Greener Nanoscience: A Proactive Approach to Advancing Applications and Reducing Implications of Nanotechnology

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ABSTRACT Nanotechnology continues to offer new materials and applications that will benefit society, yet there is growing concern about the potential health and environmental impacts of production and use of nanoscale products. Although hundreds of studies of nanomaterial hazards have been reported, due (largely) to the complexity of the nanomaterials, there is no consensus about the impact these hazards will have. This Focus describes the need for a research agenda that addresses these nanomaterial complexities through coordinated research on the applications and implications of new materials, wherein nanomaterials scientists play a central role as we move from understanding to minimizing nanomaterial hazards. Greener nanoscience is presented as an approach to determining and implementing the design rules for safer nanomaterials and safer, more efficient processes.

As we near the end of four years of research funding through the 21st Century Nanotechnology Research and Development Act[1] and Congress works toward its reauthorization, there is a renewed and intensified focus on addressing the Environmental Health and Safety (EHS) concerns related to nanotechnologies by both scientists and policymakers.[2,3] Much is at stake since nanomaterials offer significant promise as solutions to long-standing technological and environmental challenges (solar energy conversion, medicine, catalysis, water, pollution, *etc.*) and the federal government and private industry have invested billions of dollars in research and development. Meanwhile, activist groups have voiced concerns about nanotechnology safety to the extent that some have suggested banning nanomaterials. Contradictory research findings have heightened concerns about nanomaterial safety, and definitive answers about nanomaterial safety seem unlikely to be available for some time to come.[4] Despite recent investments in nanoEHS research, improved research expertise and infrastructure, and greater research activity in the field, there is a growing concern that not enough is being done to protect the environment, the public, and the federal investment in nanotechnology.[5]

To set the context for this Focus and to elaborate the roles that nanomaterial scientists can and should play in this research arena, I describe an evolving approach (Figure 1) to nanoEHS research that incorporates three phases: (1) studies of nanomaterial implications, (2) coordinated applications and implications research, and (3) a green nanoscience approach to material and process design that eliminates hazards throughout the material's life cycle. Each of these phases is overlapping, and there are research activities already being carried out in each phase. That said, the bulk of research activities are currently transitioning from phase 1 to 2. Phase 2 and 3 activities are each just beginning, and there are exciting research challenges and opportunities for nanomaterials scientists in both of them. To provide the foundation for the rest of this Focus, I first review the events that have motivated research on nanoEHS and provide new opportunities for nanomaterials scientists in this field.

During the past decade, there has been rapid growth in nanotechnology research and the establishment of companies and products by the early adopters of this technology. This period has been nanotechnology's *discovery* phase, in which researchers have rightly focused efforts on discovering new properties, transformations of matter, devices, and applications. The amounts of material used in this phase are small; thus, the primary concern is the safety of the researcher or others who handle the material directly, not society in general or the environment. Discovery phase applications are

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Published online March 25, 2008.
10.1021/nn800131j CCC: $40.75

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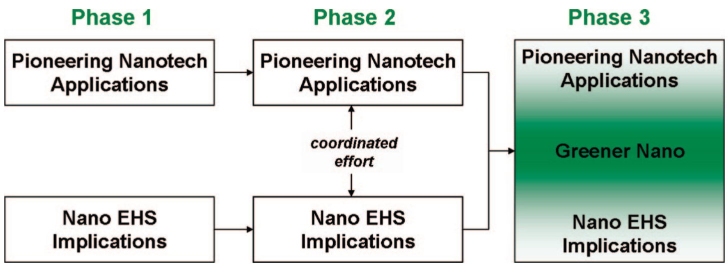

Figure 1. Evolution of the nanoEHS strategy. Early research activities focused on discovery of new nanotechnology applications. As research on the environmental and health implications developed, this was done in parallel with, but isolated from, the development of new applications (phase 1 investigations). The vertical double-headed arrow indicates the coordination of applications and implications research (phase 2 research). Phase 3 research blends applications and implications in a proactive approach (green nanoscience) that aims to develop and implement safer, greener approaches to nanomaterials design and production.

typically smaller scale or early stage research/development where there is less concern about potential process-related hazards and/or production efficiency. The efficiency of transformations and the use of hazardous reagents are of less concern because, when one needs only a few milligrams of material to study, the amounts of waste generated are not overwhelming.

