Designing Nanomaterials to Maximize Performance and Minimize Undesirable Implications Guided by the Principles of Green Chemistry

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Designing Nanomaterials to Maximize Performance and Minimize Undesirable Implications Guided by the Principles of Green Chemistry.

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Key Learning Points

1. It is now possible to strive to maximize performance and minimize implications for nanomaterials across the life cycle through application of the Principles of Green Chemistry.

2. When considering nanoparticles, functional performance and inherent hazard are not dictated solely by size and surface area, but depend on core composition and surface chemistry as well.

3. There is the opportunity to resolve those structure-property parameters of nanomaterials that impart both their functional performance and hazard response. The optimal situation, from a green design perspective, is when these parametric relationships are independent of one another (i.e., performance and hazard can be independently tuned or varied).

4. In addition to considering the performance or hazard of individual nanoparticles, researchers, product designers, materials scientists, and engineers should aim to minimize environmental and human health impacts across the nanomaterial life cycle.

5. Leveraging nanotechnology will enable innovation and market growth while providing new materials and applications that can benefit society and the environment.

Abstract

The Twelve Principles of Green Chemistry were first published in 1998 and provide a framework that has been adopted not only by chemists, but also by design practitioners and decision-makers (e.g., materials scientists and regulators). The development of the Principles was initially motivated by the need to address decades of unintended environmental pollution and human health impacts from the production and use of hazardous chemicals. Yet, for over a decade now, the Principles have been applied to the synthesis and production of engineered nanomaterials (ENMs) and the products they enable. While the combined efforts of the global scientific community have led to promising advances in the field of nanotechnology, there remain significant research gaps and the opportunity to leverage the potential global economic, societal and environmental benefits of ENMs safely and sustainably. As such, this tutorial review benchmarks the successes to date and identifies critical research gaps to be considered as future opportunities for the community to address. A sustainable material design framework is proposed that emphasizes the importance of establishing structure-property-function (SPF) and structure-property-hazard (SPH) relationships to guide the rational design of ENMs. The goal is to achieve or exceed the functional performance of current materials and the technologies they enable, while minimizing inherent hazard to avoid risk to human health and the environment at all stages of the life cycle.

Introduction

Nanotechnology involves the construction of matter at the nanoscale (1-100 nm) for the creation of materials, devices, and systems that possess novel properties and functions. While there are earlier accounts of nanotechnology-enabled applications, the field, as we know it today, emerged in the 1980's and has since experienced continued growth in government research funding, novel applications, market value, and employment opportunities. Consistent annual increases in federal/national government funding worldwide[1] provides financial support to academic, industry, and government researchers that are committed to the discovery, investigation, and translation of novel material phenomena and the ways in which they can be harnessed to develop next generation products, treatments, and remediation technologies. In turn, the market value continues to experience growth; the nanotechnology sector was estimated to generate \$225 billion in product sales in 2009,[2] and the global market of nanotechnology-enabled products is projected to reach \$3 trillion in 2020.[1]

Manipulations at the nanoscale have led to the establishment of several classes of engineered nanomaterial (ENMs), including metal (e.g., silver, gold, iron), metal oxide (e.g., titanium dioxide, zinc oxide, silicon dioxide), metal chalcogens (e.g., CdS and CdSe quantum dots), and carbon-based nanomaterials (e.g., fullerenes, carbon nanotubes, graphene). The novel physical and chemical properties of ENMs inspire a multitude of nano-enabled applications that span most industries from electronics to environmental remediation, and promise global societal, economic, and environmental advancements.[1] However, the new properties may also give rise to novel environmental and human health implications. Research regarding these negative implications became a research focus over a decade ago and remain a primary research objective calling for the development of new strategies and methodologies to ensure prevention of potentially devastating adverse impacts.[2]

Lessons learned from the widespread use and reaction to the undesirable impacts of chemicals of commerce during the 1970s and 1980s inspired a paradigm shift and the establishment of the Principles of Green Chemistry in 1998. These principles have been applied to nanotechnology for nearly a decade. One of the overarching aims of green chemistry is to reduce risk, which is a function of both hazard and exposure, by minimizing inherent hazard rather than relying on downstream exposure control mechanisms. The application of the Principles to nanotechnologies during the development stage will enable the design of next generation applications with enhanced functional efficacy and minimized potential environmental and human health unintended consequences.[3] In 2007, Dahl et al. proposed a translation of the Principles for application to nanoscience, the Greener Nanoscience and Nanotechnology Design Principles[4], to provide a guiding framework for nanotechnology practitioners for safer design across all stages of the life cycle (Table 1).

Table 1. Summary translation of the Twelve Principles to the practice of greener nanoscience and nanotechnology. Adapted from Dahl et al.[4]

		Green Nanoscience/Nanotechnology Design Principles					
		Design of safer nanomaterials	Design for reduced environmental impact	Design for waste reduction	Design for process safety	Design for materials efficiency	Design for energy efficiency
Twelve Principles of Green Chemistry	1. Prevent waste			🟩			
	2. Atom economy					🟩	
	3. Less hazardous chemical synthesis				🟩		
	4. Designing safer chemicals	🟩					
	5. Safer solvent/reaction media			🟩	🟩	🟩	
	6. Design for energy efficiency						🟩
	7. Revewable feedstocks		🟩		🟩		
	8. Reduce derivatives			🟩			
	9. Catalysis					🟩	🟩
	10. Design for degradation/Design for end of life		🟩				
	11. Real-time monitoring and process control					🟩	🟩
	12. Inherently safer chemistry	🟩			🟩		

The tutorial review presented herein builds upon the foundation established by these Greener Nanoscience and Nanotechnology Design Principles and provides an overview of the current successes and future opportunities of applying the Principles of Green Chemistry to nanotechnology. In particular, multiple ENM classes are reviewed, including metal nanoparticles (e.g., gold and silver) and carbon-based nanomaterials (e.g., carbon nanotubes, graphene, and C_{60}). The discussion of each is presented as a case study to illustrate the current state of the research and each section intends to highlight considerations across the life cycle. In addition to reviewing the accomplishments achieved to date, a number of critical research gaps are identified that may inspire future research directions.

Sustainable Nanotechnology: Green Chemistry Applied to Nanotechnology

Green Chemistry is a design framework. It is used to design molecules and materials as well as the processes used to make them in order to ensure they are nonhazardous to human health and the environment that life depends upon. The framework was developed as a *pro*active complement to the many *re*active approaches that have been used over the past decades that sought to remediate damage caused by widespread use of products and wasteful processes. Yet, traditional control and mitigation approaches are applied after new chemicals are introduced into commerce (and the environment) and the harm has already been done. As such, green chemistry was developed as a preventative approach that is applied at the first conception of new chemistries.[5]

While many engineering and process management approaches seek to minimize waste or achieve greater energy efficiency, green chemistry has sought to achieve these goals and much more. Green chemistry looks at the entire life cycle through the application of a set of principles to optimize the design (Figure 1).[6] This is important recognition because it is certainly possible to design a benign target molecule or material, perhaps a life-saving drug, and do it in a way that is polluting and contaminating. Conversely, there are ways to construct a clean and efficient manufacturing or synthetic scheme that produces a lethal poison. Considering a single life cycle stage in isolation can be, and historically has been, a mistake resulting in costly unintended consequences.

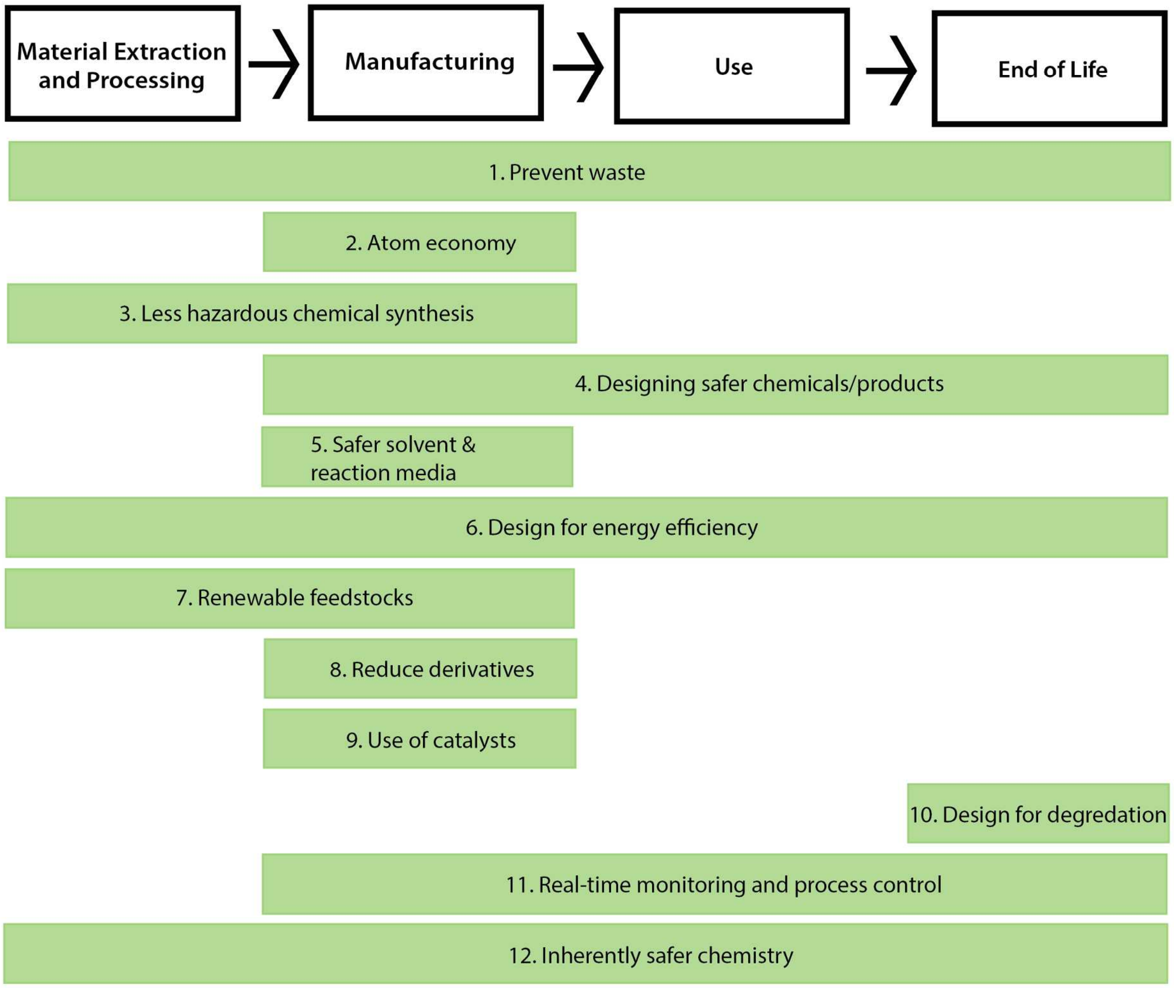


Figure 1. Schematic showing the life cycle stages applicable to each of the Twelve Principles.

