

# Approaching Risk Assessment of Nanoscale Materials

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## ABSTRACT

Developments in nanotechnology and nanomaterials (NM) are rapidly proceeding ahead of a clear understanding of their potential health effects and environmental impacts. Risk assessment will be an important tool for evaluating and potentially regulating NM to protect health and the environment. We are developing an adaptive risk assessment framework for NM that provides an approach for precautionary decision-making and considers the current toxicological uncertainties about NM. Critical NM properties that contribute to the toxicological uncertainties include: a large surface area relative to NM size, their reactivity, and the possibility that NM may translocate within an organism. Our step-wise approach integrates an evaluation of current toxicological information and sources of uncertainty about the specific NM of interest, identification of the potential exposure scenarios, and application of risk assessment tools to evaluate and prioritize management procedures for mitigating NM exposure risk.

Our adaptive approach allows for input of new information about NM to revise and refine health and safety recommendations for NM use and handling and for decision-making under uncertainty. We combine elements of risk assessment with the practices of health and safety to provide relevant NM management procedures for minimizing potential health effects and environmental impacts. This approach offers an effective tool to evaluate potential NM impacts throughout their life cycle, ranging from research and development and product manufacturing, to consumer applications and uses, and ultimately to their disposal and fate in the environment. Identifying the key exposure pathways creates the opportunity to mitigate them, and to operate in a safer work environment. Understanding the environmental, health and safety risks allows effective management of them.

**Keywords:** toxicology, risk assessment, environmental health and safety, risk management; exposure assessment

## 1. INTRODUCTION

Most recognize that nanotechnology is at an early stage in the innovation cycle and that the potential for dramatic change in manufacturing, materials science, and the use of nanoscale materials (NM) is not yet realized. Tens to hundreds of products are already on the market containing NM; hundreds of products are in development, and an even greater number are at the research stage. The promise of molecular manufacturing creates potential for dramatic shifts in the development and use of materials for industrial, consumer, and medical uses. The unique properties of NM are attractive for product development because they confer attributes such as conductivity, increased reactivity, light weight, improved strength, and self-cleaning surfaces compared to conventional materials. However, recent toxicology reports suggest that the same properties that make some NM attractive may also create biological activity and toxicity.

Currently, thousands of workers and an even greater number of consumers are potentially exposed to a wide variety of NM. Are they safe? What happens to NM as they enter the environment? Several research reports indicate that exposures by inhalation, dermal, and ingestion routes may lead to toxicity, including fibrotic formations in the lungs of mice exposed to carbon nanotubes [1], toxicity following dermal exposure [2], and uptake of fullerenes across the gills of fish [3]. Some evidence suggests that the results may be very dependent on the laboratory test conditions, and without adequate exposure information, the tests are difficult to interpret. For example, researchers at the Centre for Drug Delivery Research at the University of London's School of Pharmacy reported that carbon nanotubes functionalized to be water soluble were rapidly cleared from the blood and urine of injected animals [4].

At this stage, it is reasonable to conclude that nanomaterials have the potential to be toxic. What is unclear is how significant the potential for exposure may be because it is the exposure potential that drives health and environmental risks. Generating and reviewing the

toxicology data constitutes a hazard assessment, that is, a process to characterize the potential hazards of a material. Many toxic materials in current use do not pose a risk to the user, due to low level exposures. However, hazard assessment does not consider all aspects of real world exposures. Risk assessment considers both toxicity and exposure when characterizing the potential for harm, and provides a more complete and informative result.

Risk is a function of both the toxicity of a material and exposure of an individual or population to it. Our risk-informed evaluation framework shifts the focus from hazard potential to risk, and considers how and under what conditions human and environmental exposure may occur. Exposure considerations include intended and unintended uses, and the potential for human and environmental exposure to nanomaterials and to products throughout the life cycle. Amid uncertainties about the biological and environmental attributes of nanoscale materials, defining and analyzing the key variables for exposure assessment focuses on potential areas of concern and control points. Risk analyses can inform the broad field of risk management of nanomaterials and nanotechnology.

In this paper, we describe our approach for managing the uncertain risks of nanomaterials. The development of risk science over the last decades has contributed to improved decision making under uncertainty. Health risk assessment has been applied to environmental concerns at hazardous waste sites, from drinking water exposures, in indoor and ambient air evaluations, for food safety, and in multimedia investigations of agents. Where limited data are available, quantitative assessments may not be plausible or informative. Analysis at a screening level, however, where assumptions are used as placeholders in the absence of available data, provides insights that can inform decisions.

