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Perspectives on the design of safer nanomaterials and manufacturing processes

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Abstract

A concerted effort is being made to insert Prevention through Design principles into discussions of sustainability, occupational safety and health, and green chemistry related to nanotechnology. Prevention through Design is a set of principles that includes solutions to design out potential hazards in nanomanufacturing including the design of nanomaterials, and strategies to eliminate exposures and minimize risks that may be related to the manufacturing processes and equipment at various stages of the lifecycle of an engineered nanomaterial.

Keywords

Nanomaterial; prevention through design; responsible development

INTRODUCTION

The rapidly growing field of nanoscale science and engineering has given rise to a new form of material, the engineered nanomaterial (raw materials or formulated products containing at least one dimension in the range of 1 to 100 nanometers). Engineered nanomaterials (ENMs) show tremendous promise in revolutionizing many fields of material science research and transforming established technologies. There is a need to proceed responsibly because published toxicologic studies demonstrate that some nanomaterials have the potential to cause adverse human health effects (Shvedova *et al.*, 2008; Hubbs A, 2009; NIOSH, 2009; Porter *et al.*, 2010; Castranova, 2011; NIOSH, 2011; Sanchez *et al.*, 2011; NIOSH, 2013; Sager *et al.*, 2014). Since workers at all levels (research, manufacturing, production, use, and disposal) are the first people in society to be potentially exposed to ENMs, precautionary approaches to minimize risk from or resulting from exposure are paramount.

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

This report offers perspectives on research and practice activities that are beginning to focus on a prospective, preventive approach and draws on a workshop entitled Safe Nano Design: Molecule to Manufacturing to Market (http://www.sunycnse.com/Outreach/NIOSHPresentations.aspx) sponsored by the National Institute for Occupational Health (NIOSH) and held at the Colleges of Nanoscale Science and Engineering (CNSE) at SUNY Polytechnic Institute in Albany, N.Y during August 2012 (Figure 1). The workshop created a unique opportunity by bringing together experts in toxicology, risk assessment, exposure assessment, and process and facility design from academia, private industry, and government to share their perspectives on safe design of nanomaterials, processes and facilities. The purpose of this report is to introduce the reader to Prevention through Design (PtD) principles and discuss their applicability to design of safer nano-enabled products; approached from the molecule side and from the facility, tool, and task side; and how the outcomes of a prevention approach will support an environmental, health, and safety management system approach. Ideas and concepts for which there appeared to be general agreement among workshop attendees were identified, but no effort was made to reach group consensus on any topic. Therefore, this report should not be viewed as reflecting the opinion of all workshop participants, their affiliated organizations, or the workshop sponsors or organizers.

PREVENTION THROUGH DESIGN

The national initiative on PtD involves all of the efforts to anticipate and design out hazards to workers in facilities, work methods and operations, processes, equipment, tools, products, materials, new technologies, and the organization of work (Schulte *et al.*, 2008; NIOSH, 2010). PtD takes many of the long-standing principles of ‘safety-by-design” and expands the effort by adding research and education elements so that practices can be anticipatory for a given technology. PtD is applicable to nanotechnology at both the molecular and process levels. PtD, like current safety management systems, utilizes the traditional hierarchy of controls by focusing on hazard elimination and substitution followed by risk minimization through the application of engineering controls, administrative controls and the use of personal protective equipment (PPE) applied during design, re-design, and retrofit activities (Peterson, 1973; Schulte *et al.*, 2008). PtD principles including the design of nanomaterials, and strategies to eliminate exposures and minimize risks that may be related to the manufacturing processes and equipment, can be applied at all stages of the lifecycle of an engineered nanomaterial. The best time to think of preventing workplace exposures and incidents that lead to injuries and illnesses is early in the technology, process, or product development. PtD promotes the practice of prevention for nanomaterials as early as during the design of a new engineered nanomaterial, even before applications development has started.

As businesses adopt hazard controls and risk management practices higher in the “hierarchy of controls”, i.e. designing-out hazards and minimizing risk, business value increases (Figure 2)(AIHA, 2008) These improvements in business value are related not only to lower workers’ compensation rates and health care costs for injured workers, but also to improving time to market, market share, operational efficiency, employee morale, and product quality, while decreasing employee absenteeism and turnover (AIHA, 2008).

It is important to incorporate workers' experience and knowledge at all stages of the PtD schema. Historically in the cases of asbestos, lead, and silica, harmful health effects were not known until workers who had been exposed to these materials suffered illnesses. More recently the worker health experience seen with flavorings or potent pharmaceuticals, points out the need for preventative thinking early in the adoption of materials or processes (Kreiss, 2012; Roussel C, 2014). A PtD approach to working with ENMs, with its focus on prevention, will allow us to avoid the repetition of the history with the aforementioned materials. Worker input into nano-EHS considerations should be captured in all phases of the design program and should be applied throughout the product lifecycle.