As nanotechnology emerges from the discovery phase—characterized by continued investment, the emergence of hundreds of consumer products,[6] the formation of companies, and attention from the public—the real and/or perceived negative impacts need to be addressed lest they become barriers to future development of the field. Indeed, the future of nanoscience and nanotechnology will be influenced by public perception. These perceptions, in turn, will be influenced by scientific reports on nanomaterial safety and product performance in the market. To ensure the brightest future for nanoscience, it is important to reduce uncertainty in the minds of the public who support this research through federal investment and by purchasing nano-based consumer products.

As nanotechnology matures, questions are being posed about whether the products or materials of nanotechnology will present hazards to human health or the environment and whether the production of these materials will generate new hazards or wastestreams. The point has been made that if the promise of nanotechnology lies in the new properties of nanoscale materials, then it is likely that new size-dependent hazards will also be found. Although research investments under the 21st Century Nanotechnology Research and Development Act provided a focus on and some initial funding to address "ethical, legal, environmental and other appropriate societal concerns", very few data on these hazards are available, and some of what is available is contradictory.

The need to develop a research strategy to address nanoEHS concerns is widely acknowledged, and recent reports from the National Nanotechnology Initiative (NNI) Nanotechnology Environmental and Health Implications Working Group[2] and the Environmental Protection Agency[3] highlight research needs and ongoing research related to understanding hazards and risks of engineered nanomaterials. These frameworks aim to build the knowledge base needed for managing the potential risks of nanomaterials and thus focus on understanding how these materials interact with humans and the environment, routes of exposure, and activities related to characterizing and detecting these nanomaterials. In these frameworks, the roles of nanoscientists who design, synthesize, characterize, and study new materials are embedded within research priorities most specifically defined in terms of instrumentation, metrology, and analytical methods.[2]

As I will explain in this Focus, the active participation of nanoscientists is critical to successfully shaping and carrying out the nanoEHS research strategy. They have extensive experience working with and understanding the properties and transformations of these complex materials, have a vested interest in the future of the field, and, in collaboration with scientists from other fields, have the ability to (re)design materials with enhanced safety. As the nanoEHS research strategy evolves, the opportunities and responsibilities for nanoscientists within these frameworks should become much more prominent.

The Need for Data—Implications Research. The desire to have data on nanomaterial safety to guide decision-making is not new. The need for these data is now understood to be essential for producers, formulators, consumers, and regulators of consumer products to make sound decisions about nanomaterial safety. For example, the traditional risk framework that manages risk by limiting exposure to hazardous materials is well-established, but it presupposes that we know the hazards and that we understand and can control the routes of exposure. At this stage in nanotechnology, we are not able to do this because of the lack of data on the hazards, fate and transport, exposure routes, persistence, *etc.* of these materials.

During the past five years, there has been a slowly building emphasis on understanding the EHS implications of the products of nanotechnology. Much of this effort has been placed (rightly so) on studying those materials that are thought to be nearer commercialization, *e.g.*, carbon nanotubes and semiconductor quantum dots. Despite these

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efforts, there is still considerable uncertainty about these hazards. For example, the Material Safety Data Sheets for commercially available carbon nanotubes still contain information for composition, hazards, accidental release measures, and personal protection that were defined for graphite powder rather than the nanoscale material. Thus, despite a focus on nanoEHS in the 21st Century Nanotechnology Research and Development Act and now hundreds of scientific studies on nanoEHS, there still are not definitive answers about the safety of these materials.