This paper describes an adaptive risk framework for nanotechnology that allows critical and precautionary decision making under uncertainty. As new information develops, key assumptions are revisited, and risk estimates revised. The iterative process moves toward more detailed characterization of risks as the technical information is developed to inform it. The framework provides a structure for proactive and protective environmental health and safety decision making about nanotechnology in research, manufacturing, and consumer environments.

A critical element of our approach is identifying the unique properties and characteristics of each NM, its associated processes and uses, and how these processes and uses may create hazards and/or risks. The framework is designed to consider the toxicological uncertainties of NM, to allow for decision making under these uncertainties, and to provide relevant recommendations that incorporate health, safety, and environmental considerations. Importantly, this is an adaptive approach that allows for input of new NM

information and revision of recommendations based on changes in knowledge or processes. Over time, improved understanding of toxicity and exposure will lead to refinement of the risk assessment. This adaptability also provides the opportunity to anticipate and plan appropriately for new NM and their processes.

We have applied the framework to two companies developing and using NM. A critical component is the on-site evaluations of NM work environments to identify specific work practices and conditions that may present hazards and exposures to NM, and hence create risks. Information and observations from these evaluations inform the assessment hazards and risk and lead to recommendations to minimize potential adverse effects and manage risks of NM on the health of workers and consumers and on the environment. Two examples are described

Risk assessment is a well defined, decision-oriented process for analyzing complex problems. The four steps of the process, Hazard Identification, Dose Response Assessment, Exposure Assessment, and Risk Assessment, consider key aspects of potentially hazardous materials, including the probability and magnitude of potential effects. The framework applies these steps to evaluate the potential risks associated with the development and use of nanoscale materials and inform risk management approaches for using them. This approach is especially useful for product development, since it can easily be adapted and reiterated as processes and materials develop, and also can inform manufacturing design by early identification of potential health, safety or environmental risks.

Life cycle analysis (LCA) is an analytical tool that considers environmental impacts from a product's cradle (generation) to its grave (disposal, recycling or reuse). While there is a current lack of consensus, LCA generally evaluates broad categories of impact, such as resource consumption, ozone depletion, climate change, and eutrophication. Some approaches consider impacts on health and ecological receptors in terms of toxicity, but less frequently consider exposure or risk [5]. This adaptive risk framework specifically considers exposure throughout the life cycle, adapting the life cycle approach into the risk analysis process. Others have suggested this combined approach may be called "Comprehensive Environmental Assessment" [6].

## 2 METHODS

The adaptive risk assessment framework for nanomaterials and their products steps through the life cycle of product development, exemplified in Figure 1, and conducts screening level risk assessments at each step. The framework applies a risk assessment approach for decision-

making regarding the safe use of nanomaterials. The framework is a decision tree structured to inform decisions by analyzing risks; that is, it considers the potential health and safety risks in a step-wise process. Each step is considered individually, defining hazards, exposure and risk. Where uncertainties are great, a range of alternative inputs is used. The effect of the alternative input variables is then evaluated for its overall effect on the risks.

Hazard identification is the first of four steps in risk assessment. Hazard identification describes the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population [7]. The scope of the hazards identified defines the parameters of the analysis. Hazard identification for nanoscale materials includes specific characterization and measurement of a range of properties that relate to environmental transport and fate. These may include chemical composition, reactivity, physical dimensions, observed behavior, thermal and electrical properties, and may also evaluate behavior in ambient aqueous and cellular environments. At each step in the lifecycle, the materials used and health, safety and environmental hazards of those materials are identified.

Toxicity assessments consider the effects of the materials on exposed biological systems. For human health toxicity, any information regarding past human exposure is considered, as well as information from short-term and long-term animal bioassays for a range of health endpoints. *In vitro* testing in cell cultures can also inform toxicity assessments. Where limited information on the toxicity of materials exists, assumptions are made based on similar materials. That is, the risk assessment may proceed without specific toxicological characterization of a nanomaterial. In its absence, we can simply assume toxicity by all routes of exposure, or can refine estimates with available information in subsequent iterations.

Exposure assessment is the process that evaluates how materials move through environments. This phase is the critical foundation of our risk assessment framework for analyzing the movement of nanomaterials through their synthesis, generation, and use. Exposure assessment is the evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives).