ELIMINATION AND SUBSTITUTION

Molecular, Structural, and Physical Modifications to Reduce Toxicity

The most effective approach, at the top of the hierarchy of controls, is to eliminate or design out hazards (Schulte *et al.*, 2008). This can be accomplished for some nanomaterials by modifying specific physicochemical parameters of the material that alter its biological activity. The idea is that by modifying the functionality of the nanomaterials the commercial utility of the material can be maintained while the potential toxicity is reduced or mitigated (Schulte *et al.*, 2014).

A change in a nanomaterial's properties, such as size, shape, surface functionalization, surface charge, and aggregation state, can profoundly affect that particle's toxicological properties and interactions with biological systems (Castranova, 2011; Albanese *et al.*, 2012). One aspect of PtD, grounded in molecular design, seeks to minimize nanomaterial toxicity by modification of physical properties. However, to modify nanomaterial-specific properties with the necessary control, more research is needed to establish the connections between particle physical properties and biological interactions.

One of the largest hurdles to overcome in property-driven molecular design is the specificity of effective formulation techniques to a given material. One example of this is a study that was centered on how the length of a multi-walled carbon nanotube (MWCNT) affects cellular uptake (Shi *et al.*, 2011). Results show that longer MWCNTs are more likely to be absorbed by cells and thus pose a greater risk to human health. Orientation of the MWCNT is also significant because side-wall contact did not lead to uptake by the cell. Rather, cells appear to absorb MWCNTs tip first, like sucking up a noodle of spaghetti. A second example is a study on nanosilver that indicated that the antibacterial properties, as well as the toxicity to humans, of nanosilver arise from release of Ag^+ ions (Liu *et al.*, 2010). Nanosilver can be formulated to suppress Ag^+ release; however, doing so could compromise antibacterial function. A third example is a study that investigated if graphene poses an inhalation health risk. Preliminary findings show that there is a dependence on lateral size in the uptake of graphene into the macrophage (Sanchez *et al.*, 2011).

One strategy, predictive risk modeling, has proven useful in overcoming the issue of non-toxic formulations being specific to particular nanomaterials. Statistical analysis of a series of *in vitro* assays can give rise to models that predict the relative toxicity of derivations and formulations of some parent materials. Experience with pristine and functionalized multi-walled CNT illustrates the relative role of surface modification of ENMs. Starting with the hypothesis that altering multi-walled carbon nanotubes' (MWCNT) surface chemistry will change MWCNT bioactivity, investigators undertook *in vitro* and *in vivo* studies on functionalized and bare MWCNTs, developed a statistical predictive model for the impact of surface area on nanomaterial bioactivity, and applied the model to the inexpensive and rapid screening of a given nanomaterial for bioactivity. They concluded that surface modification decreased bioactivity and pathogenicity of MWCNTs, and bioactivity of MWCNT samples correlate with differential activation of the NALP3 inflammasome (Sager *et al.*, 2014). Further research could look into whether *in vitro* inflammasome activation can be used as a rapid, low-cost, screening assay for predicting the bioactivity of nanoparticles.

At present, data-driven methodologies are underrepresented in nanotoxicology. There is the need to leverage effective data gathering and data management techniques for both *in vitro* and *in vivo* assays, as well as for the development of models from assays in biological matrices to support characterization and biological activity prediction (Figure 3). Work is being done through the NNI Nanomaterials Knowledge Infrastructure initiative, the Nanotechnology Characterization Laboratory, and the Nanomaterial Registry to support these efforts.

The relationship between a particle's physical and chemical properties and the biological effects it induces is important to ascertain. For instance, the pH of a nanomaterial suspension as compared to its isoelectric point is one of the most important factors in determining that material's agglomeration state (Berg *et al.*, 2009). This in turn dictates how the material interacts with a cell surface and governs cell viability upon exposure. Similarly, metal oxide oxidation state has a marked impact on cellular uptake (Berg *et al.*, 2009). These observations should serve as an impetus for further research into the mechanisms by which cells interact with nanoparticles and the way particle physicochemical characteristics shape those mechanisms. This type of research would facilitate the prediction of nanomaterial interactions in novel biological environments and the prediction of unknown material interactions in known biological matrices.

Some nano-sized particles pose a greater inhalation health risk compared to their larger particle counterparts. This provides unique challenges to the field of nanotoxicology. With regard to inhalation, nanoparticles produce more inflammation, are capable of greater deposition in alveolar and interstitial space, and have a greater potential to translocate to systemic sites (Oberdörster *et al.*, 2004; Shvedova *et al.*, 2008; Hubbs A, 2009; Porter *et al.*, 2010; Castranova, 2011). Nanoparticles are removed with greater difficulty from the lungs by normal clearance mechanisms and interstitial effects play a large role in nanotoxicity. However, more research is needed in the deposition and fate of ENMs in biological systems, as well as in the dose/response and time course of inhaled nanoparticles.