The absence of data or seemingly conflicting data—for example, research articles and subsequent media reports that contribute to uncertainty about the hazards of carbon nanotubes—reduce public confidence in product safety and invigorate activist groups that aim to prevent the use of nanomaterials in products of commerce. Without relevant data, innovators are forced to rely on "reasonable worst case scenarios" in applying risk management frameworks[7] or they may not discover product hazards until late in product development. The lack of information on material safety hinders innovation and places companies at considerable risk of failure. NanoEHS is now recognized as a potential barrier to commercialization of nanomaterials.[8]

Why do we not have answers? Why are reports of hazards conflicting? The short answer is that nanomaterials are complex, and so are their interactions with biological/environmental media. The use of a wide range of biological assays, different methods of quantifying dose, and the influence of aggregation of nanomaterials in biological media have been described, and these factors certainly contribute to the varied results on nanomaterial toxicology thus far. However, even if these approaches become standardized, nanomaterials are complex due to their widely tunable composition and structure. Organic, inorganic, and hybrid materials can be produced in various sizes, shapes, surface areas, surface functionalities, and compositions. Most nanomaterials cannot be described as a uniform molecular species since they tend to have variations in composition and structure leading to dispersions in size, shape, surface area, and surface functionality. To confound the situation further, the methods of production are still immature for most materials, often resulting in batch-to-batch variability in composition and purity. Impurities are especially problematic because they may be hard to detect, can associate with the surfaces of the nanomaterial, and may be difficult to extract from the nanomaterial.

The variability in sample composition would not be such a problem if each sample could be easily characterized. Unfortunately, characterization methods and strategies are still being developed and may not detect impurities within a sample. For example, transmission electron microscopy (TEM) is a good method to determine the size and shape of an inorganic nanoparticle, but it is a poor method to detect or to quantify small-molecule impurities. Even well-defined, purified samples can present problems that arise due to sample degradation during storage and/or use. The reactivity (*i.e.*, surface reactions, catalytic activity, or photolytic activity) of nanomaterials resulting from their size-dependent properties can transform the material upon storage or once in the biological system. For example, the photochemical action of semiconductor quantum dots can lead to oxidation of stabilizing ligands, thereby destabilizing the particles over time.[9]

Coordinating Applications and Implications Research. Interdisciplinary teams that partner life, environmental, and nanomaterials scientists need to work together to define standard approaches and share expertise to accelerate the collection of definitive data on nanomaterial hazards[10] given the complexity of nanomaterials (i) production and purification, (ii) characterization, and (iii) bio/eco studies described above. Thus far, research on applications and implications of nanotechnology have been carried out in isolation from each other, and, in most cases, the experts in nanomaterials, nanoscale characterization, and toxicology are working in isolation

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as well. This situation, at best, slows progress and, at worst, leads to erroneous reports that fuel public fear and mistrust. Thus, applications and implications research (including materials design/synthesis, characterization, and bio/eco impact studies) need to be coordinated.[10] Recent examples of emerging efforts to coordinate the facets of this problem are the Nanotechnology Characterization Laboratory (a collaboration between the National Cancer Institute, the National Institute of Standards and Technology, and the Food and Drug Administration)[11] and the newly launched NanoHealth Enterprise.[12]

Within such a coordinated approach, the challenge for nanomaterials scientists in addressing this research problem is to develop the means of producing materials that are "well-defined", and do so reproducibly. "Well-defined" are those samples wherein the size, shape, surface chemistry, and purity can be measured and controlled. Thus, developing new methods of synthesis that provide a greater degree of control over the composition, structure, and size dispersity is an important objective. Improved syntheses that reduce the number of byproducts produced will also simplify purification of the samples (*vide infra*). Meeting this objective will likely require an improved understanding of the mechanisms of formation, transformation, and functionalization of nanomaterials.[13] In addition to developing enhanced methods of synthetic control, improved methods of purification and characterization will be needed to produce materials with known impurity profiles and to provide characterization data for comparison of different nanomaterial samples, respectively.