When designing through the Principles of Green Chemistry, as with any multi-parameter system, there may be trade-offs between principles given our current technical capabilities. However, because there is no evidence to suggest that any of these potential trade-offs are intrinsic – that Principles *necessarily* must be in opposition – it is simply a design challenge to maximize the synergies and align the Principles for optimal design solutions.

To begin the life cycle approach, origins of the feedstocks (Principle 7) is one essential element of the Twelve Principles that specifies that starting materials should be renewable rather than depleting wherever possible. While renewable is often a term used describe bio-based (i.e., recently synthesized or rapidly cycling) rather than fossil-based carbon feedstocks, this is often only applicable to a subset of ENM classes. Much of what would need to be considered with many ENMs is whether the elements are in short supply or derived from conflict minerals. Sources of feedstocks in these cases can have environmental, geopolitical, and economic considerations. As has been seen by small-scale, high value chemical products in the past, it is easy to dismiss consequences of feedstocks based on what is considered to be small quantities, yet when the consequences of these residues cascade through the life cycle and supply chain, they can become dominant issues to manufacture and product viability. One example is that of pharmaceuticals, which are considered very small volume and of high value; yet, their release and persistence in the environment causes significant concern for both human and ecosystem health.

The manufacturing life cycle stage has several principles that are directly relevant (Principles 1-3, 8, 11). First, there is a goal that every atom that enters into the manufacturing scheme winds up as product and not as waste. Clearly, this is understood as an ideal to strive toward. Several metrics, namely atom economy[7] and the environmental factor (E-factor)[8], have been developed to quantify how closely a process comes to achieving this goal. Recent studies demonstrated that ENM syntheses perform poorly with respect to these measures; significantly more waste can be generated than during pharmaceuticals and specialty chemicals manufacture, which are considered to be material and energy consumptive processes.[8, 9]

One, typically large material requirement are solvents and auxiliary substances (Principle 5), which can be critical in the synthesis and isolation of ENM products. Approaches have used a range of solvents with a variety of environmental impacts such as ozone depletion, formation of volatile organic carbons (VOCs), and human health impacts including cancer and neurological effects. The development of green chemistry alternatives to these traditional solvents is an ongoing active research area. Some of these alternatives include carrying out certain organic transformations in aqueous systems where it was not thought possible.[10] Further, the use of supercritical carbon dioxide, once thought to be useful only as an extraction solvent, has received increasing attention as a reaction medium as well.[11] More recently, the advantages of room temperature ionic liquids have been exploited as a novel medium to carry out new reactions. The 'green' benefits derive simply from the fact that ionic liquids have negligible vapor pressure, and thus reduce human exposure.[12]

Another manufacturing consideration in the synthesis of ENMs involves using stoichiometric quantities of reagents or a catalytic approach (Principles 6 and 9). The Principles of Green Chemistry explicitly recognize the material and energy advantages of catalytic transformations, and the case studies presented in this tutorial will provide examples of these techniques. Energy is another primary major concern in the synthesis of ENMs.[13] While these considerations are important at the laboratory scale, they can become critical at the industrial scale. Thus, a Principle of Green Chemistry specifies the use of ambient temperatures and pressures where possible and practical.

The use phase of the life cycle, and the desired functional properties of a target molecule or nanomaterial, is often the sole consideration in chemical design. As such, the inherent ability of that product to cause adverse consequence to humans and the environment, an essential focus of green chemistry, is often overlooked. Principle 4 states that chemical products should be designed to preserve efficacy of function while reducing or eliminating hazard. In recent years, this principle has been the focus of extensive research to elucidate not only the elements that contribute to molecular and ENM toxicity, but also to inform design guidelines such that the next generation of materials is inherently less toxic. Although designing molecules, let alone ENMs, from first principles to have predictable biological activity is still viewed as an immense challenge (e.g., efforts in pharmaceutical and pesticide design), the intersection of recent advances in mechanistic toxicology and computational chemistry provide the foundation necessary to identify the essential desirable properties for minimizing adverse biological effects. Significant contributions have been made to advance rational design of safer chemicals,[14] demonstrating the ability to delineate a diverse group of chemicals with reduced acute aquatic toxicity[15] using property indicators for bioavailability (i.e., octanol-water partition coefficient) and reactivity (i.e., HUMO-LOMO gap). Applying such guidelines can result in a two-to-five fold increase in the likelihood of designing a chemical with little to no aquatic toxicity concern.[16] Similar molecular-level design approaches are needed for ENMs. The combined efforts in the design of safer molecules and ENMs necessarily include the equality of the goal outlined in Principle 4, "to preserve efficacy of function" while making these design improvements.

Finally, the fate of a material or product after their useful or commercial life is a critical and often neglected consideration of the design process. Designing for "afterlife" (Principle 10) is something that has traditionally been ignored, and this is notably true of ENMs. Given the high level of environmental awareness attained it is unfortunate that still much of nanotechnology has not incorporated the prevention of these problems into the early development of the field. The Principles, including design for degradation, non-persistence, and non-bioaccumulation/biomagnification, are thus, important considerations when first conceiving of a new ENM or nano-enabled product.

Considering the full life cycle at a pre-market stage is a critical first step towards reducing unintended consequences. Preemptively determining this balance of benefits and undesirable impacts of a novel material, device, or application is essential to ensure safe and sustainable implementation. As such, the simple concept of quantifying these tradeoffs as a ratio of the life cycle impacts and benefits has been proposed:

$$\text{Impact-Benefit Ratio} = \frac{\text{Life Cycle Impacts}}{\text{Functional Performance Benefits}} \qquad (1).^{17}$$

The goal is to achieve the lowest ratio possible, indicating that the realization of functional performance benefits (e.g., decreased energy demand, longer product life time, lower operation temperature, increased detection limit or specificity) outweigh the life cycle impacts (e.g., environmental, economic, and human health costs from upstream manufacturing or release during the use or end of life phases).

The initial case study in which this ratio was applied, the impacts were quantified in units of disability-adjusted life years (DALYs); the numerator (impacts) was determined via application of life cycle impact assessment methods and the denominator (benefits) calculated directly from occupational health data.[17] While the initial application of the ratio is to human health, it can be considered and applied within a number of contexts and thus, when quantifiable, can manifest as a variety of units. In addition to the mentioned human health benefits quantified as DALYs preserved (e.g., prevention of occupational fatalities through improved technology), the ratio can be applied to quantify the potential net life cycle economic benefit (e.g., \$, dollars saved), or environmental benefit in terms of reduced carbon (CO_2 equivalents) or green house gas emissions (e.g., improved energy efficiency, use of renewable feedstocks in manufacturing process).

The Principles of Green Chemistry can be used as framework to ensure that the ENMs of the future are safe and efficacious throughout their life cycle while contributing to a sustainable society and economy. This strategy preserves innovation while minimizing unintended consequence in this important area of research and development. In the following sections, the successes to date and future opportunities in the application of the Principles to nanoscience and nanotechnology are discussed in the context of two case studies. The first case study focuses on metal nanoparticles, gold (Au) and silver (Ag), and the second on carbon-based nanomaterials, carbon nanotubes (CNTs), graphene, and fullerenes (C_{60}). While significant advances have been achieved for gold and silver in terms of controlled synthesis, safer alternative feedstocks, solvents, and process efficiencies, there remain several challenges and research gaps, which are identified and discussed. On the other hand, there is less resolution of synthetic pathways, mechanisms, and process efficiencies for carbon-based nanomaterials, offering critical opportunities for research contributions. Furthermore, in discussing each class independently, challenges common to both emerge and again, offer critically important research opportunities. Finally, research efforts to resolve structure-property-function (SPF) and structure-property-hazard (SPH) relationships within both ENM categories discussed provide a foundation from which researchers and practitioners can build.

A Success Case Study: Gold and Silver Nanoparticles

The application of green chemistry to the design and synthesis of gold and silver nanoparticles (AuNP and AgNP, respectively) was implemented early.[18] Ligand-stabilized AuNPs have been used successfully to develop many of the state-of-the-art approaches to green nanotechnology. In this section, these successes (organized around the design principles shown in Table 1) are examined to inform sustainable molecular level design and synthesis of nanomaterials in general.

Design of Safer Nanomaterials. To design new nanoparticles that meet performance specifications and pose minimal health and environmental impacts, one must develop relationships that relate ENM properties to functional performance and hazard: the SPF and SPH relationships, respectively. Function and hazard are related to nanomaterial properties, and those properties, in turn, derive from structures that can be designed and controlled through synthesis. If structure and purity are known, then properties and functions can be linked to that structure and to each other. Although it is now widely accepted that nanoparticles will be transformed (often rapidly) through biological and environmental processes, the initial design and structure influence those transformations. Thus, the initial structure remains the most important design challenge and opportunity.

Establishing robust SPH relationships has been challenging because nanoparticles are diverse, multifunctional structures. In addition, they are often produced and studied as complex mixtures that include reaction byproducts and degradation products (Figure 2). Thiol-stabilized gold nanoparticles are an excellent model system to evaluate the nanoparticle-specific SPH relationships because their structures can be deliberately modified, samples can be thoroughly purified and their structures can be determined. Since toxic ions are not leached from the core and the ligands are bound tightly, the hazard and function are strictly a result of the intact nanoparticle. The covalently bound ligand shell displays a specific set of functional groups on the particle's periphery. Libraries containing a wide variety of surface chemistries and core sizes have been produced.[19]

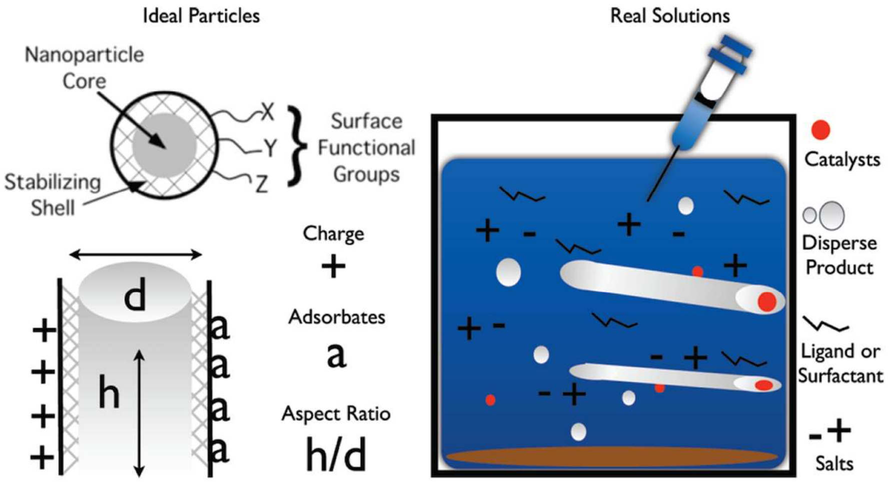


Figure 2. Schematic comparing ideal nanoparticle attributes, such as may be found in highly purified ligand-stabilized nanoparticle samples, to those of the complex mixtures that typify commonly used nanoparticle samples. Samples with known purity and well-defined structural features are well suited for studies to determine SPH relationships. The presence of impurities (such as ions, surfactants or reaction byproducts) and/or the lack of structural definition of the nanoparticle sample in real solutions blur the SPH relationships. The amounts of such impurities often vary from sample to sample, further complicating the process defining and using these relationships. (Reprinted with permission from Richman, E. K. and Hutchison, J. E. ACS Nano **2009**, *3*, 2441, Figure2. Copyright 2009 American Chemical Society.)