Oxidative stress is a biological response often seen with exposure to ENMs (Li *et al.*, 2008). Reactive oxygen species (ROS) are indirectly created through membrane damage and photoactivation. These ROS induce inflammation in organisms, and chronic inflammation is known to be responsible for a host of ailments. Inflammatory markers may be used for nanomaterial assessment (Castranova, 2011). Epithelial cells or macrophages that are seeded in nanofibrous matrices can be exposed to endotoxins and their resultant inflammatory responses quantified. In this way, the understanding of the pathological activity of these materials can be increased.

Toxicologic Screening and Characterizing

Using high-throughput screening and evaluation techniques has the potential to aid in more rapid identification of nanomaterial hazards and the mechanisms of nanomaterial toxicity. They also allow for the development of predictive models to design inherently safer products and greener nanotechnology. Scientists need to look at early responses that predict adverse outcomes. This is illustrated with data from an Automated Embryo Placement System used to evaluate zebrafish embryos (Harper *et al.*, 2011; Mandrell *et al.*, 2012). Specific toxic endpoints were observed after exposure to various functionalized ENMs. The ability to screen large numbers of embryos at once offers a discovery platform on which to apply these methods. These methods, in turn, allow for the simultaneous collection and analysis of huge volumes of data and thus promote the development of data-driven models for nanomaterial toxicity. High-throughput screening and evaluation techniques are quickly becoming indispensable tools for biologists and toxicologists as well as for those who work at the interface of these and other disciplines.

To achieve meaningful worker protection, material design must consider the relationships among molecular design, particle properties and the biological activity screening of ENMs; if the biological activity is considered in the molecular design, downstream characterization approaches can be tailored to the specific properties of the materials, enabling more streamlined, economic, and effective screening protocols. Libraries populated by nanomaterial data obtained from high throughput screening assays in biologically relevant matrices will aid in both the predictive and practical aspects of nanomaterial characterization. Further investigation into the pathways through which and the mechanics by which nano-sized objects interact with cells will enable a clarified and more focused approach to the above-mentioned techniques.

Nanoparticle Hazard Indices, Exposure Bands, and Occupational Exposure Limits

For bulk particles, calculation of exposure dose in toxicological studies is relatively straightforward. For ENMs, however, such calculations are fraught with ambiguities and challenges (Gangwal *et al.*, 2011). There are physical difficulties associated with the characterization of ENM dose, including low mass as compared to particle number, large surface area, and agglomeration states and dissociation potentials which are highly environment dependent. For example, the dispersion state of TiO_2 in its carrier medium impacts the toxicologic outcome for acute exposure. Increasing sonication time (and thus increasing the dispersion of TiO_2 in solution) has been found to decrease inflammation in *in vivo* models (Kim *et al.*, 2010; Baisch *et al.*, 2014). More research is needed to better understand the connections between nanomaterial physical properties, polymorph distribution, and toxicological response.

Grouping objects by similar attributes is a powerful practice used to great effect in many scientific disciplines, including toxicology. Establishing hazard indices and grouping materials into well-defined ranges and hazards bands, represent standard practices in toxicological risk assessment. These indices and bands inform the establishment of Occupational Exposure Limits (OELs) for potentially toxic materials. Engineered nanomaterials, however, are underrepresented in such toxicological classification schemes that form a pillar of PtD techniques, although some progress is being made in this regard (Brouwer, 2012).

There are various approaches for developing hazard characterization and risk assessment schemes. Comparing *in vitro* and *in vivo* studies, exposure concentration and retained dose in rats using extrapolation techniques allow for the estimation of the retained dose in humans for a given exposure This point is illustrated in a study investigating subchronic rodent inhalation of MWCNTs in which dosimetric extrapolation was used to determine the human dose equivalent (Kuempel, 2011; NIOSH, 2013). This type of extrapolation reinforces the need for consideration of the most important endpoints for post-experimental analysis early in experimental design so that the appropriate data is collected.

It is useful to take advantage of well characterized materials as references in the classification of ENMs. One way to do this is by using a benchmark approach to the classification and risk assessment of ENMs. This involves establishing and maintaining libraries of well-characterized reference materials, standardized assay techniques in hazard assessment and occupational hazard banding, and prioritizing materials for further testing. With tightly controlled and well characterized reference materials, structure-activity relationships can be exploited to give estimated lower bounds for the OEL of related materials (Kuempel *et al.*, 2012).

There is an important interplay between the predictive and experimental toxicology of ENMs and their use in the construction of risk assessment models. The International Organization for Standardization (ISO) technical committees have already taken some steps in establishing standardized ENM characterization and testing methods (ISO, 2005). The availability of accurate and effective screening of nanomaterials by an interdisciplinary team is important for both qualitative and quantitative hazard control indices, as well as effective PtD implementation.