Although impurities have been recognized to impact the toxicity, reactivity, and properties of nanoparticulate materials, the detection, quantification, and removal of impurities in nanomaterial samples are seldom addressed. Recently, it has been shown that the presence of small-molecule impurities (starting reagents, catalysts, or excess ligand) can cloud the results of toxicity testing[14] or even impede chemical self-assembly reactions.[15] The fact that materials prepared using different synthetic methods (or even those prepared by the same method, but in different batches) have different impurity profiles leads to inconsistent results in toxicity or other biological testing, leading to uncertainty about the relationship between nanomaterial structure and impact. In some cases, the impurities themselves may be the agent responsible for the biological response. In other cases, the presence of "inactive" impurities will dilute the dose and may act synergistically with the nanomaterial. In light of the seemingly contradictory reports about nanomaterial toxicity, detecting and quantifying the varying types and levels of impurities are important steps in reducing uncertainty about the hazards of these nanomaterials.

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One of the reasons that impurities may go undetected in nanomaterial samples is that the methods for nanomaterial characterization (TEM, optical absorption spectroscopy, light scattering, *etc.*) are often insensitive to small-molecule impurities. Thus, a nanoparticulate sample that has the desired size, shape and size distribution as determined by TEM may contain large quantities of small-molecule impurities (ligands, catalysts, or other reagents). As an example, a number of studies have now documented the large range of impurities present in different batches of "as-prepared" carbon nanotubes.[16–20] One of the keys to detecting the presence of impurities in new nanomaterial samples is to employ a suite of analytical techniques to each sample (e.g., a combination that assesses composition, core size and shape, surface functionality, and purity) and to utilize techniques that easily detect small-molecule impurities. NMR, TGA, and chromatographic techniques such as HPLC or GPC are particularly helpful in this regard. Quantifying the levels of impurities is also challenging because the nanomaterial stability may not allow the use of chromatographic methods, size dispersity may preclude the use of elemental analysis, and some of the best methods for identifying the presence of small molecule impurities (NMR, TGA) do not have low detection limits.

When impurities are present in samples, they need to be removed and/or quantified. Challenges are faced in both of these areas. Traditional methods for obtaining pure nanoparticles are cumbersome because they often involve series of precipitations, extensive solvent washes, fractional crystallizations, or sequences of washes and centrifugations. These methods are time-consuming, wasteful, and often ineffective. Until improved methods can be developed, the best strategy for addressing this challenge is to focus on reducing impurities until they can no longer be detected by the most sensitive technique.

Compared to some of the more traditional purification methods, new purification strategies are being developed that are more effective and less wasteful. For example, purification of Au nanoparticles may be carried out *via* dialysis or diafiltration, procedures that efficiently remove any remaining excess salts and unreacted materials. In diafiltration, materials are placed in the diafiltration unit and, as they circulate through the unit, the nanoparticles are retained and impurities are removed.[21] Compared to the traditional purification methods described above that use 15 L of solvent/g of nanoparticle and typically take 3 days to perform, the diafiltration method requires no organic solvent and only 15 min. The process of diafiltration as a purification method can effectively reduce solvent consumption and provide cleaner, well-defined building blocks.

Unfortunately, many nanomaterials are reactive and may be transformed or degraded during handling or storage. This is another issue that can lead to uncertainty regarding the impacts of nanomaterials. Thus, in the context of nanoEHS, nanomaterials scientists will need to investigate and document under what conditions these transformations occur and to communicate proper handling procedures to those involved in testing their materials. They should also be involved in evaluating the materials at intervals to see if the composition or purity has changed.