The characterization of nanoparticle structure and composition is key to developing SPF/SPH relationships and remains a challenge despite increased awareness of its importance over the last few years. Studies that seek to relate structure to properties or function/hazard must evaluate samples sufficiently so that these are robust relationships. While this may sound obvious or straightforward, in practice it is not. The first issue is purity. The byproducts of metal nanoparticle synthesis often include metal complexes, free stabilizers, surfactants, and salts. At even 1% by weight, such impurities can translate to greater than 100 molar excess (i.e., moles impurity per moles nanoparticle) for a nanoparticle containing a gold core that is 15 nm in diameter (e.g., assuming impurity and nanoparticle molar mass of 150 g/mol and 1,500 kg/mol, respectively). Serial precipitations, diafiltration, and chromatographic methods have been employed to produce higher purity samples. Establishing a high level of purity can be done through high performance liquid chromatography (HPLC) or nuclear magnetic resonance (NMR) analysis. Ligands bound to the surface exhibit broad peaks whereas free impurities can be detected as sharp peaks in NMR spectra.

Once purity is established, the structure of the nanoparticle must be determined, typically through multiple complementary and corroborative analysis techniques.[20] During synthesis of a new material, it may be necessary to use a wide array of techniques to determine composition and structure. After the key techniques are established, it may be possible (and is advisable) to adopt a *minimal characterization* set to monitor key aspects of the composition or structure that might tend to vary from one synthesis batch to another.[20] There has been much debate about what constitutes sufficient material description for studies that seek to link structure to properties and function. It is clear that characterization is somewhat dependent on material class. For example, the key material descriptors for a ligand-stabilized gold nanoparticle will be different than a multi-walled carbon nanotube. Depending upon the material class, the core composition may, or may not, be significant. If the core is inert, it may simply be a scaffold for the surface layer, whereas, in the case of a reactive core like silver, the dissolution of ions from the surface can significantly alter the properties and function. Size, shape, and surface composition are widely applicable structural attributes that are expected to significantly influence properties and function.

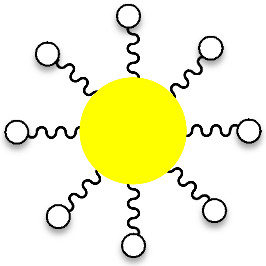
These attributes need to be conveyed as specific and unique material descriptors when ascribing properties, functions or hazards to a nanostructure. Although such descriptions are commonplace for chemical structures (e.g., SMILES strings), it has not been the practice for ENMs. Historically, the properties of ENMs that captured scientists' attention were those of the core material: for example, optical properties of semiconductor quantum dots and plasmon absorbance of gold nanoparticles. As a consequence, many ENMs have been described solely by the core material. However, if the goal is to link properties and functions to structure, a descriptor such as "gold nanoparticles" is incomplete, especially in light of the importance of surface chemistry in SPH relationships (vide supra). At a minimum, one should articulate what is known about (1) the core composition, size and size dispersity, (2) the ligand shell constituents and composition, and (3) the purity of the sample. If the particles are non-spherical, a description of the shape should also be included.

Some ENMs have more complex and dynamic structures that make description and characterization more challenging. While studies of these ENMs continue, material selection and controlled design is necessary if one seeks to correlate structure with properties and function/hazard. In the case of AuNPs, particles that are passivated by omega-terminated alkanethiol ligands are relatively more stable and easier to characterize than those that are weakly passivated by polymers, surfactants, or citrate.[20] Studies of the monolayer-stabilized nanoparticles have proven useful in defining SPF and SPH relationships.[21]

The investigation of nanoparticle hazard potential is typically performed in aqueous media that may contain a variety of salts, buffers, natural organic matter (NOM), or proteins. Although it is expected that these species may transform ENMs (and this is important for understanding the mechanisms of action), in the case of metal nanoparticles, they can also lead to destabilization and precipitation of the material. As a consequence, it is important to monitor the stability of the nanomaterials to ensure that they remain in stable dispersion if the dose of the primary material is to be related to properties or effects. For example, and perhaps unsurprisingly, Truong et al. found that nanoparticles that possess carboxylic acid groups on their periphery rapidly agglomerate and precipitate from the medium in the presence of zebrafish embryo media that contains divalent cations.[22] In that case, the nanoparticles showed no to little acute toxicity to the embryos, which is perhaps due to limited exposure. When the particles were dispersed in deionized water, the particles remained dispersed for days and were found to be toxic to the embryos.

Gold nanoparticles can be stabilized with either weakly bound coatings (e.g., citrate, polyvinyl pyrrolidone (PVP), or other polymers) or strongly bound ligands (typically thiols). With respect to acute toxicity, the major difference between these two classes appears to be the stability of the nanoparticles in the exposure medium. The former class is typically more prone to agglomerate in the presence of salts, buffers, or other additives in exposure media. For both classes, surface charge appears to be the dominant physicochemical property that influences acute toxicity.[21, 23] Across a range of organisms, positively-charged nanoparticles are many times more toxic than those with neutral or negatively-charged surfaces.[21, 23] Prolonged exposures show that both charge types can cause developmental impacts (Table 2). Some surface coatings (e.g., glutathione and polyether oligomers) show little to no toxicity or developmental effects. Another common finding is that the toxicity of ligands bound to particles are often more toxic than those same ligands in their free form.[21] There remains much to learn about the details of the interactions of specific functional groups on nanoparticles with biomolecules and biological structures; nevertheless, design rules regarding the general relationships between ligand charge and observed toxicity are emerging.

Table 2: SPH relationships of thiol-ligated AuNPs. The ligand dimensions are scaled approximately with reference to the core. The biological impact (hazard) is evaluated using a high throughput embryonic zebrafish assay.[21, 22] In the event that the ligands are bound to the nanoparticle surface through a thiolate bond, the structure on the other end (termed the omega functional groups, indicated by the open circles in the schematic) can be directly correlated with the observed hazard response.

	**Coating type (∿○)**	**Biological impact (hazard)**
	Cationic (e.g. $-CH_2NR_3^+$)	Acute toxicity, mortality
	Anionic (e.g. $-SO_3^-$)	Developmental effects, malformations
	Neutral (e.g. $-OCH_2CH_2OH$)	Little to no effects
	Zwitterionic (e.g. glutathione)	Little to no effects

Nanoparticle size and shape are expected to play some role in the toxicity of AuNPs and AgNPs because the dimensions will influence the uptake mechanisms and distribution in tissue. Several studies suggest that smaller AuNPs are more cytotoxic and lead to greater mortality *in vivo* when evaluated on a mass basis.[21, 24] However, if one considers that for an equivalent mass of 1.5 nm and 15 nm AuNPs there are approximately 1,000 times more small (1.5 nm) nanoparticles, the larger particles (15 nm) appear to be more toxic on a per particle basis.[21] Yet, as nanoparticles get bigger, they are expected to cease being bioavailable due to agglomeration or restricted uptake.

There have been similar observations for silver nanoparticles. The situation with silver is more complicated owing to the fact that the surfaces of AgNPs are readily oxidized in aerobic aqueous solutions. Upon oxidation, silver ions are released and contribute to the overall toxicity. Many studies have aimed to determine whether there is a nanoparticle-specific toxicity. Most studies have shown that silver ions are primarily responsible for observed toxicity; however, whether nanoparticle transport within an organism can focus ionic release in a particular compartment remains an open question. From a greener design perspective, some approaches to address the complexities of AgNP speciation and resulting toxicity include suppressing the release of ions (e.g., through ligand passivation), limiting nanoparticle transport to sensitive biological compartments, or finding alternatives to the use of silver, except in cases where the release of silver ions is inherent to the product's function (e.g., all anti-viral and anti-bacterial applications).

Lessons for future design of safer nanomaterials. What are the lessons for greener design that can be gleaned from what is known about AuNPs and AgNPs? In 2008 Hutchison stated, "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."[25] Although this is a simple design rule, the role of toxic ion release (silver, cadmium, and lead) and toxic surfactants (e.g., cetyl trimethyl ammonium bromide (CTAB)) have proven important contributors to the impacts of these materials. Given the relatively large molar excess of these small molecules compared to the nanoparticles, their presence is likely to dominate the toxicity. Thus, the first question to ask is: "Will ions or other small molecules be released and dominate the response?" Once this aspect is considered, the stability of the solution or dispersion of the material should be addressed. If the material rapidly precipitates or aggregates, the primary particles are not likely to contribute to effects. If the nanoparticles remain dispersed, the surface chemistry plays a significant role in determining the toxicity as described above, and, across a number of studies, positive charge on the periphery leads to the highest toxicity.

There is still much to learn about the SPH relationships in these model systems. What is the role of the core composition given the same surface chemistry? How do hazards depend upon polyvalency of reactive groups within the ligand shell? How do the lessons learned in the AuNP systems translate to other systems (e.g., other metals and the metal chalcogenides)? The lessons learned within this system about material purity, characterization, and definition should facilitate those studies and provide ample basis for hypothesis-driven research on those systems.

Most of the preceding discussion has focused on SPH relationships. It is important to consider how one integrates an understanding of SPH and SPF relationships in nanoparticle design. In many cases, the approaches to design structures that co-optimize maximal function and minimal hazard remain to be discovered. An example from the AuNP system illustrates how this co-optimization can be done. If the desired *function* is water-dispersibility, one could choose a charged or hydrophilic neutral surface ligand as the *structure* to impart this function. Based upon the SPH relationship for these nanoparticles, choosing the neutral ligand provides the desired *function* while minimizing the *hazard*. In other cases it may not be currently possible to define the structures that maximize functional performance while minimizing hazard. This is a rich area for future research.

