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.

Quantifying Exposure to Engineered Nanomaterials (QEEN) from Manufactured Products

Addressing Environmental, Health, and Safety Implications

Workshop Proceedings
July 7–8, 2015

Sponsored by the
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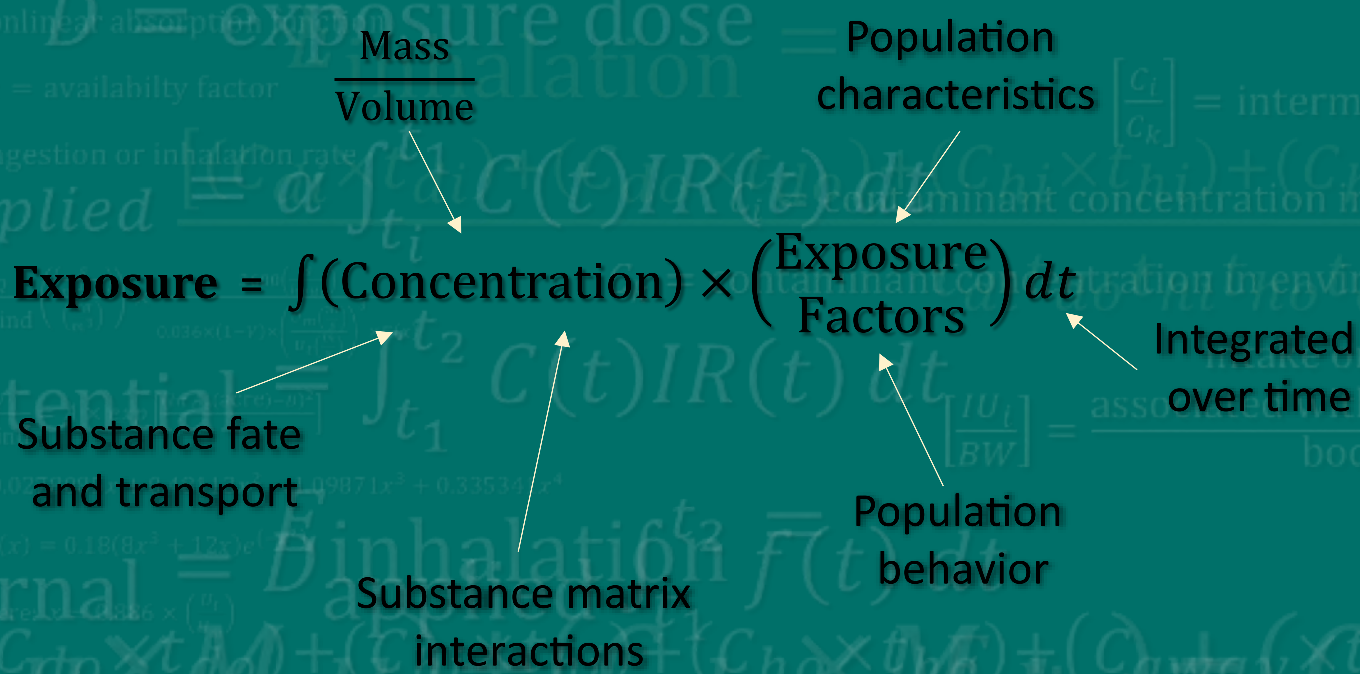

About the National Nanotechnology Initiative

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

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