A final challenge for materials chemists and nanomaterial characterization experts is determining the fate of nanomaterials that are exposed to complex media such as those inherent under biological and environmental testing conditions. This is particularly challenging because of the difficulty of finding and tracking the material, since it is essentially the proverbial "needle in a haystack" problem, and the difficulty in characterizing the transformed material *in situ*. New analytical and tracking methods are needed to assess the transformations of these materials.

Greener Nanoscience. As important as the coordinated approach to nanoEHS described above is to bolstering the reliability of data on nanomaterial hazards, it is only a beginning, and it has certain limitations. The approach necessarily focuses on determining the hazards of a narrow subset of nanomaterials that is closest to commercialization. Although these materials warrant immediate attention, the information received from these studies will not provide broad enough correlations between nanomaterial structure and material hazard to design alternatives to those materials found to have an unacceptable level of hazard. A broader focus is needed to determine the design rules so that (re)design for product safety does not stall innovation and commercialization. These design rules are also needed to guide the design of new classes of nanomaterials to be safer from the outset. Finally, the focus on materials implications testing does not address hazards and other impacts throughout the materials life cycle, notably the production phase. To address these shortcomings, a research approach is needed that (i) begins to develop safer *alternative materials* that can be used if a nanomaterial is found to be toxic or bioaccumulative in commercial or near-commercial phase, (ii) identifies the *design rules* for new nanomaterial classes that have desirable properties and a high degree of safety, and (iii) reduces the hazards and increases the efficiency of *nanomaterials production*. *Green nanoscience* is such an approach that aims to create and apply design rules proactively for greener nanomaterials *and* to develop efficient synthetic strategies to produce nanomaterials reproducibly with defined composition, structure, and purity.

Green nanoscience, like green chemistry, strives to reduce or eliminate hazards to human health and the environment through product design and process optimization.

Green nanoscience[13,22,23] applies the well-known 12 principles of green chemistry[24] to the design, production, and use of nanomaterials. Green nanoscience, like green chemistry, strives to reduce or eliminate hazards to human health and the environment through product design and process optimization. The application of the 12 principles of green chemistry to nanoscience has recently been described, as reproduced in Figure 2.[13] In order to reduce those principles to practice, we need to develop the knowledge base and tools (synthetic methods, mechanistic understanding, characterization tools and strategies, bio/eco testing procedures) so that we can act quickly to find replacements for materials that are not safe enough, to design novel materials, and to produce well-defined materials reliably and efficiently. To complement these strategies, we will also need analysis tools that aid in the decision-making processes required to weigh the merits of competing technologies.

Green nanoscience/technology can provide three additional benefits. It can spur innovation through the exploration of new materials and properties, enable commercialization by reducing uncertainty about material safety and providing more efficient manufacturing approaches, and protect our investment in nanotechnology from the threats of public/consumer fears about the uncertain risks of the technology.

Toward Greener Nanomaterial Design Rules. The nanomaterials of concern are those that are freely dispersed or those that may become dislodged from a bulk material during the use of a material that contains embedded nanostructures. Al-