Greener synthesis of nanoparticles. There have been many advances in greener synthesis of nanoparticles in the last decade. The application of the principles of green chemistry have proven successful in reducing solvent use, minimizing energy and water consumption and reducing the hazards of reagents used. Over the same period, it has become clear that material properties and functions depend keenly upon precise structures. Greater control and definition of structure and composition are required. New greener syntheses must produce materials with equivalent or improved performance *in addition* to reducing impacts.

The earliest reported synthesis of gold nanoparticles is the reduction of tetrachloroaurate by sodium citrate in boiling water. This classic synthesis illustrates many attributes of a greener synthesis and produces nanoparticles with useful optical properties that have made possible a rich range of applications. However, this relatively ‘green’ method suffers from two key limitations: (1) it is not possible to make the smallest AuNPs that exhibit unique catalytic activity and optical properties, and (2) it is difficult to incorporate the rich range of surface chemistry that can be used to control solubility, targeting, and biocompatibility. To address the need for smaller nanoparticles and particles with specific functional groups on their periphery, new chemistries were developed. However, to implement these new chemistries, researchers used more hazardous solvents and reagents to solubilize reagents and control metal salt reduction kinetics. Thus, the challenge is for greener nanosynthesis to discover new approaches to produce these new materials with the desired properties while reducing the hazards and inefficiencies of the processes.

Design for process safety. From the outset, reducing the hazards of the reagents and solvents was a high priority, thus, greener alternatives were identified and exploited. For example, toluene (which is less toxic) replaced benzene and sodium borohydride replaced diborane. Given that the target materials are AuNPs, it is difficult to identify a significantly greener feedstock than $HAuCl_4$. There are now a number of synthetic approaches that produce monolayer-protected AuNPs either through direct synthesis or by ligand exchange to change the surface chemistry. The resultant materials have well-defined core sizes and size distributions and have strongly passivating ligand shells that are relatively easy to characterize.[19, 26]

Within the last decade, many syntheses have been reported that, like the citrate reduction method, utilize a benign reductant (e.g., plant extracts, microbes, plants). However, there is no deliberate control over the nature of the surface chemistry and the syntheses offer varying degrees of control over size and size distribution, which are primary challenges of these approaches. In most cases the nanoparticles are not purified, so reaction byproducts and excess stabilizers are present. In the event that the nanoparticles are suitable for the desired application and the byproducts are not detrimental, these syntheses offer some advantages. On the other hand, many demanding applications require nanoparticles with tightly controlled core sizes, well-defined ligand shell architectures and a high degree of purity. Attaining these higher performance attributes leads to greater impacts. Thus, caution should be exercised in comparing the 'greenness' of materials if they have significantly different performance criteria. For example, because purification is the largest contributor to materials use and waste generation in nanoparticle production,[8] it would only be appropriate to compare the greenness of nanoparticles of similar functional characteristics and purity.

Design for waste reduction. Due to the large volumes of organic solvent (and/or acids) used to remove impurities from nanoparticles, purification is a major contributor to resource use and waste production. For the production of phosphine- or alkanethiol-stabilized AuNPs, traditional purification processes can contribute 5 – 20 times more waste than the synthetic process itself. Sweeney et al. pioneered diafiltration as a powerful method to remove small molecular impurities from water-soluble nanoparticle samples (Figure 3).[27] This approach is rapid, convenient, scalable, and it is now widely used to purify ligand-stabilized nanoparticles.

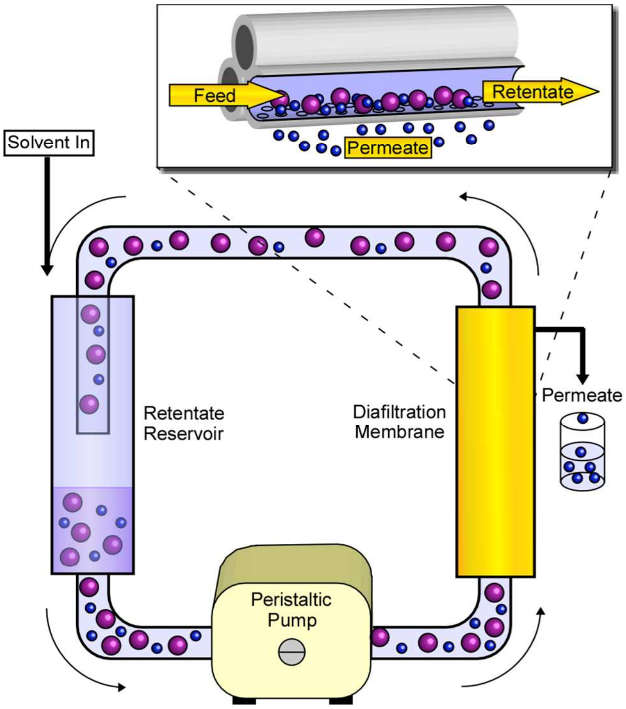


Figure 3. Schematic of the continuous diafiltration setup used to purify water-soluble nanoparticle samples. Impurities, including small molecules, ions or small nanoparticles (indicated by the smaller, blue spheres), are eluted in the permeate, while the larger nanoparticles (depicted as the larger, purple spheres) are retained. The expanded view of the hollow-fiber-type diafiltration membrane illustrates the permeation of the smaller impurities through the nanoscale pores within the membrane and the retention of the nanoparticles. After sufficient circulation through the membrane to remove the impurities, the pure nanoparticles can be concentrated and collected. (Reprinted with permission from Sweeney, S. F.; Woehrle, G. H.; Hutchison, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 3190, Figure 1. Copyright 2006 American Chemical Society.)

Similar approaches to the purification of water-soluble nanoparticles remain to be developed. In those cases, precipitation or column chromatography is employed. As noted above, even small amounts of impurities can have significant impacts on toxicity and/or performance of a nanoparticle sample, especially if the impurity itself is toxic. An alternative strategy that has been employed throughout the literature involves avoiding the use of toxic stabilizers and surfactants altogether, so they are excluded from the nanoparticle product *a priori*.

Design for material efficiency and design for waste reduction. The next steps in the greening of AuNP synthesis would be to develop improved direct synthesis methods that would obviate the need for ligand exchange or ligand modification methods. With extant direct (i.e., single step) synthetic methods, it is difficult to control the nanoparticle core diameter *and* introduce specific types or mixtures of desired ligands containing desired functional groups, simultaneously. General synthetic methods to control diameters over a range of 1 – 30 nm with precise control over the ligand shell composition (including mixtures) in a direct synthesis would reduce steps, and thus waste, while providing access to new generations of specifically functionalized nanoparticles for SPF studies as well as practical applications. Further, such methods would likely improve yields compared to multistep processes.

Design to reduce environmental impact. Products that are most likely to have environmental impact are those high in the nanotechnology value chain, which are frequently used by consumers. These are predominately nanoparticle-enabled products. Although understanding the SPF/SPH relationships are important for free nanoparticles, many nanoparticles will be incorporated into other materials or bound to the surfaces of products. One example of this product class involves the use of nanosilver as an antimicrobial and/or antiodor agent in clothing. Many silver or nanosilver-containing products are already in commerce. The forms of silver used in these products ranges for metallic silver threads, ionic silver deposits, silver bound in inert matrices and AgNPs. Here, we focus on AgNPs, although much of this discussion may apply to the other forms. The principles of greener production of AgNP-enabled materials are similar to those of green chemistry in general. One would like complete utilization of the coating solutions used to treat the fabric so that byproducts are minimized. Ideally, the coating process could be carried out in water or a non-volatile (and recoverable) solvent near room temperature.

A key question unique to nanotechnology is how tethering a nanoparticle to a surface influences its chemistry? Given an understanding of this reactivity, green chemistry principles may be applied to influence or improve product designs. When the nanoparticle is bound to a surface, it is no longer bioavailable unless it is released. The optimal use of AgNPs in these antimicrobial applications *relies* on the slow release of silver ion from the nanoparticle reservoir throughout the lifespan of the treated material. As a necessary consequence, silver will be released during use and upon washing. If the silver is released too quickly, not only will there be larger bursts of silver released to the environment, but also the fabric coating will rapidly lose its effectiveness. Thus, gradual release that generates just enough silver ion to remain effective will extend product performance and reduce unwanted environmental impacts (e.g., indiscriminant or untargeted bacterial inactivation). The best designs would hold the nanoparticles tightly on the surface (to ensure the particles are not lost), and allow for the slow release of silver ions (e.g., by controlling silver oxidation rate or silver ion transport).

In the process of evaluating the loss of AgNPs linked to a planar TEM analysis grid, Glover et al. observed that tightly held nanoparticles were not desorbed, but that they underwent a surprising transformation, even in humid air.[28] Small nanoparticles grew in the vicinity of the tethered AgNPs (initially 75 nm diameter). It was subsequently demonstrated that bulk, metallic forms of silver (such as cutlery or jewelry) also produced small AgNPs.[28] These initially surprising results suggest that organisms may have been in contact with AgNPs for millennia and demonstrate that the size of the silver structures (from ionic to macroscale metallic) on the fabric may not necessarily dictate the form released due to the complex and dynamic physical transformation processes at play.

From the perspective of greener design of AgNP-enabled fabrics, it appears that it is not the form of silver that matters, but rather the total amount used. Once these controlled-release and minimum-loading approaches are developed, it will be important to compare the cumulative life cycle impacts and benefits of these new technologies (e.g., via eq 1) with those of conventional (non-nanosilver) alternatives. For example, proposed benefits of the AgNP-enabled garments include reduced washing and longer product lifetime. These benefits, cast in terms of reduced use of petroleum feedstocks, water, energy, and detergent, can be translated into life cycle environmental and human health impact savings (presuming adaptation of consumer behavior). Those savings can be quantitatively compared with the impacts associated with the use of silver (e.g., mining, refining, processing, nanoparticle synthesis, and silver release to the environment during the use-phase) and the net benefits compared to alternative approaches as described by Equation 1.

A Work in Progress: Carbon-Based Nanomaterials

Carbon-based nanomaterials represent a wide array of structures that are nearly as diverse as the metal and metalloid ENMs. Nevertheless, the parent structures can be grossly divided into five classes of materials: black carbon soot (BC), multi-walled carbon nanotubes (MWCNTs), single-walled carbon nanotubes (SWCNTs), fullerenes (C_{60}), and graphene. In this section, we describe the design successes and future opportunities as they relate to the application of greener nanoscience and nanotechnology.

