly Jones
Howard University

Debbie Kaiser
National Institute of Standards and Technology

Linda Katz
Food and Drug Administration

Mike Kiley
National Nanotechnology Coordination Office

Frederick Klaessig
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Appendix D. Glossary

ADME – ADME is an abbreviation in pharmacokinetics and pharmacology for "absorption, distribution, metabolism, and excretion," and describes the disposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug.

Adverse outcome pathway (AOP)– An analytical construct that describes a sequential chain of causally linked events at different levels of biological organization that lead to an adverse health or ecotoxicological effect (see figure). AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning [*248*].

BEAS-2B – This cell line is derived from normal bronchial epithelium obtained from autopsy of non-cancerous individuals. Cells were infected with a replication-defective SV40/adenovirus 12 hybrid and cloned.

Box model – a simplified version of a complex system that allows for analysis. Factors within a box are assumed to be mixed homogeneously. Within a given box, the concentration of any substance is therefore uniform. A ***simple box model*** is a box model with a small number of boxes whose properties (e.g., their volume) do not change with time. They are often useful to derive analytical formulas describing the dynamics and steady-state abundance of a chemical species. More complex box models are usually solved using numerical techniques.

Carbon nanotube (CNT) – Carbon molecule with a cylindrical shape. The structure and chemical bonds of CNTs result in unique strength, electrical, and thermal properties.

Colloid – Nanoscale or microscale particles suspended in another medium; colloids include gels, aerosols, and emulsions.

DNA – Deoxyribonucleic acid – the double-helix molecule that provides the basis of genetic heredity, about 2 nanometers in diameter but often several millimeters in length.

EC_{50} – The EC_{50}, or "effective concentration of 50%" is the concentration of a drug that gives a half-maximal response.

Electronic waste (e-waste) – Discarded electrical or electronic devices. Used electronics, which are destined for reuse, resale, salvage, recycling, or disposal, are also considered e-waste.

Engineered nanomaterial – a manufactured particle with any external dimension on the nanoscale.

Environmental compartment – a hypothetical box (see "box model") representing a complex system in which the concentration of a material of interest is characterized. An environmental compartment can be used to estimate environmental exposure. An environment can be divided into compartments of soil, sediment, and suspended matter, consisting of three phases: air (only relevant in soil), solids, and water [*32*].

Exposure science – the study of the contact between receptors (such as humans or ecosystems) and physical, chemical, or biologic stressors… including the roles of space and time [*218*].

Face validity – the subjectively viewed value of a test to measure what it purports to measure. Face validity is often contrasted with content validity and construct validity.

Fullerene – A category of roughly spherical carbon nanoscale structures named after Buckminster Fuller's geodesic spheres.

Genetic sequence – The ordered set of nucleotides in a particular sample of DNA or RNA.

Genome – The complete set of genetic material contained in an organism, or a separately inherited portion of an organism. For instance, the mitochondrial genome is inherited maternally, whereas the nuclear genome is inherited from both parents.

Genomics – The study of the complete set of genetic material contained in an organism, or a separately inherited portion of an organism, above the level of the individual gene.

Incidental nanomaterial – A nanomaterial generated as an unintentional by-product of a process.

Ionic – A molecule or atom is ionic when it has either gained or lost an electron, thereby acquiring a charge.

Manufactured nanomaterial – A nanomaterial intentionally produced for commercial purposes to have specific properties or specific composition.

Margin of exposure – Margin of exposure (MOE) between a point of departure on the dose–response for oral toxicity in animal studies and estimates of human exposure is one method of estimating risk to human health. If the MOE is very large then there is a low level of human health concern.

Multiwalled carbon nanotube (MWCNT) – A Carbon molecule that consists of multiple rolled layers (concentric tubes) of graphene. See also ***carbon nanotube***.

Nanocomposite – A material composed of two or more substances, of which at least one has a nanoscale dimension, such as nanoparticles dispersed throughout another solid material.

Nanometer – A distance unit representing one-billionth of a meter, or one-millionth of a millimeter, or roughly one-millionth the thickness of an American dime.

Nanoporous – Substances that have holes or pores on the nanoscale, used, for example, to separate particles or molecules by size.

Nanoscale – The size range roughly 1 to 100 nanometers, where many of the fundamental structures of biology are formed, composite materials may take on their distinctive characteristics, and many important physical phenomena are found.

Nanoscience – The study of unique properties of matter at the nanoscale; an interdisciplinary field of science combining physics, materials science, the chemistry of complex molecules, and related disciplines.

Nanotechnology product – This term represents one or more of: (1) a manufactured nanomaterial or engineered nanomaterial, (2) a nano-enhanced or nanotechnology-enabled intermediate product, or (3) a nano-enhanced or nanotechnology-enabled final product.