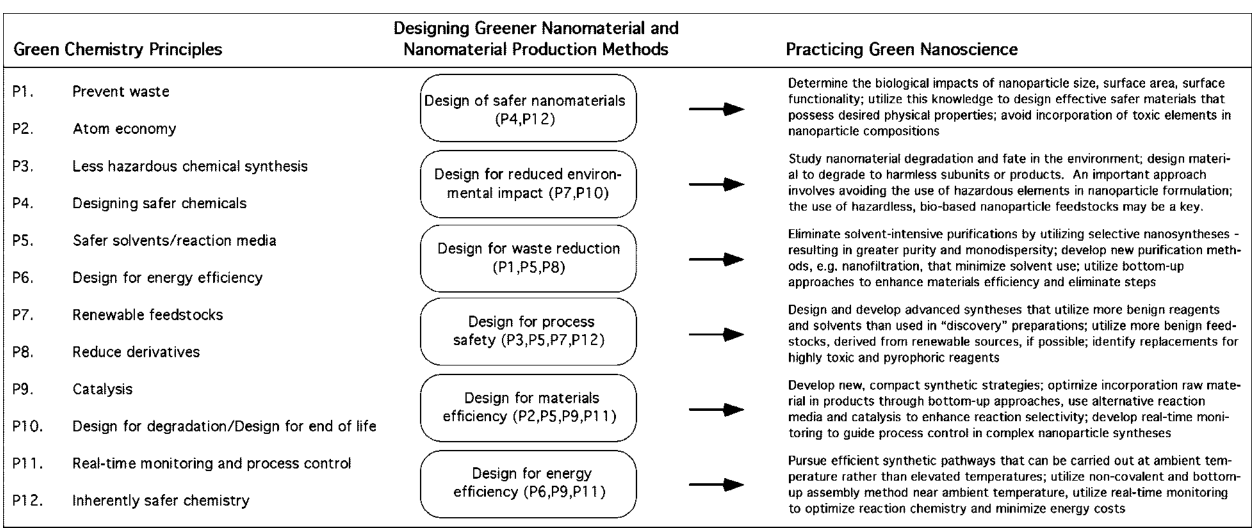

Figure 2. Translating the 12 green chemistry principles for application in the practice of green nanoscience. The principles are listed, in abbreviated form, along with the general approaches to designing greener nanomaterials and nanomaterial production methods and specific examples of how these approaches are being implemented in green nanoscience. Within the figure, P*X*, where *X* = 1–12, indicates the applicable green chemistry principle. Reprinted with permission from ref 13. Copyright 2007 American Chemical Society.

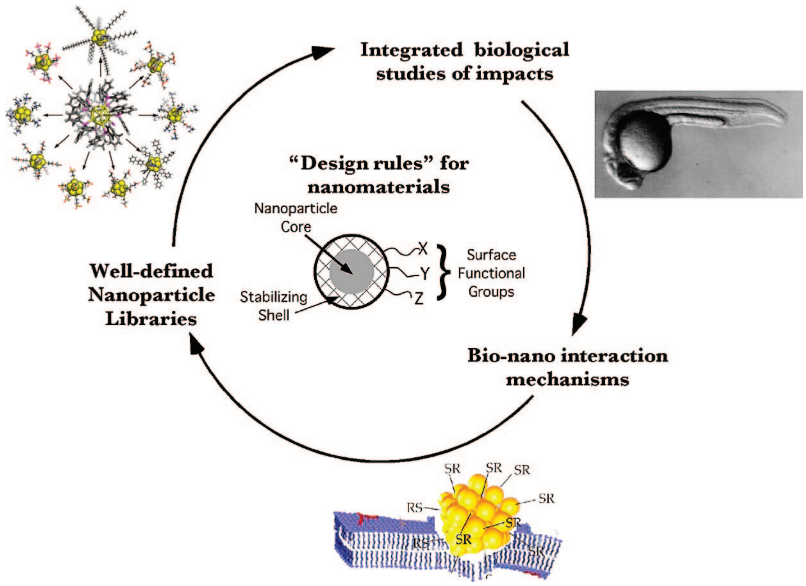

Figure 3. Approach to developing the "design rules" for greener nanomaterials. Structurally and compositionally well-defined nanomaterials are chosen for study to test hypotheses about the influence of nanostructure on biological impact. Thorough characterization and tests of purity are needed to ensure that impacts can be related to structural features. Biological testing is carried out to determine impacts and the mechanisms of action for specific endpoints. New hypotheses are generated that contribute to material (re)design. Subsequent iterations of this process lead to improved understanding of the structure/activity relationships and to "design rules" for greener nanomaterials.

though hundreds of studies of nanomaterial hazards have been reported in the literature, it remains unclear which attributes of nanomaterials contribute to specific hazards.[4] As mentioned in the previous section, coordinated applications and implications research should reveal the impacts of the selected materials employed in those studies. To complement the studies of those commercial or near-commercial materials, hypothesis-driven studies and assessment of series of nanoparticles with systematically varied structural features (see Figure 3) are needed to provide data sets that may reveal the design rules for safer nanomaterials. Again, this challenge requires a coordinated, interdisciplinary effort to define the material and to measure and interpret the interactions of the material with the biological or environmental medium. Studies in our laboratories and others are underway to identify the structural features that are important and to develop predictive approaches that are desperately needed for materials design.