ENGINEERING CONTROLS

Process Containment

Simply developing safer nanomaterials (though not so simple) is no substitute for minimizing or eliminating exposures through proper containment and control of materials in the workplace. There is an ongoing need to appropriately design controls and develop risk management strategies. PtD principles can be implemented beginning with R&D labs and moving into scale up manufacturing and distribution. Environmental, health, and safety (EHS) considerations should be embedded in the design process and re-evaluated at each stage of production and extend to equipment, room cleaning and maintenance activities. Published recommendations for risk management and safe handling should be consulted (Environmental Defense Fund, 2007; NIOSH, 2009; NIOSH, 2011; NIOSH, 2013). The entire lifecycle of ENMs needs to be considered to ensure they have minimal human health and environmental impact.

Engineering controls isolate the process or equipment or contain the hazard. Information on the following variables will assist in determining which exposure controls are appropriate for a given process: the quantity of nanomaterials being handled or produced, their physical form and dispersibility, and the task duration (NIOSH, 2009). As each one of these variables increases, the chance of exposure becomes greater, as does the need for more efficient exposure control measures (Figure 4). Operations involving easily dispersed dry nanomaterials, such as powders, deserve more attention and more stringent controls (e.g., enclosure) than those involving nanomaterials that are suspended in a liquid matrix or embedded in a solid. Liquid nanoparticle suspensions typically offer less of an inhalation risk during routine operations, but the likelihood of exposure can increase significantly if they are aerosolized through sonication or in unexpected situations such as a spill (Johnson, 2009).

Containment is an important strategy in maintaining a safe workplace for those who manufacture or handle ENMs. The best choices to minimize operator contact when handling bulk ENMs, are recirculating air downflow booths and isolators, and enclosures that are sealed to some standard of leak tightness. Reactors and spray dryers should be designed to isolate the process and provide containment of materials during removal. Including these items in the design process exemplifies cautious prevention by means of the containment hierarchy of controls. This overall approach highlights the need for containing and controlling the ENM as an essential product or ingredient, versus being a contaminant emitted by a process.

A suite of flexible containment apparatuses for high containment of nanopowders are useful and should be considered for a task-based control strategy. Other forms of containment—laminar flow booths, split butterfly valves, isolators—are costly and not easily retrofitted to existing processes. Flexible containment technology is a good solution because it's easily retrofitted, takes less space, requires fewer utilities, is portable and can grow or reduce to meet business needs. Plus, installation time for flexible containment is minimal, ergonomics are designed into the system, and it costs less to own compared to hard-wall type systems. Flexible systems are considered single-use technology, thus eliminating the cost and risk associated with cleaning, which is one of the most likely sources of exposure. However, flexible containment systems may not be as effective at controlling exposure risks long term for the high volume processes as engineered systems. In addition, the cost of disposing of the flexible containment systems must be considered.

In a laboratory the chemical fume hood is routinely considered a primary control device, and this belief carries over to handling of nanoparticles. Traditional benchmarks of fume hood performance, such as tests using smoke, tracer gas or face velocity are still effective when considering tasks involving ENMs. However, conventional fume hood designs may allow significant releases of ENMs because nanomaterials are considerably more prone to aerosolization than their bulk counterparts and their aerodynamic buoyancy makes them more subject to migration caused by turbulence generated by fume hoods. Some nano-specific fume hoods are designed to decrease migration due to turbulence by making use of inlet airfoils on the sidepost and sash, airflow sensors, and a fan/HEPA filtration unit. Computational fluid dynamics has been used to model airstreams surrounding fume hoods in order to develop flow parameters effective in minimizing nanoparticle release (Tsai *et al.*, 2010).

To know where PtD is most needed it is important to determine which tasks pose the highest risk of exposure to ENMs. One illustration of this is from a NIOSH industrywide exposure assessment study on manufacturers and users of carbon nanotubes and nanofibers (Schubauer-Berigan *et al.*, 2011). Exposure concentrations were ranked by process or task. The highest levels of exposure were found for tasks involving dry powder handling, production, and harvesting (Dahm *et al.*, 2011). Wet handling procedures were found to reduce emissions that could result in potential exposures.

While no large-scale dust explosions of ENMs have occurred to date, explosions of bulk dusts are sobering enough when they do occur to warrant research into the understanding and prevention of explosions when processing a nanoscale dust. Some types of single-walled and multi-walled carbon nanotubes and nanofibers have been confirmed to be in the St-1 explosion class, with fullerene in the borderline St-1/St-2 explosion class (Turkevich, 2015). Since some types of carbon nanotubes or metal nanomaterials may be explosive in a spark ignition scenario, so it is imperative to avoid creating dust clouds in enclosed areas, minimize open heat sources and avoid sparks. Accordingly, planning for explosion hazards and obtaining a systematic evaluation of the explosion potential are essential aspects of working with ENMs.