Design of safer nanomaterials. Within the material classes of carbonaceous nanomaterials, there are abundant potential modifications of both a covalent and non-covalent nature. For example, sorptive association with macromolecules in the environment (such as DNA or natural organic matter) are inevitable and demonstrated; oxygenation reactions following environmental release are possible but understudied kinetically; and intentional surface modification with other non-metal heteroatoms (e.g., S, N, P, and O) is feasible and possible, but not yet done on the industrial scale. To further complicate the composition, industrially produced materials often have synthetic impurities that can range from 1 – 70% (by weight) of the bulk nanomaterial content and include metals, amorphous carbon, or other carbon nanoforms.[29, 30] Due to this heterogeneity, it is not yet possible to draw generalizations about the inherent hazard or environmental fate of these materials, or consequently, meet the objectives of the design for safer nanomaterials criterion.

Early efforts to assess inherent ecotoxicity of the carbon-based nanomaterials were confounded by three primary challenges: (1) comprehensive characterization of the materials and their associated impurities was not available, (2) the materials themselves are not stable in water, and (3) concentrations required to elicit a response and/or a measurable analytical signal were often very high (e.g., milligrams per liter). The first challenge has obvious shortcomings, in that any observation of hazard must be attributed to some structural component or some associated by-product or impurity.[31] Without adequate characterization, this is impossible. The second challenge led to the use of surfactants or co-solvents (e.g., tetrahydrofuran (THF)), coupled with sonication to create semi-stable aqueous suspensions of material. Drawbacks to this approach were numerous: (a) particles sizes changed[32] (e.g., nanotubes cleaved), (b) surface oxygenation increased, (c) surfactant load exceeded ENM load by both mass and volume in order to render a stable suspension, (d) surfactant choices were often environmentally and/or industrially irrelevant, and (e) ultimately, the material used in the assays bore little resemblance to the native materials or even ones that might exist at some later point after environmental “post processing” (i.e., transformation). Thus, even with robust characterization of the starting materials, the resultant characteristics of the ENMs following sonication and surfactant treatments (i.e., the material to which test organisms were actually exposed) may not have reflected the initial measurements. As a consequence of these experimental constraints, the valiant efforts to describe ENM hazard have left the community of researchers without clear understanding of the causative mechanisms and few general design principles. The third challenge remains menacing: in order to measure carbon-based ENMs, micrograms or milligrams per liter of material must be employed due to limitations in analytical methods, and these concentrations are of little environmental relevance, a common phenomena in traditional environmental toxicity studies for chemicals as well. In some sense, it is reassuring that high concentrations of ENMs are needed before an adverse response is observed. However, as higher material loadings enhance agglomeration,[33] which in turn encourages gravitational settling, *exposure to nanoparticles could be lower at higher nanoparticle loadings*. Thus, the overwhelming evidence that nanomaterials are safe at microgram per liter levels (in water) might be obfuscating more realistic exposure scenarios.

While these challenges persist, several researchers have leveraged the inherent heterogeneity of carbon-based nanomaterials or strategically induced structural diversity as a means to discern the origins of ENM hazard. Such efforts have begun to elucidate structural parameters that correlate with empirical toxicity endpoints at both the mammalian inhalation exposure and cellular aquatic levels. Inhalation studies, typically performed on mice or similar mammalian model organisms, are most applicable to occupational exposure risk assessment. If the particle agglomerate sizes are respirable (and many are not), there is a general consensus that long aspect ratio CNTs could frustrate phagocytosis in lung tissue and lead to the formation of granulomas.[34, 35] With regard to aquatic ecotoxicity of unicellular organisms and embryonic zebrafish, Gilbertson et al. have made efforts to elucidate relationships between empirical toxicity endpoints (e.g., cell viability, embryonic mortality) and some measurable ENM property (e.g., surface oxygen functional group type) for MWCNTs.[36-38] The aim of these efforts was not necessarily to elucidate the chemical mechanisms of toxicity, but to instead discover which, if any, ENM properties were correlated with or could be used to predict toxicity, with the ultimate goal of developing design rules. These SPH relationships might hold for other types of carbon-based ENMs and, if so, could accelerate the pace of discovery and ensure safer designs for novel materials coming to market.

In order to increase the practical utility of these design principles, it would be helpful to understand how tuning a particular material property associated with toxicity influences the material's performance. For example, if the thermal conductivity of a CNT is relatively unchanged with surface oxygen content, but the toxicity varies widely, CNTs with the lowest-toxicity oxygen content can be used. In contrast, if there is a toxicity-performance tradeoff (i.e., the two are anti-correlated), a particular functionalization scheme can be chosen that co-optimizes performance and toxicity (i.e., maximizes and minimizes each, respectively).[39] Furthermore, when the material performance is inextricably linked to material toxicity, rigorous encapsulation strategies or alternative technologies must be employed. Since no material or chemical can be made, used, and disposed of without some release to the environment, green synthetic strategies must avoid the use of toxic materials. To accomplish this goal with minimal cost to each individual innovator, a curated catalog of SPF and SPH relationships, examples of which are provided below, should be established. Such a collection of robust data would not only help expedite identification of the underlying chemical mechanisms of toxicity, but also allow material designers to pre-select materials that meet both functional performance requirements without exceeding desired toxicity thresholds.

Greener synthesis of carbon-based nanomaterials. Taken as a whole, the Twelve Principles of Green Chemistry are largely focused on the chemical manufacturing process (Figure 1). However, the past decade's effort to assess the environmental health and safety implications of nanotechnology have focused on the materials themselves, rather than their respective syntheses and targeted industrial processes. There are two primary arguments around this: (1) the approach to focus on the novel ENMs makes good sense, as there is an urgent need to evaluate material transport, transformation, and toxicity early in order to predict and minimize risk and (2) the industrial-scale methods for ENM production were not fully established and continue to evolve today. Recent work suggested that the largest ecotoxicity impacts associated with CNTs are those derived from the material fabrication[13, 29, 40], and the same could be true of other carbon-based nanomaterials that share similar synthetic routes (described below). By and large, these syntheses have not been optimized for any of the Green Chemistry or Green Nanoscience/Nanotechnology Design Objectives (e.g., atom economy, energy minimization, or waste minimization with respect to starting materials and emissions). Meeting these objectives represents an enormous research opportunity that would not only improve the environmental and economic efficiencies of the processes, but could also enable enhanced synthetic control at the lower temperatures needed to realize some of the currently unattainable material hierarchies that rely on ENMs.

The favored route for industrial-scale synthesis of carbon-based nanomaterials is catalytic chemical vapor deposition (CVD). Each nanomaterial requires unique treatments, but generally involves (a) the use of a carbon-containing gas as a starting material (e.g., methane, ethylene, acetylene, specialty alkynes, carbon monoxide, or mixtures thereof) and sometimes hydrogen, (b) high temperature (500 – 1200°C) to both "crack" the gas into other hydrocarbon precursors and provide the reaction activation energy, and (c) a "catalyst" material that is either introduced as a powder or affixed to a substrate. Note that the metal "catalysts" used do not meet the strict definition of a catalyst, as they are not regenerated in perpetuity and may or may not reduce the reaction's activation energy. Instead, the metals used in carbon-based nanomaterial syntheses are "nanopositors," physical templates for ENM formation. (The nanopositors do play a chemical role, albeit a poorly understood one). The majority of the reactors operate in batch mode with occasional, but not frequent, recycle, are hot-walled rather than cold-walled, and are kept at atmospheric pressure, except for graphene and ultra-tall (e.g., 10 mm – cm) CNT synthesis, which rely on the use of vacuum. The environmental consequences of the CVD routes, as they exist today, include low atom conversion efficiencies (<10%)[9, 41], high energy demands[13, 40], and unwanted by-product formation.[41, 42] Further, many obstacles remain before atomic-scale control over carbon-based nanomaterials becomes a reality. Thus, applying the Green Chemistry Principles and Green Nanoscience/Nanotechnology Design Objectives now could illuminate a route toward environmentally and economically sustainable practices that enable superior performance of the resultant ENM-enabled products.

Designing for process safety and reduced environmental impact. Process safety objectives often have to do with the choice of chemical starting materials used as part of the reaction (e.g., hydrogen and carbon) and as carriers in CVD. The "solvents" used for CVD are inert carrier gasses, such as argon, helium, or nitrogen, so the design guideline promoting safer solvents and reaction media is not as directly relevant as it is for wet chemical synthesis and post processing. Note that it could become increasingly relevant if gaseous acids are used in future *in situ* functionalization schemes and are relevant today for any type of post-CVD wet chemical processes. (Currently, the post-CVD chemical purification of CNTs relies on either or both high temperature and large volumes of concentrated acids; there are clear environmental impacts associated with these that are similar to other solvent-based industrial processes). In CVD, the carbon feedstock itself could, in principle, be derived from renewable sources, but, in practice, is not.[29] Hydrogen gas is often used as a reductant, dewetting, and/or delaminating agent during the synthesis. Poor reactor flushing or weak seals in a reactor could allow oxygen gas to come in contact with a hydrogen-rich environment, generating a highly exothermic reaction that can cause explosive fireballs. These are a clear occupational hazard and represent the primary risk associated with CVD, save toxic byproduct emissions.

Designing for waste reduction and materials efficiency. Current CNT synthetic approaches release 10 – 100,000 times as much carbon as is incorporated into CNT structures. This is an embarrassingly low atom economy that is restricted by our chemical understanding of the limits to CNT growth efficiency and nanopositor nucleation efficiency (~10%). Efforts to improve this efficiency have been met with only modest achievements of 10-fold improvements by using trace chemical dopants that accelerate CNT formation rate and yield[42], but could be improved via enhanced understanding of the nanotube formation mechanism. In addition to the clear economic motivation to improve the atom economy metric, there is a performance-based desire to increase CNT nucleation density in order to improve nanotube alignment in aligned systems, improve nanotube packing for water-treatment membrane formation using vertically-aligned tubes, and improve nanotube connectivity for electrical and thermal conductivity applications.

At the tailpipe of CVD systems, the majority of the material exiting the reactor is untransformed hydrocarbon starting material, while a small percentage is converted to volatile organic compounds (VOCs), hazardous air pollutants, green house gasses, and polycyclic aromatic hydrocarbons (PAHs).[41] Since these emissions are largely untreated today, and the industry is expected to grow even before synthetic improvements are made, these trace emissions could amount to sizable and significant contributions to local pollution inventories. Furthermore, the unwanted byproducts formed in the gas phase of the CVD reactor could sorb to the solid CNTs (i.e., as amorphous carbon) and deteriorate the material performance, presenting another incentive to reduce unwanted byproducts.