In the absence of definitive answers about nanomaterial safety, what steps can be taken to minimize the chances of designing hazardous materials? Given the many choices available in designing new nanomaterials, which building blocks should we use? Until we have more guiding information, two approaches would seem prudent. First, avoid compositions containing toxic elements. Although some such elements are commonly used within embedded structures, free nanomaterials may be easily dispersed and, due to higher surface area, have greater propensity to leach those elements than an embedded bulk material. Thus, avoiding the use of elements in which the ions or small molecules pose recognized hazards to human health or the environment seems a reasonable rule of thumb until more data on possible exposures, fate, and transport are available. Second, consider the hazards of molecular and micrometer-scale materials of the targeted composition and avoid compositions bracketed by smaller and larger materials with known hazards—"dimensional bracketing". If both the molecular and micrometer-scale forms pose hazards, the nanomaterial bracketed by these two is likely to possess hazardous properties as well because, although nanoscale materials have properties different from the bulk, they also share functions and properties with the analogues that have slightly smaller and larger dimensions. Of course, the lack of hazards for either bracketing material does not guarantee a safe nanomaterial. In all cases, design of safer materials will benefit from more systematic data regarding the way in which structure influences biological or environmental impacts.

Next-Generation Nanomaterials Production Methods. Related to the design of greener nanomaterials is the development of higher performance and greener production methods. In support of the efforts to develop the design rules, improved syntheses that provide convenient access to well-defined materials with reproducible purity profiles are important. In terms of greener production, one would like to avoid use of hazardous materials and minimize the production of hazardous byproduct. Efficiency is also important to minimizing impact and enhancing manufacturability, e.g., by increasing throughput, improving material efficiency, gaining precise product control, and reducing waste.

Although a few nanomaterials may be considered *commodity* materials (*i.e.*, ZnO and TiO_2), these are not typically highly refined nanomaterials in that their surface chemistry, degree of aggregation, and size dispersity are not controlled. On the other hand, nanoparticles with properties that depend strongly on each of their structural features (composition, size, shape, surface coating, *etc.*) might be referred to as *fine* nanomaterials. The current methods of nanoparticle production for fine nanomaterials are typically based upon the initial "discovery" routes. They often involve higher reactive and/or toxic reagents and have poor efficiencies (*E*-factors of 1,000–10,000). The hazards and inefficiencies of these routes pose significant risks during production and severely limit production throughput. For these reasons, the synthesis/production of nanoscale materials and devices (nanomanufacturing) is an area where green chemistry principles can and should be readily applied to guide process improvement and innovation.

The principles of green chemistry apply well to the production of nanomaterials (see Figure 2). A number of examples are known that illustrate the implementation of those principles and show how greener approaches often enhance the manufacturability of the material by reducing costs and improving throughput. For example, we substituted sodium borohydride and toluene for diborane and benzene, respectively, in the production of phosphine-stabilized gold nanoparticles.[25] The changes to this synthesis eliminate half the steps in the synthesis, allow it to be carried out in air without the need for the specialized apparatus and rigorous inert atmosphere conditions required in the previous synthesis, permit the production of significantly more material (~1 g/day *vs* ~100 mg/day), and allow it to be easily scaled to larger batches, while substantially reducing the cost to prepare the material.[25]