There are still gaps in control practices for workers who handle ENMs. Special fume hood design, combustion safeguards, and adaptable containment systems are important in ensuring the minimization of worker exposure to occupational hazards in the nanotechnology sector. This effort exemplifies a critical stage of a PtD-informed hazard-reduction process: the strategic survey of potential hazard exposure avenues and possible failure modes for conventional practices.

ADMINISTRATIVE CONTROLS

Overview of Occupational Health and Safety Management Systems

A management systems approach is invaluable to the safe commercialization of ENMs through a PtD-enabled approach (Figure 5) (Schulte *et al.*, 2008). An effective management system begins with an executive position statement that details all activities from bench scale to production. The project concept stage is the ideal time to establish EHS goals, identify hazards, and determine appropriate nanoparticle exposure control categories. Using a step-by-step approach to safe commercialization refines the decision-making process and enables the rational discovery of occupational hazards for elimination, modification, or control. A systems approach to management encourages the view of an organization as a whole including an inventory of the workforce and material resources available; this way, substructures and subsystems may be organized and resources may be allocated to them in the most efficient and effective way.

It is important to consider procurement, manufacturing, and distribution environmental, health, and safety concerns whenever they are applicable. Considering work at the project level, execution of the health and safety management program should include safety reviews prior to startup, exhaustive Standard Operating Procedure (SOP) development, and extensive worker training. Through these methods, project managers can take a high-level view of the work to be done and ensure that no aspect of worker safety is overlooked. Of course, it is just as important to consider these aspects after the completion of the project, in the safe decommissioning of the worksite and disposal of engineered nanomaterials, all while keeping abreast of new occupational health and safety findings.

One critical type of administrative control is hazard communication. Adherence to the Occupational Safety and Health Hazard Communication Standard is critical to occupational safety and health protection. The standard hinges on the safety data sheet (SDS) information as the core reference (OSHA, 2012). Nanomaterials, however, often exhibit properties decidedly different from those listed on their corresponding SDS for the larger, “bulk” form of the same material (Eastlake *et al.*, 2012). The ISO Standard ISO/TR 13329:2012 Nanomaterials -- Preparation of material safety data sheet (MSDS), provides guidance on the content development of, and consistency in, the communication of information on safety, health and environmental matters in (SDS) for substances classified as manufactured nanomaterials and for chemical products containing manufactured nanomaterials (ISO, 2012).

One illustration of a systems approach is the NanoRisk Framework developed by the Environmental Defense –Dupont Nano Partnership and adopted as mandatory by DuPont in June 2007 (Environmental Defense Fund, 2007). The objective of the framework is to develop a systematic and disciplined six-step process for identifying, managing, and reducing potential EHS risks of engineered nanomaterials across all stages of a product's lifecycle. The six steps include: describe the material and application; profile the product lifecycle; evaluate risks; assess risk management; decide, document and act; and review and adapt (Figure 6). DuPont relies on the NanoRisk Framework to provide a rigorous, data driven, comprehensive, flexible, practical, and organized thought process.

All companies that employ workers at elevated levels of risk are confronted with daunting insurance issues. Companies with workers who handle nanomaterials are in a particularly precarious situation because, at present, there is limited data specific to the risks associated with nanomaterials. Difficulty in assessing the risk of working with nanomaterials could be reflected in the price of insurance options. However, when compliance with standards such as ISO 9001 (Quality management systems), ISO 14000 (Environmental management), and ANSI Z10 (Occupational health and safety management systems) are factored into risk assessment, these may impact selection and pricing of policies (ISO, 2004; ISO, 2008; ANSI, 2012). Standards are not guarantees, but are indicative of management support and employee involvement in safety. Risk assessment is crucial, and companies that adhere to standards will be in a better negotiation position with respect to insurance options.

Exposure Monitoring and Sample Analysis

Accurate screening, detection, and characterization methods are necessary to design, implement and demonstrate the effectiveness of a strategy to control occupational exposure to ENMs. The NIOSH Nanotechnology Field Studies Team was formed in 2006 to provide voluntary assessments of occupational exposures to ENMs in nanotechnology production and handling operations (Methner *et al.*, 2010). This voluntary assessment provides valuable exposure date needed for NIOSH risk assessments and provides facilities with a free characterization of occupational exposures to ENMs. NIOSH collects time-weighted average (TWA) exposure measurements, where possible to assess the actual exposure dose experienced by workers. This is best accomplished by collecting samples in the workers' personal breathing zone (PBZ) during workers activities over the course of a full workday. Where interest exists in identifying task-specific exposure information, additional time-integrated air samples are placed in the worker's breathing zone and operated only for the duration of that specific task. Real time direct reading instrumentation is used to supplement the PBZ samples. Real-time data from particle counters provide information on peak exposures of concern that could be used to identify the need for modifications to work practices and the application of engineering control strategies. A critical piece of the occupational exposure assessment is the collection of real-time background data over the course of a full sampling period to better understand background fluctuations and specifically identify significant events not related to the nanomaterial production.