Nanotube – Hollow, cylindrical structures, with a diameter usually less than 5 nanometers. They are often but not necessarily, composed of carbon, and have remarkable strength and electrical properties.

Polymer – A chemical compound, typically formed by connecting smaller molecules together, that consists of repeating structures, often arranged in a chain.

Proteomics The study of the complete set of proteins produced by a genome.

Quantum dot – A nanoscale crystal with a diameter that is typically between 2-20 nm, having unique electrical and optical properties that are dependent on its size. Quantum dots can be found in light sources, are used for enhanced medical imaging, and are being explored as components in spintronic quantum computers.

Reference dose – An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Risk assessment – A set of analytic approaches in the decision, risk, and management sciences, typically considering both the probability and the potential cost of a particular type of event.

Toxicity – The extent to which a chemical substance is poisonous or, through chemical action, destroys living tissue.

Appendix E. List of Acronyms

ADME	absorption, distribution, metabolism, and excretion
AgNPs	silver nanoparticles
AMS	aerosol mass spectrometry
AOP	adverse outcome pathway
AP-MS	affinity purification mass spectrometry
APS	aerodynamic particle sizer
ASTM	American Society for Testing and Materials
ATR-IR	attenuated total reflectance infrared spectroscopy
BET	BET surface area measurement (BET from Brunauer, Emmett, Teller)
CEIN	Center for Environmental Implications of Nanotechnology, University of California, Los Angeles
CEINT	Center for the Environmental Implications of NanoTechnology, Duke University
CMP	chemical mechanical planarization
CNC	condensation nucleus counter
CNF	carbon nanofiber
CNSE	College of Nanoscale Science and Engineering, State University of New York Polytechnic Institute
CNT	carbon nanotube
CPC	condensation particle counter
CPSC	Consumer Product Safety Commission
CPWR	Center for Construction Research and Training
DLS	dynamic light scattering
DMA	differential mobility analyzer
DREAM	DeRmal Exposure Assessment Method
EDS, EDX, or EDXS	energy-dispersive x-ray spectroscopy
EELS	electron energy loss spectroscopy
EFM	environmental fate modeling
EHS	environment(al), health, and safety
ENM	engineered nanomaterial
ENP	engineered nanoparticle
EPA	Environmental Protection Agency
EU	European Union
F&T	fate and transport
FDA	Food and Drug Administration
FT-IR	Fourier transform infrared spectroscopy
HAADF	high angle annular dark field
HRTEM	high-resolution transmission electron microscopy
ICCR	International Cooperation on Cosmetics Regulation
ICP-MS	inductively coupled plasma mass spectroscopy
LC	liquid chromatography
LCA	life cycle assessment
LCIA	life cycle inventory assessment
LCPM	particulate matter emitted during the life cycle
LDPE	low-density polyethylene
LN/DMA	liquid nebulization/differential mobility analysis
LSCM	laser scanning confocal microscopy
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

MFA	material flow analysis
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MWCNT	multiwalled carbon nanotubes
nanoEHS	nanotechnology environmental, health, and safety
NEP	nanotechnology-enabled product
NIOSH	National Institute of Occupational Safety and Health
NIST	National Institute of Standards and Technology
NM	nanomaterial
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NOAA	nano-objects, and aggregates or agglomerates of nano-objects greater than 100 nm
NP	nanoparticle
NRC	National Research Council of the National Academies
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of NSTC
NSTC	National Science and Technology Council
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure level
ORN	olfactory receptor neuron
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy
PAH	polyaromatic hydrocarbon
PEC	predicted environmental concentrations
PEN	Project on Emerging Nanotechnologies (Woodrow Wilson Institute)
PEP(s)	(laser) printer-emitted engineered particle(s)
PM	particulate matter
PNEC	predicted no effect concentrations
PSD	particle size distribution
QEEN	Quantifying Exposure to Engineered Nanomaterials from Manufactured Products (workshop)
REL/ROEL	recommended exposure level/recommended occupational exposure level
RfD	reference dose
SEM	scanning electron microscope/microscopy
SERS	surface-enhanced Raman spectroscopy
SMPS	scanning mobility particle sizer
spICP-MS	single particle inductively coupled plasma mass spectroscopy
SUNY	State University of New York
TEM/STEM	transmission electron microscopy/ scanning transmission electron microscopy
TOF-MS	time-of-flight mass spectrometry
TWA	time weighted average
USACE	U.S. Army Corps of Engineers
UV	ultraviolet
XAFS	x-ray absorption fine structure
XANES	XRF mode x-ray absorption near edge structure imaging (a type of XAFS)
XAS	x-ray absorption spectroscopy
XRF	x-ray fluorescence
µ-XRF	micro x-ray fluorescence

Appendix F. Tools and Methods Index

Appendix G. Author Index

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