The "derivatives" issue in CNT synthesis may be the flagship problem that prevents full realization of CNTs' commercial potential. Every CNT synthetic route generates a mixture of nanotubes with variable chiralities. In MWCNT formation, concentric tubes in a single structure have heterogeneous chiral angles. The best chiral selection in CVD is achieved through the use of either (a) pre-selected nanotube seeds with subsequent vapor addition (which is not industrially viable today) or (b) the Co-MCM-41 and CoMoCAT processes developed by Pfefferle's group[43] and Resasco's group[44], respectively, which select for a particular tube chirality (n,m = 6,5) via an unknown mechanism. Considering the staggering heterogeneity of the CNT product with respect to chirality, it is clear that applications that rely on a single chiral angle CNTs would have proportionately lower synthetic efficiencies and higher energy and material demands associated with post-synthetic purification or extraction steps. This presents future opportunities in terms of improving specificity to yield the desired product and avoiding the need for purification steps altogether.

The preceding discussion has focused on CNTs because little is known about the manufacturing waste streams of graphene synthesis; those are expected to face similar challenges. Graphene synthesis is commonly done under vacuum making it difficult to obtain a sample with sufficient byproduct mass to accurately identify the emissions composition (i.e., the reaction stream is too dilute for even the most sensitive analytical methods). In contrast, the atom economy of graphene synthesis could be easily measured, but is presumably very low and has ample opportunity for improvement. Explicitly, high carbon flow rates coupled with a vacuum system imply that much of the carbon source material is pumped past the catalyst without an opportunity to react. An optimization of this process that incorporates environmental objectives would systematically probe the carbon conversion efficiency and seek opportunities for material and energy minimization improvement there (i.e., minimize feedstock requirements and operate closer-to-ambient vacuum conditions).

Design for energy efficiency. Carbon-based nanomaterial production is one of the most energetically expensive manufacturing processes known to date[13], and the energy requirements drive the ecotoxicity footprint due to emissions associated with energy production.[40] The reasons for the energy intensive process are two-fold: (a) thermal decomposition and rearrangement of the hydrocarbon precursor is necessary and (b) the nanopositor-hydrocarbon reaction activation energy must be surmounted. Plata et al.[41, 42] demonstrated that the thermal requirements for the gas rearrangement could be alleviated if the important thermally-generated precursors were added directly to the synthesis, instead of relying on thermal energy to generate the precursors *in situ*. This approach could save nearly 50% of the energy requirements associated with CNT production. It remains to show that the industrial preparation of the critical precursors (alkynes) is energetically competitive with the *in situ* thermal production approach via a life cycle analysis (i.e., that the net energy benefit of using alkynes is not outweighed by an additional upstream energy cost associated with their manufacture).

With respect to graphene, opportunities for energy minimization in manufacture may be limited. The approach to making graphene at scale generally relies on (a) introduction of a carbonaceous gas (usually methane or a natural gas mixture) over (b) an atomically-smooth "catalyst" plane (usually copper) that is (c) at high temperature (e.g., 900 – 1200 ^{o}C).[45] (The "Scotch Tape® Method" for graphene production (i.e., exfoliation) is inherently unscalable, but has a low energy footprint. Wet chemical synthetic methods are scalable, in principle, but far from commercialization to date). The temperature and vacuum requirements have clear implications for energy utilization, and these could only be surmounted with an improved understanding of the graphene formation mechanism *and* if that mechanism could be achieved at closer-to-ambient conditions. Currently, the prevailing theory is that carbon atoms or small molecules diffuse into the upper layers of the copper catalyst and then re-emerge (in a type of precipitation) on top of the metal in a one- or two- atom thick layer of aromatized carbon.[45] While elegant, if true, this route relies on high temperature (to promote atom diffusion within the solid catalyst) and vacuum (to provide a low-total-carbon atmosphere). Further, opportunities for structural control are few if both catalyst and carbon are fluid and no directable metal-carbon bond exists.

Armed with an understanding of the mechanisms of thermal gas transformation and a comprehensive description of the chemicals present in the reactive atmosphere of CVD, one can hypothesize the carbon bond building mechanisms taking place there. Using novel reactors that deconvolute the thermal effect on the gas and the catalyst,[41, 42] one could finally interrogate the actual activation energy associated with nanotube formation. This seemingly fundamental knowledge is currently unavailable, and that limits both the ability to make carbon nanostructures precisely and the ability to minimize the energy requirements of the process. Without precision synthesis, the diverse and urgently needed applications of carbon-based nanomaterials may never be realized. Without energy minimization, the environmental implications of ENM production will persist and a limited number of growth substrates will be possible. For example, in order for CNTs to serve as interconnects in novel semiconductors, they must be fabricated on CMOS (compatible metal oxide semiconductor) supports. These materials are not stable above 450°C, and ENM synthesis at these lower temperatures would be an achievement not only from an environmental optimization perspective, but also a materials science one.

Current Challenges

While the adoption and application of a more sustainable and 'greener' approach to ENM synthesis and nano-enabled product development has gained momentum, there remain significant challenges. With less than 10% of the National Nanotechnology Initiative budget allocated for environmental health and safety research, the development of hazard and risk profiles cannot keep pace with the rapid advancements of innovative applications. A Nano Focus article published in 2007 highlights several barriers preventing rapid progress in the nanotechnology field.[25] The following section provides an updated perspective and underlines several areas in need of urgent attention.

Standardization and metrics. A critical and ongoing challenge for nanotechnology stakeholders is the lack of globally established standards and metrics for ENM synthesis, characterization, and hazard evaluation. There are numerous synthesis techniques for every class of ENMs, including bottom up and top down methods, a host of catalysts, reducing and stabilizing agents, and reaction parameters (e.g., temperature, pressure, feedstocks). As is the case with carbon nanomaterials, the mechanism of synthesis remains largely unknown. The lack of standardized methods of synthesis and transparency of information to the purchaser leads to extreme batch-to-batch heterogeneity in terms of composition and purity, and transfers the responsibility of comprehensive characterization to the end user prior to the use. In addition to significant resource requirements, there is oftentimes limited access to the advanced tools and equipment necessary for the end user to fully characterize the ENM of interest. Furthermore, while minimum characterization standards have been proposed, they have not yet been widely harmonized or adopted. This contributes to inconsistent research findings throughout the literature and thus, prevents the establishment of generalizable principles to inform risk and life cycle assessment models. Furthermore, this influences the ability to accurately predict potential environmental and human health implications resulting from the production, incorporation, and use of ENM and nano-enabled products.

As was discussed in previous sections, specific material descriptors and detailed physicochemical property characterization is vital to evaluate the successful synthesis and purity of the intended ENM as well as to the understanding of potential hazards and environmental fate and transport of ENMs throughout the life cycle. The current rapid progress in nanotechnology requires the capability to resolve material properties at increasingly smaller length scales and at higher resolutions.[20] Many conventional instrument technologies are stressed to produce reliable results at or beyond their limit of detection. The demand for improved characterization capabilities at the nano and sub-nano scale as well as the establishment of appropriate universal standards has prompted the establishment of an entire field devoted to instrument, metrology and standards research.[2]

Effective ENM characterization is vitally important to the progress in resolving proposed environmental and human health risk.[2] Reported inconsistency among *in vitro* and *in vivo* toxicity studies are in part, due to poor or lack of accompanying ENM characterization data. Inherent properties, such as the tendency to aggregate and insolubility (i.e., carbon-based ENMs), complicate the use of conventional toxicity assays.[46] In addition, the chemical nature of some ENMs has been shown to influence interaction with growth media micronutrients and dye molecules that are commonly used in conventional viability assays. Experimental techniques that minimize these confounding factors have demonstrated their ability to reliably evaluate comparative ENM toxicity. The establishment of universal standard methods to assess ENM property and hazard characteristics, including an appropriate dose metric (e.g., by mass, M, number of particles, or surface area, nm^2 or nm^2/g), will enable consistency among studies, compilation of their findings, and the achievement of a holistic understanding of the potential negative environmental and human health implications.

Furthermore, studies that investigate the toxic potential of ENMs are commonly conducted in biological media inappropriate for a given assay and at unrealistically high concentrations. In addition to preventing extrapolation to environmentally relevant scenarios, these conventional practices also introduce the question of whether ENMs should be considered 'nano' in the aggregated form induced under certain media and concentration scenarios. Finally, given the insoluble nature of some classes of ENMs, the challenge surrounding the delivered dose remains a topic of debate within the nanotoxicology community. Resolution of best practices and standardized methods followed by widespread adoption will enable continuity among research findings and ultimately, bring clarity to ENM hazard profiles.

Despite these challenges, ENMs are incorporated into nano-enabled products and are entering the market at an increasing rate. The lack of a standardized framework for monitoring and regulating ENM incorporation into products suggests that there are an even greater number of ENM-enabled products on the market than indicated through national product inventories and registries. Furthermore, there is no globally accepted quantitative metric to determine the life cycle impacts and realized benefits associated with the production and implementation of nano-enabled products. As such, the impact-benefit ratio (eq 1) is a straightforward approach used to quantitatively represent these life cycle tradeoffs. The ability to differentiate during the prototype or pre-production stage those nano-enabled products that promise a realized net benefit over those where the life cycle impacts outweigh the potential realization of a functional performance, environmental, or human health benefit is essential to the sustainable development of the field.

The 'nano' life cycle. Challenges at the material level propagate throughout the life cycle. Resolution of synthetic, hazard, fate, and transport mechanisms as well as establishment of standardized methods, including physicochemical property characterization, is critical to inform and perform robust life cycle impact assessments (LCIAs). While many of these challenges remain unresolved, the development of hybrid approaches[47, 48] offer strategies to address the current uncertainty garnered by these challenges. Still, there remain significant opportunities for improving the application of LCIA to nanotechnologies. The preferred approach, as outlined in this review, is to minimize the trade-offs presented in an LCIA by decreasing the inherent hazard of nanomaterials to reduce the concern over environmental and human exposures. In addition, early application of LCIA to the development of ENMs and nano-enabled products will prevent shifting the burden between life cycle stages.

One of the first steps in conducting any impact assessment is establishing the functional unit, which defines *what* is being studied, the functional *service* provided, and provides the reference for all of the inputs and outputs within the system boundary. For gate-to-gate (single process) and cradle-to-gate (raw material acquisition through manufacture) impact assessments, the reference flow is often the product of interest (e.g., a sensor or t-shirt). For cradle-to-grave (raw material acquisition through end of life) impact assessments, the functional unit must include the service provided (e.g., efficacy, realized benefit). Comprehensive life cycle assessment of novel nanotechnology-enabled applications should include consideration of both the impacts (e.g., raw material inputs, solvents, process parameters) and functional benefits (e.g., increased energy efficiency, enhanced detection sensitivity/selectivity, longer lifetime), particularly when comparing to the conventional alternative. The impact-benefit ratio (eq 1) provides such an approach that is quantitative and adaptable to economic, environmental, and human health metrics.