Nanoparticles are found everywhere in the environment making it difficult to distinguish between natural, incidental and engineered nanoparticles. Direct reading instruments do not distinguish between different types of nanoparticles. Integrating microscopic techniques (such as scanning electron microscopy [SEM] and transmission electron microscopy [TEM]) into exposure assessment programs can help determine the presence of ENMs. Electron microscopy (EM) can be used to distinguish between intentionally generated and naturally occurring nanoparticles. It can also be used to determine the size, count, projected area, and elemental composition. However, EM instrumentation is expensive and the analysis can be time consuming and costly. Focusing EM analysis only on samples that warrant detailed analysis can help reduce analytical costs.

Because quantification is essential in both preventive and after-the-fact methodologies, technologies that provide particle counts are in high demand. In development is a new personal nano sampler that uses thermal precipitation technology for collection of ENMs. This technique would allow for non-destructive collection of particles directly onto an EM grid used as a collection substrate (Leith *et al.*, 2013). Analytical techniques are also being developed that will use dark-field hyperspectral microscopy imaging to determine a ENM presence in biologic material (Ma *et al.*, 2012). This technique is being explored as a means to count ENMs on fiber membranes and could find applicability in quantitatively estimating ENM concentration based on the number captured per area in a filter's fibers. This technique may also provide a means for automated quantitation of materials trapped in filter membranes and for in-vivo biological testing.

PERSONAL PROTECTIVE EQUIPMENT

PtD, when ideally implemented, should minimize the need for PPE. Workers should only be outfitted with PPE as the last line of defense when all other safety mechanisms have failed, when the effectiveness of the containment system has not been verified, or as a redundant control. Whenever validating untested methods or equipment for handling ENMs, it is necessary for employers to provide and workers to use extensive PPE appropriate to a given situation. Gloves, aprons, and Tyvek® suits are the most effective prophylactic measures for dermal exposure, whereas fit-tested respirators are most effective in preventing respiratory exposure. NIOSH research suggests traditional respirator selection tools used for fine and ultrafine particles also apply to nanoparticles (Shaffer and Rengasamy, 2009). Laboratory coats primarily made of cotton woven material are not recommended for worker protection against nanoparticle exposure because of potential particle contamination and release ability (Tsai, 2015). More focused research is needed on gloves and respirator filters that offer effective protection from ENMs.

RESPONSIBLE DEVELOPMENT OF AN EMERGING TECHNOLOGY

Nanotechnology, and the ENMs resulting from its application, is regarded as a highly adaptive, enabling technology that will revolutionize material science and applications. Currently there are still significant barriers to ENMs achieving the widespread formulation in industrial products and processes that their properties should guarantee. A potential barrier is not enough engagement between industry, researchers, and policy makers. For example, one such barrier is the lack of engagement concerning establishing new, nanomaterial-specific policy or effective application of existing policy to ENMs. To address this barrier, there is a need for an array of functioning partnerships to address how governmental agencies and private sector companies can work together. Such partnerships are important because potential investors may be hesitant to put money into an industry (whether emerging or established) that may develop unforeseen risks and potential regulatory roadblocks. Adherence to and, in the relatively new case of ENMs, construction of relevant occupational safety practice and policy, should be present from the beginning rather than implemented later as a reaction to unsafe conditions.

Another barrier to widespread formulation is a basic understanding of the environmental, health, and safety needs and how these relate to the challenges of scaling up from research to full production. There may be a disparity between the goals of academic researchers and the goals of a private company attempting to commercialize a nanomaterial application or product.

CONCLUSIONS

Traditionally the most efficient means of preventing high-risk exposure is to remove the material and substitute a less hazardous one. For obvious reasons, substituting a nanomaterial for another material is normally not an option. Designing nanomaterials with lower toxicity decreases the hazard. Prevention of occupational exposures at the production and use levels can be accomplished by designing processes and equipment that control exposure. Hazards and associated risks to workers from exposure to nanomaterials can potentially be designed out in the synthesis phase and certainly can be designed out at the production and use phases.

Here, we are presenting the concept of nano-PtD as a potential forward-looking mechanism to anticipate and reduce workplace accidents and exposure. PtD principles, when followed effectively, will support and enhance existing safety management systems. Fortunately, PtD further serves as an answer to the budding gap between technologies among those professionals with different goals who work with ENMs by identifying opportunities for a risk-focused dialogue up and down the life cycle. Prevention through Design, by its basic nature, encourages an interdisciplinary approach to the design phase of any project. Consequently, an increased awareness of and appreciation for different but aligned techniques and approaches to an ENM-conscious occupational safety program is established through the development of a PtD-enabled exposure minimization program. Upon reflection, one of the most important trends that is developing in the nanotechnology community is exposure of leaders in ENM molecular design and synthesis, and those in process containment design, to research and methods that may be immensely different from their own; yet aligned with the common objective of minimizing or eliminating risk. The increased awareness so engendered in all parties in the state of the art of nanomaterial design, detection, containment, policy, and regulation was and is an invaluable boon to shaping the future face of ENM research and development.