For many reactions, a significant obstacle will be scaling production levels while retaining the nanomaterial quality that can be attained at the discovery scale. As the scale increases, inhomogeneities in reagent concentration and temperature can lead to loss of product control. For example, in the case of gold nanoparticle production, the reaction rate is often faster than mixing can occur. In these situations, improved product control may be obtained by utilizing continuous-flow microreactors for synthesis wherein rapid mixing and tight control over the process conditions can lead to improved product definition and quality. For other classes of syntheses, these types of reactors have been previously shown to ease scaling of reactions to larger scales, improve production efficiency, and reduce waste.[26,27]

Another example of a greener approach in nanomaterial production is the rapid, effective, and efficient purification of water-soluble nanoparticles by diafiltration, a continuous-flow nanoporous membrane separation technique (Figure 4).[21] Compared to conventional purification methods (such as extensive solvent washing, fractional crystallization, dialysis, extractions, centrifugation, and chromatography), diafiltration is an efficient method for removing small-molecule impurities from nanoparticles. Diafiltration is easily scalable to large volumes, so purification of kilogram quantities can be easily accomplished. The traditional methods for obtaining pure nanoparticles are also time-consuming (up to 3 days per sample) and wasteful (consuming as much as 15 L of organic solvent per gram of nanoparticles).

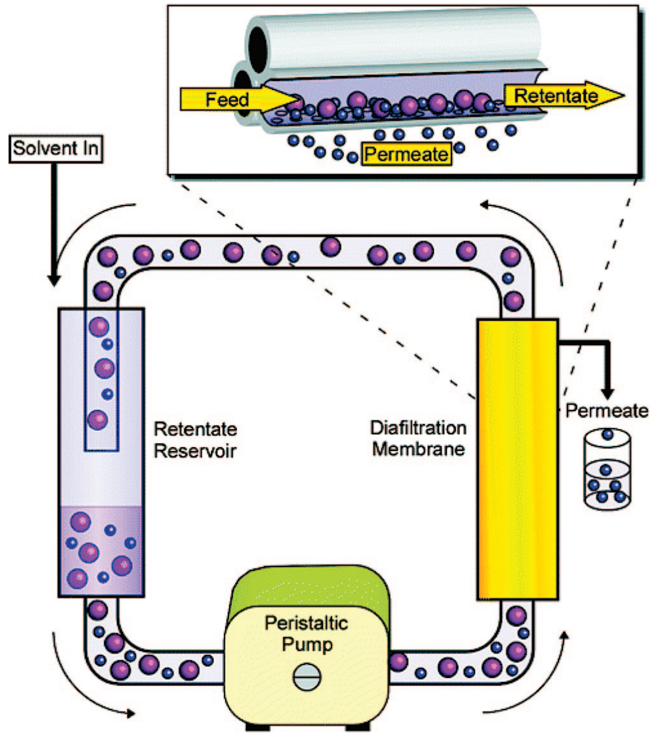

Figure 4. Schematic of a continuous diafiltration setup. Diafiltration is an ideal method for removing small-molecule impurities from nanoparticles, since it is easily scalable to large volumes and is less time-consuming and wasteful compared to traditional filtration methods. Reprinted with permission from ref 21. Copyright 2006 American Chemical Society.

The few examples provided here from our research only begin to illustrate the application of the green chemistry principles to the practice of nanoscience and nanotechnology. The challenges of greener nanomaterial design and greener production of these materials represent a substantial opportunity for new research that can address nanoEHS concerns while producing new materials and products with superior performance and economics.

SUMMARY

As nanomaterials researchers, we have considerable opportunity to contribute to the efforts to help define and to reduce uncertainty about materials hazards, to reduce barriers to commercialization and facilitate societal benefit, and to advance the field's ability to design, produce, purify, characterize, and understand nanomaterials. Specifically, we can develop new synthesis, purification, and characterization methods, coordinate these efforts with relevant and related efforts with colleagues in the life, environmental, and analytical sciences, and communicate these efforts to the public to further their understanding of ways in which nanotechnology, and our approach to it, can benefit society and the environment.

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