Establishment of parametric relationships between ENM properties and their functional efficacy, hazard profile, transport and fate behavior across all life cycle stages will enable the development of appropriate characterization factors used in impact assessment models to evaluate the environmental and human health impacts.[49] Current characterization factors and life cycle models were developed around conventional chemicals and are not equipped with appropriate nano-specific information and model parameters necessary to complete robust impact assessments for ENMs and nano-enabled products. In addition to modifying current life cycle models, it is important to recognize their limitations and simultaneously develop complementary prospective models and approaches to meet the challenges that accompany emerging technologies.[50] Well informed LCIAs will enable rigorous and accurate (1) comparisons between design, process and material choices, (2) quantitative assessment of tradeoffs associated with various alternatives, (3) identification of those aspects of a given design, process, or material choice that contribute most significantly to the overall life cycle impacts, (4) uncertainty and sensitivity analyses around these identified parameters, and (5) communication of risks and benefits among stakeholders and consumers.[49]

Given the current state of knowledge on AgNPs and AuNPs, including synthetic, hazard, and transport mechanisms, there is the opportunity to begin updating and adapting current life cycle models and characterization factors. These initial efforts to modify and develop new models applicable to ENMs will provide an invaluable foundation from which expeditious adaptations for other nanomaterial classes will be possible when adequate information becomes available.

Coordinating stakeholder engagement. Effective transmission of research findings and coordinated interdisciplinary discussion between industry, innovators, and researchers remains inadequate considering the rapid development of the field. Applications of nanotechnology have the potential to impact all aspects of our lives, the environment, and the sustainability of essential resources. The absence of robust synergies between these stakeholders limits sustainable progress and the lack of focus on manufacturing and design principles precludes the opportunity to advise on how to anticipate or improve upon the status quo. Integrated dissemination of research findings and technological advancements, as it relates to developing nanotechnology, as well as the establishment of collaborative partnerships that transcend traditional boundaries are essential to promote rapid advancement of technologies and to develop appropriate risk management strategies.

Current Opportunities to Catalyze Further Application of the Twelve Principles to Nanotechnology

Given the anticipated market value, projected production volumes, and advancing promising applications, it is inevitable that there will be potential environmental and human health exposures to ENMs and nano-enabled products contributing to enhanced risk. As discussed previously, the Principles of Green Chemistry aim to minimize or eliminate risk, not through exposure control, but through the design and use of inherently non-hazardous materials wherever possible. In case of ENMs, unlike emerging advances for molecules, there is a general lack of information regarding the inherent structures and physiochemical properties that are associated with desired functionalities or unintended toxicological harm. This contributes to significant uncertainty in the ability to predict and reduce potential risks from ENMs or nano-enabled products across their life cycles. As such, there is a tremendous opportunity to engage with these emerging materials and products to fill these knowledge gaps and develop insights to inform a rational design framework for enhanced functionality and minimal toxicity.

As discussed above, there are significant challenges to utilizing the currently available toxicity data about ENMs and nano-enabled products due to the lack of standardized protocols and metrics for material characterization (i.e., structure and properties) and toxicity endpoint identification. With enhanced characterization quantification and toxicity outcomes, further research can be pursued to understand the mechanistic basis for which structures and/or properties enable which adverse outcome pathways leading to SPH relationships grounded in first principles. Further, this enhanced physicochemical characterization can be used to establish SPF relationships. Utilizing physicochemical characteristics as the basis for functionality and safety provides a common design handle as material scientists and chemists are familiar with meeting objectives related to property values or ranges.

Sustainability by Design: A Proposed Framework to Inform Design of Emerging Materials. Despite the number of inherent limitations within the nanotechnology field that prevent widespread application of the Twelve Principles, the holistic and comprehensive approach presented herein provides a vision for a successful path forward. The framework, when implemented, will address the identified knowledge gaps and improve collective efforts towards achieving sustainable nanotechnology. The opportunities and global implications of successful development and adoption of sustainable nanotechnology are outlined in the following sections. As shown in Figure 4a, the framework aims to differentiate ENM structures and properties that are related to the to both the material function and hazard. Given the current state of knowledge and lack of established SPF and SPH relationships, ENM function and hazard cannot be differentiated by a given structure/property. As such ENM design cannot be informed to reduce unintended toxic outcomes (Figure 4c). As research in this area progresses, there is the opportunity to resolve SPF and SPH relationships. If a specific structure/property is related to both the desired function and hazard (i.e., substantial overlap), then it will be necessary to manage the risk of these materials through exposure controls because the inherent nature of the ENM will be toxic in order to perform as intended (Figure 4b). There is an exception, which is to consider those applications in which the desired function is an intended hazard outcome (e.g., antimicrobial or biocide applications). In that case, the established relationships can be used to inform more sophisticated design of targeted hazard delivery, enabling maintenance of the biodiversity, for example. If on the other hand, the function and hazard are differentiable (i.e., no overlap), the identified SPF and SPH relationships can be used to inform design of ENMs and nano-enabled products that meet their performance objectives while dramatically decreasing their potential to cause harm (Figure 4d).

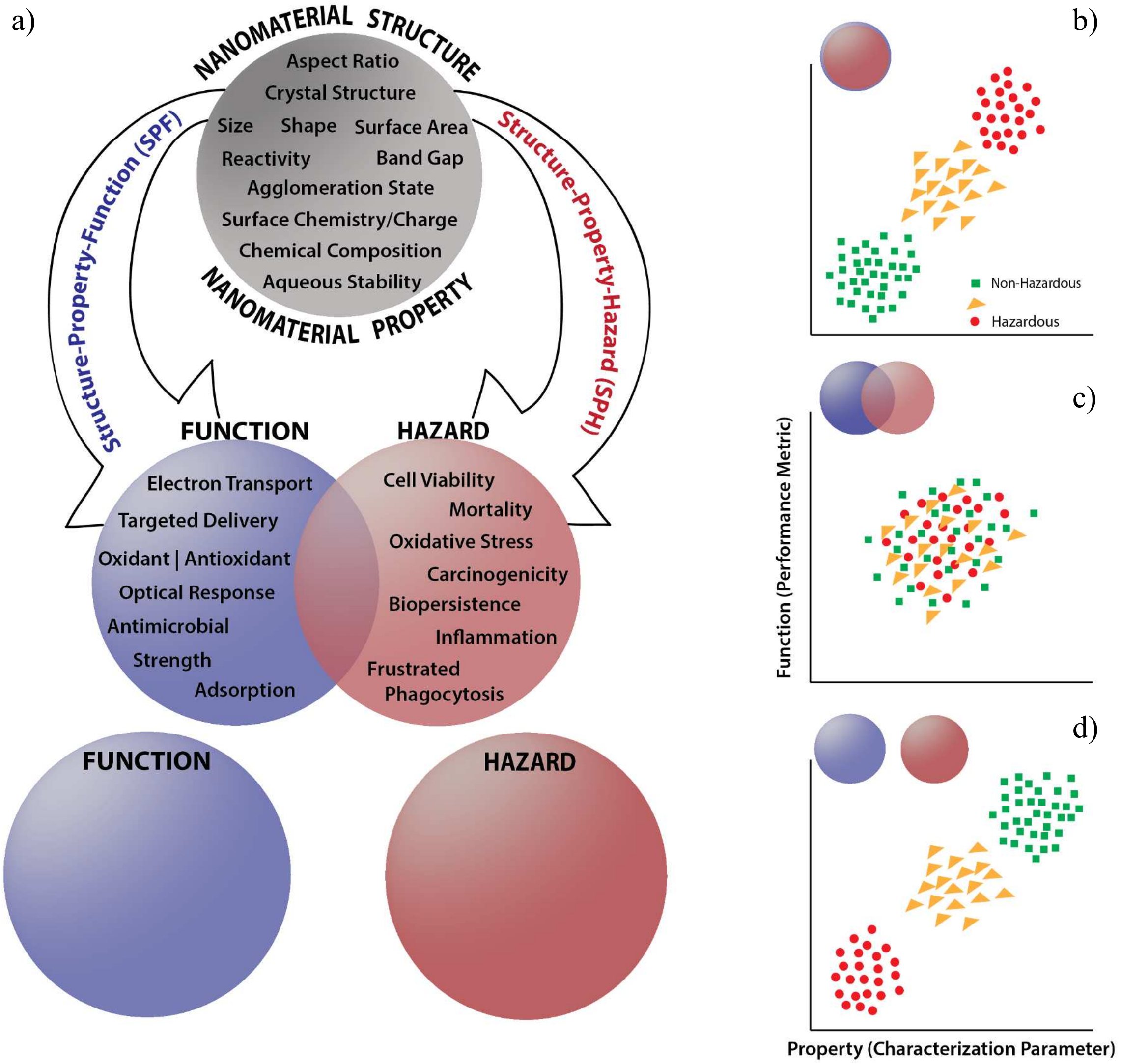


Figure 4. Schematic representation of parametric relationships between nanomaterial structure, physicochemical properties, and their functional performance and hazard profiles. The application of the design principles for greener nanoscience/nanotechnology (Table 1) aims to maximize function and minimize hazard through rational design and control of nanomaterial structure. As such, the overlap of these two spheres, function and hazard, is reduced (as indicated at the bottom of the diagram). The accompanying parametric relationship plots (b-d) distinguish three potential SPF and SPH scenarios.

Taking data from previously published work on MWCNTs[26, 27, 38] and AuNPs[21, 22, 36, 37], Figure 5 illustrates examples of how these three scenarios can manifest into useful design guidelines. Figure 5a depicts the case where the MWCNT property of “total percent oxygen” does not provide design information about achieving the intended function, electrochemical activity, nor does it differentiate between observed cytotoxic outcomes. That is, at a given percent surface oxygen, a range of electrochemical activity and cytotoxic effects are observed. However, when the ratio of carbonyl:carboxylic acid surface functional groups is plotted on the horizontal axis (Figure 5b), very relevant information is elucidated about functional performance (SPF) and cytotoxicity (SPH). In this case, an SPF-SPH design guideline can be established, though the same property value that leads to the highest functional performance also results in the most cytotoxic effects (case of Figure 4b). This suggests that this property is related to enhanced electrochemical activity, which is also the likely mechanism for the observed cytotoxicity, rendering the design of a non-hazardous and highly electrochemically active MWCNTs difficult. However, it does suggest that when electrochemical activity is not required as part of the intended function, rather that the carbonyl:carboxylic acid surface groups can be tailored to control MWCNT cytotoxicity.