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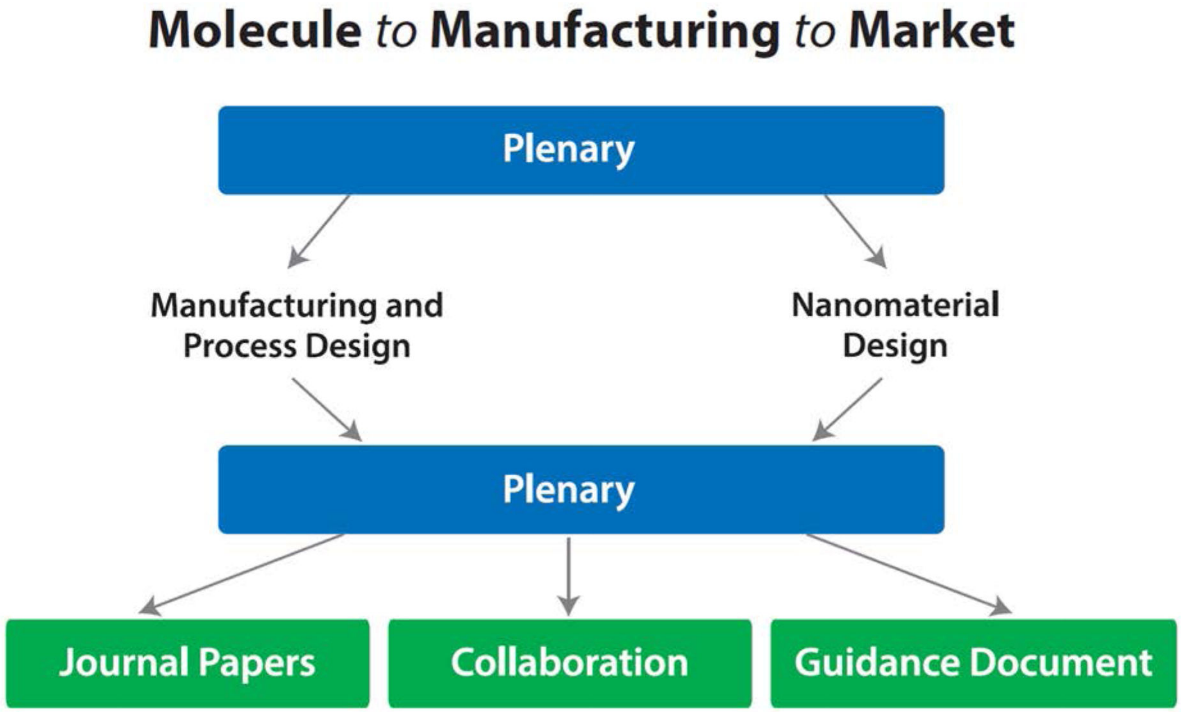

Figure 1.
The format and projected outputs from the Safe Nano Design Conference

Figure 2.
Prevention through Design using hierarchy of controls (Peterson, 1973)

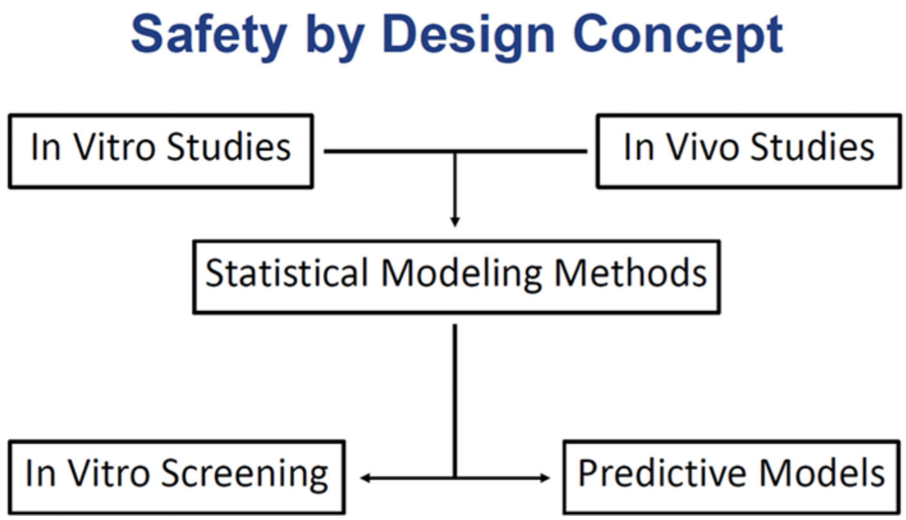

Figure 3.
The use of in-vitro and in-vivo data to develop predictive models that support characterization and biological activity prediction