In the exposure assessment, we identify and characterize the probability and magnitude of exposure for each step of the product life cycle. Exposure dose is calculated by making assumptions or obtaining data on the pathways of exposure under specific scenarios. Exposure can be measured or modeled or broadly defined in qualitative terms, such as “widely dispersive,” or “low”. This information allows us to identify the specific concerns for each product in each stage of its development. The exposure assessment informs the safe management of

nanoscale material development by characterizing the significance of potential exposures for specific processes as they relate to worker health and safety, and product user scenarios. Understanding the exposure pathways creates the opportunity to mitigate them, and to operate in a safer work environment and product use cycle.

In this adaptive framework, risk, or risk potential is characterized at a screening level for each step of a material’s life cycle. The screening level risk characterization identifies the factors contributing to risk at each step. Uncertainties are identified that are addressed either at the time, or in subsequent iterations of the analysis. We characterize the potential significance of the risks for health, safety, and environment. Even if the characterization is qualitative, it is informative, since we can prioritize the next steps for more detailed characterization, or alternatively, we can recommend mitigation measures to reduce the risk.

This approach represents a screening analysis that is refined to the user’s requirements for precision. Where information is missing, the analysis identifies what is needed, and helps to prioritize the gathering of additional information. Data gaps are accounted for by making a range of estimates that can be considered to bound the analysis, by including conservative or maximum assumptions, and comparing with less conservative or more realistic assumptions. The results may be qualitative, or semi-quantitative.

The evaluation can lead to alternative data gathering, modeling, or conservative estimation for variables that greatly affect the risk. Risk assessment considers both the hazard potential and the opportunities for exposure. Understanding the environmental, health and safety risks allows effective management of them.

### 3 RESULTS

We are applying the adaptive risk framework for a variety of nanotechnology manufacturing environments. In a small NM startup firm, the major risks were from unsafe working conditions (safety hazards), inadequate chemical hygiene, and insufficient ventilation. Key concerns included spontaneous combustion of NM, inhalation exposures to NM and to their precursors, and dermal exposures following NM deposition onto work surfaces. The lack of basic safety measures increased the potential for occupational exposures during normal work activities, and from accidental releases.

We applied our adaptive risk framework to a company developing products using NM that is presently focused on a scale-up of their manufacturing process. We identified great attention to mitigating airborne exposures during

fabrication of the NM, but inadequate evaluation of the potential for accidental releases that may impact worker safety at the packaging step. Packaging involves two main steps, deposition of materials in a liquid suspension on a substrate, and manual manipulation of the dried, coated product into secure housing. Each of these steps creates the potential for exposure. The current deposition process could result in exposure for the worker to NM by aerosolization during the pouring process or following a spill. Under normal conditions, splashing may create aerosols containing NM, that could lead to direct ingestion exposure, and may contaminate the work environment, where subsequent aerosol and dermal exposure may occur.

The current pouring process also creates ergonomic hazards that could release up to 1 gm of NM in an open manufacturing environment if a spill occurred, creating additional dermal and aerosol exposures during cleanup up, and perhaps over time as well. Lack of containment increases the potential impact of an accidental release. Finally, the waste liquid is released to a public waste water treatment facility, and has not been evaluated for the presence of NM, a potential public exposure.

Our risk characterization for this firm challenged the assumption that material generation held the greatest potential for risk, instead finding multiple hazards at the post fabrication phase, potentially impacting worker health as well as the surrounding community through accidental and incidental exposures. In this case, we recommended analysis of effluent for the presence of NM, and changes to the packaging step to reduce safety concerns and worker exposures.

#### 4 DISCUSSION

The clear value of our proactive risk-based approach is borne out by safer work environments and a reduction in potential liabilities for investors, employees who work directly with these new materials and for consumers who use products containing NM. These evaluations will be helpful for regulators as they consider how or whether to regulate NM. Organizations gain definite advantage by early consideration of the potential impacts of NM throughout their life cycle, ranging from research and development and product manufacturing, to consumer applications and uses, and ultimately the disposal and fate of NM in the environment.

As we have stated, there are gaps in the information available to assess risks. Therefore, the framework is iterative and makes conservative and protective assumptions where there are large uncertainties; these uncertainties are revisited as new information becomes available. The analysis is iterated, refining the assessment as new information is developed. This adaptive approach allows for rapid input of new information to revise and refine decision-making regarding health and safety recommendations for the use of NM. The approach integrates evaluation of current toxicological information for the different types of NM, an understanding of the potential exposure scenarios, and application of risk assessment tools to evaluate and prioritize mitigation of the potential health risks. This information derived from this approach provides the basis for recommendations for appropriate health and safety practices for work with NM.

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**Figure 1. Simplified Product Life Cycle**