In addition to elucidating informative SPF relationships within the context of bacterial cytotoxicity, it is important to consider applying the framework across multiple hazard endpoints to elucidate SPF-SPH relationships are pertinent to a range of material application and potential exposure scenarios. Thus, the same ENM (oxygen functionalized MWCNTs), functional performance parameter (electrochemical activity), and a different hazard endpoint (embryonic zebrafish mortality as non- or acute toxicity) are considered. Interestingly, the SPF relationship that resolves the MWCNT hazard is not oxygen functional group type as before, rather the surface charge, quantified as the point of zero charge (Figure 5c). In this case, the SPF-SPH relationships are distinct and the MWCNTs are distinguishable in a way that informs design to maximize functional performance while minimizing inherent material hazard.

Finally, a robust framework will be applicable across multiple hazard endpoints and multiple classes of ENMs. Since there has been significant progress in synthetic processes to control AuNP size as well as tailor their properties depending on the intended application via surface functionalization and core encapsulation, for example, they serve as an interesting class of ENMs to investigate. Data was collected for AuNP of the same size (core diameters = 1.2 – 1.5 nm) that were functionalized with ligands possessing different surface charge (i.e., positive, neutral, and negative) to achieve aqueous stability. The scenario presents another case in which SPF-SPH relationships are distinguishable.[18, 19] In this case, positively charged AuNP have been shown to induce significant acute toxicity (measured as embryonic zebrafish mortality), while negatively charged AuNP promote more developmental malformations or chronic toxicity endpoints, and neutrally charged particles present the most benign alternative. Thus, when the desired functional performance is stability of dispersion, this can be achieved with minimal hazard potential by designing and utilizing particles that exhibit a net neutral charge.

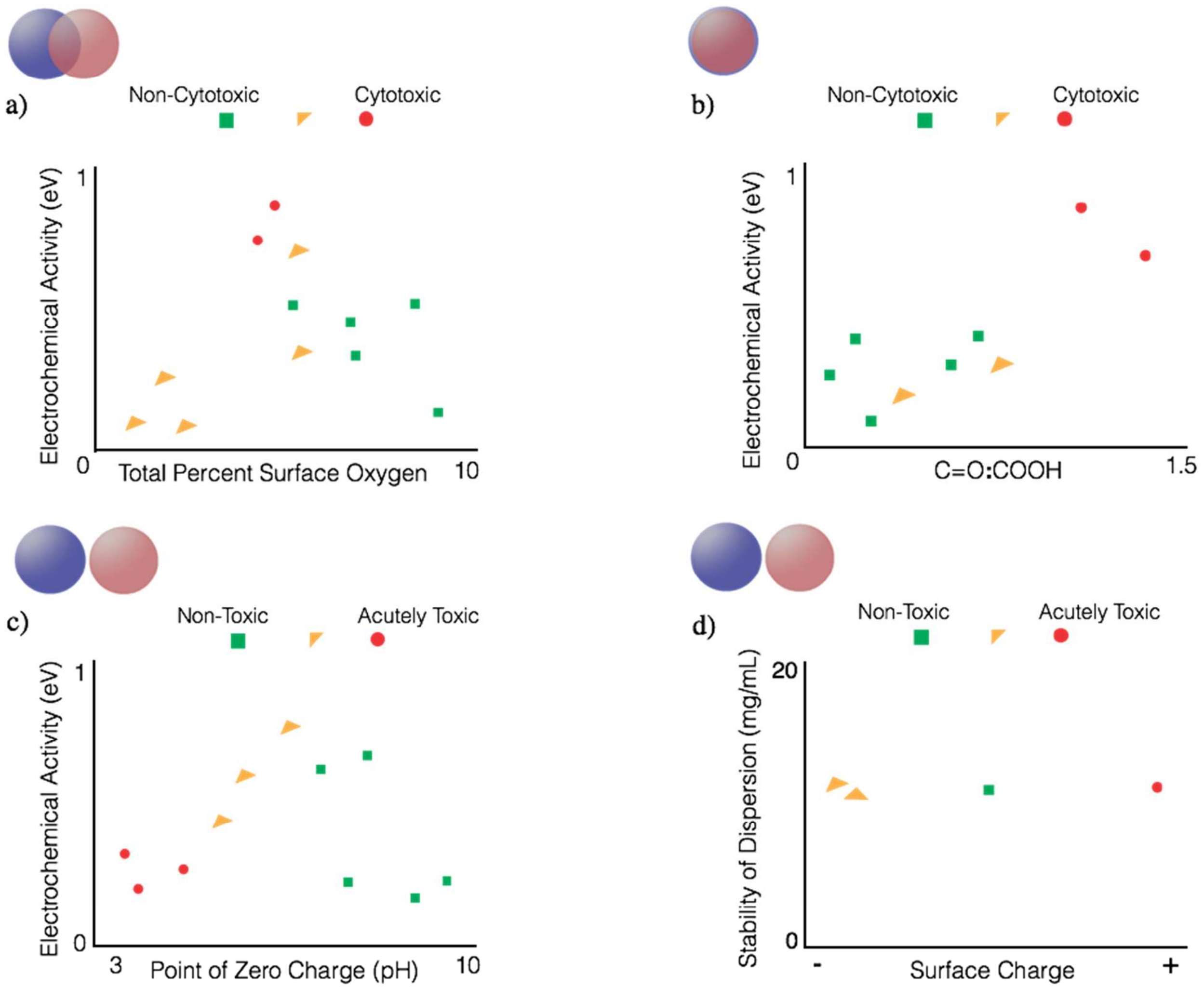


Figure 5. Parametric relationship plots for data collected on systematically treated and comprehensively characterized MWCNTs[36-38] (a-c), and ligand functionalized AuNPs[21, 22] (d). a) When the percent surface oxygen (ENM property) in considered alone, there is no resolution of observed cytotoxicity based on the chosen performance metric (electrochemical activity). b) Further resolution of oxygen functional group type (carbonyl, C=O, and carboxylic acid, COOH) enables establishment of a functional relationship between electrochemical activity, the type of oxygen functional group present on the MWCNT surface, and the observed cytotoxicity. Yet, the direct relationship between property-function and property-hazard results in overlap between these two representative spheres. c) When a different hazard endpoint is investigated (embryonic zebrafish mortality) for the same MWCNTs, different SPF-SPH relationships are able to inform material design to maximize functional performance while minimizing the potential for unintended consequences. d) Controlled synthesis of ligand functionalized AuNPs between 1.2-1.5 nm result in stable dispersions (at least 10 mg/mL) regardless of surface charge, yet positively charged particles have been shown to induce significant acute toxicity (measured as mortality to embryonic zebrafish), presenting the scenario in which SPF and SPH relationships are distinguishable.

These examples demonstrate the significant potential of these SPF and SPH relationships to inform the development of design guidelines for ENMS with enhanced functional performance and minimized hazard. However, it also suggests that there is an incredible need to increase efforts to collect the data that is necessary to establish these relationships across and within ENM classes, their various functional performance metrics, and toxicity endpoints including standard collection and reporting of physicochemical characterization. Further, to advance broad adoption of this approach, a comprehensive publically-available curated catalog needs to be developed, curated, and maintained where relevant information can be securely stored, accessed, and validated enabling the community to collectively provide and utilize this data and information that is vital to advancing the design of safer nanomaterials. Ideally this catalog will be created and maintained in collaboration with multiple stakeholders (e.g., academia, government, and/or industry) to ensure sustained applicability.

Implications

Avoided risk and liability. One thread that unites the development of chemicals and materials for the past 200 years is that they have achieved functionality yet at the same time produce concerns, hazards, and occasionally unintended tragedies for humans and the environment. As illustrated by the problem caused by asbestos, chlorofluorocarbons, dichloro-diphenyl-trichlorethan (DDT), leaded gasoline, polychlorinated biphenyls (PCBs), and numerous other substances, the fact that a product is useful does not ensure that it is benign to health or the environment.[51] Furthermore, if the danger becomes known after the product is widely adopted, the consequences can go beyond human suffering and environmental harm to include lengthy regulatory battles, costly remediation efforts, expensive litigation quagmires, and painful public-relations debacles.[51] While sometimes these tragedies are real and tangible, other times the public reaction is to a perceived risk, rather than one that is measurable. This inability to delineate genuine from perceived risk associated with genetically modified organisms (GMO), embryonic stem-cell research, or biotechnology for example, can be detrimental to the long term success and sustainability of a given field. In the case of GMO, negative public sentiment has had an adverse effect on governmental funding of research and market penetration, especially in Europe.[52]

Development and commercialization of nanotechnology-enabled products continues at an increasing rate, and the market value is projected to reach $3 trillion by 2020.[1] Without a convincing and validated framework to establish potential risks and manage perceived risks, there is a significant chance that nanotechnology will not realize its full economic potential, let alone the potential contribution to societal benefits. By pursuing the framework laid out in the section above, there is significant potential for the emerging field of nanotechnology to avoid the challenges faced by these other emerging technologies and to demonstrate leadership in simultaneously advancing the goals of functionality and safety by considering implications at the design stage.

Establishment of a rational regulatory framework for best practices: Can we do better than regulation? In general, the regulatory environment surrounding nanotechnology is fragmented and highly uncertain. In some instances ENMs will fall under the significantly limited current US chemicals management framework. Given that the Toxics Substances Control Act is administered based on chemical composition of matter, the unique properties, and therefore functions and potential hazards, are not effectively considered. Future policy for chemicals management should be grounded in a fundamental understanding of the structure-property relationships as this is the mechanistic basis for hazard. This will circumvent the current and laborious chemical-by-chemical process, which limits the ability to effectively predict the potential hazards of new chemicals or materials because relevant information of homologous chemicals or materials is not carried over. By utilizing a SPF/SPH relationship-based system, researchers and businesses would have a clear path to innovate driving continuous improvement towards safer, high performing and competitive novel ENMs and nano-enabled products.

Advancement of many other societal goals through development of nano-enabled products. It is vital that these novel safe ENMs and nano-enabled products can developed as there continues to be enthusiasm for the these innovations to benefit human health and the environment with applications related to climate change mitigation (i.e., advanced solar cells, carbon capture and storage), healthcare (i.e., medical imaging, targeted drug delivery), water purification (i.e., multifunctional, selective sorbents, antimicrobial infrastructure surfaces), and energy generation, distribution, and storage (i.e., water splitting catalysts, active membranes for fuel cells, next generation batteries). With a fundamental understanding of the SPF and SPH relationships, nanomaterials and nano-enabled products can overcome the current real and perceived safety concerns allowing the realization of their full potential to effectively and efficiently advance sustainability goals.

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