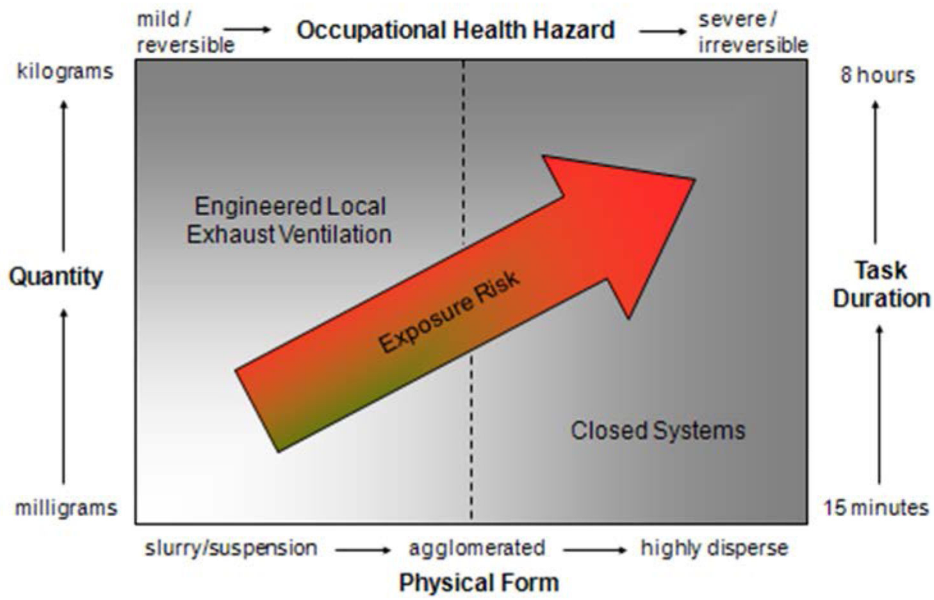

Figure 4.
Factors influencing control selection (NIOSH, 2009).

Figure 5.

Components of an overall health and safety program that includes nanomaterial risk management (Schulte *et al.*, 2008).

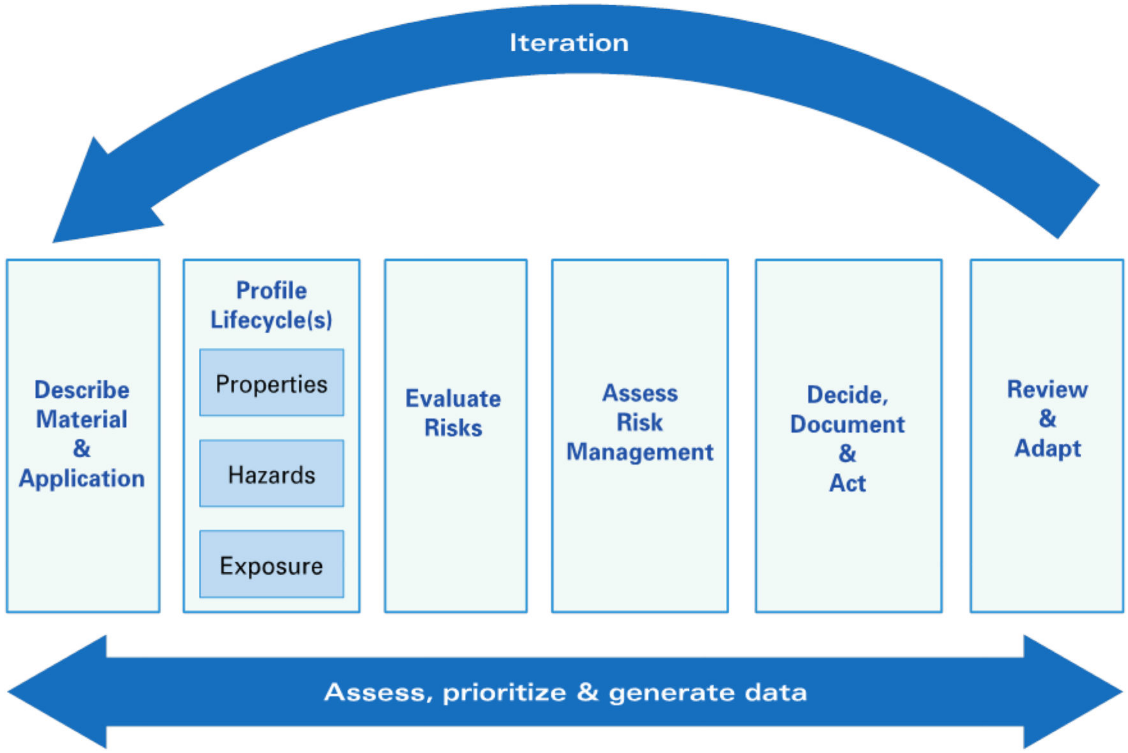

Figure 6.
The six steps of the Environmental Defense / Dupont Nano Risk Framework (Environmental Defense Fund, 2007).