Health Risk Assessment of Products Containing Nano-engineered Materials

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ABSTRACT

Engineered nano-scale materials are increasingly being used in a variety of consumer products. Health risk assessments are critical to evaluate the potential hazards associated with release of these materials and to ensure regulatory and public acceptance. Exposure and toxicity comprise the main components of risk. Materials science evaluations of nano-engineered particle exposures during production and throughout product lifetime may involve relatively simple tribology and reliability testing, and long-term stability assessment. Even without testing, existing knowledge of the properties of resins and binders can be used to formulate durable products that retain nanomaterials. Standard screening tests for toxicity are currently under development. Research has focused on some of the most common types of nanomaterials in or destined for products. A wealth of related information is also available from ultrafine particles (UFPs), metal fumes, volatile organic compounds, and mineral fibers. The presented approach describes the interplay between exposure, materials science, and toxicity, which when taken together, can aid in characterizing risk of products, engineering "safety" in products containing nanomaterials.

Keywords: risk assessment, materials science, exposure potential, toxicity, screening approach

1 MOTIVATION

The Woodrow Wilson International Center for Scholars recently published an on-line listing of almost 400 consumer products from 18 different countries that contain nanomaterials [1]. These products include clothing, cosmetics and personal care items, dietary supplements and certain foods, and children's goods. The United States manufactured about 60% of the listed products, with the largest category of products labeled as health and fitness, followed by home and garden, electronics and computer, and then food and beverage. The public's acceptance of products already on the market – and development of new products – is critical for their success. Lessons learned from the discovery of long-term health effects of asbestos, for example, years after the widespread use of this material in products, teach us that risk assessments of consumer products should be performed early in the process of product development. These assessment should be aimed at presenting a balanced analysis of the exposure and toxicity issues that might play a role in health risk, and should discuss the both the benefits and risks to allow for informed decisions regarding these products.

2 HEALTH RISK ASSESSMENT FRAMEWORK

A schematic of the four-step risk assessment process is shown in Figure 1.

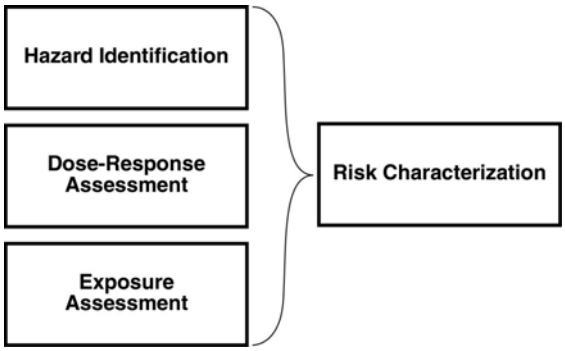

Figure 1. The risk assessment process [2].

This process was adapted to nano-engineered particles and adapted to aid in the assessment of health risks of consumer products containing these materials, with particular focus on exposure assessment and dose-response (toxicity) assessment to better characterize risk.

3 EXPOSURE ASSESSMENT

Assessment of exposure should involve a life-cycle analysis from manufacture to disposal or attrition of a particular product. At the present time, workers and academic researchers likely experience the highest exposures to raw nanomaterials; however, consideration must be given to consumers, the general public, and the environment, which is the ultimate sink for these materials. The exposure assessment should address the following questions:

- How does the exposure occur?
- Who (or what) was exposed?
- How much exposure occurs? Where and when did it occur?

- How uncertain are exposure measurements?
- How does exposure vary?
- What is the likelihood or probability that exposure will occur?

This section focuses on the latter three questions as they relate to products and to consumers who may be exposed to these products via primarily the inhalation and dermal routes, and to some extent, ingestion (e.g., food products).

3.1 Measurement Techniques

There are currently no agreed upon methods for measuring exposure to nano-engineered particles (NPs). Conventional methods based on mass (mg/m^3) or number concentration (particles/cc) may be inadequate. For NPs, surface area and shape are very important exposure metrics [3–5], as the reactivity of a particle is directly related to its surface area, which is extremely high. Measurement techniques and sampling designs must also be able to distinguish ambient or background of particles in the nano-scale range from airborne concentrations of specific engineered materials of interest (*e.g.*, from specific product, rather than background) for sampling. For example, nanoparticles measured in air at a nanomaterials processing facility resulted from combustion emissions from the heated-air system, rather than the engineered nanomaterials being processed at the facility [6,7].

Despite the debate as to the appropriate exposure metric and paucity of quantitative studies, the exposure to nanomaterials is not entirely new. There is a wealth of exposure information available for other similar substance that can aid in evaluating the factors that might be of importance for exposure to nano-engineered materials. UFPs represent a large database of information, providing studies of exposure on substances such as diesel, coal dust, and air pollution, a component of which contains multi-walled carbon nanotubes (CNTs) [8]. Studies of smelter and foundry workers and welders also provide insight into nano-sized fractions of metal fumes [*e.g.*, 9,10]. Finally, although not necessarily nano-sized, the abundant literature on mineral fibers, such as asbestos, can aid in understanding properties affecting exposure, such as physico-chemical factors, dimension, dose, biopersistence, and durability [*e.g.*, 11].

Current measurement techniques fall loosely into four categories of instrumentation: condensation particle counters, differential mobility analyzers, electrical low-pressure impact, and aerosol surface area measurement [3,4,12,13]. The last category is currently being avidly researched, and some portable, battery-operated instruments have been commercially introduced [*e.g.*, 14,15]. These instruments allow for measurement of biologically relevant surface areas when these exposures result in lung deposition, providing real-time measurements of exposures of particles that may deposit in the tracheobronchial and/or alveolar regions of the human respiratory tract. Currently, however, there are no standardized methods for exposure testing.

Given the lack of standard methodology for quantifying exposure, a key focus for manufacturers should be on engineering processes and consumer products that encapsulate or limit liberation of free nanomaterials, and that maintain this encapsulation even during wear or weathering of the product. This can be achieved using the well-established discipline of materials science.

3.2 Materials Science Analysis

Materials science can aid in evaluating manufacturing-related operational health exposure during production and throughout product lifetime through relatively simple testing. These tests aid in determining how exposure may vary, both from the standpoint of product-to-product variability, as well as any changes over time, such as due to wear or weathering. By leveraging existing knowledge of the properties of resins and binders in products, a design for reliability methodology can be used to formulate products that retain NPs. This will aid in "engineering safety" into products before they hit the market, ensuring that these products eliminate or minimize exposure.

3.2.1 Tribology Testing

The process of wear is one of the major areas of study of tribology and is a critical area for products containing NPs to provide significant information relating to the exposure potential for consumers. Wear is primarily composed of four processes: surface fatigue, abrasive wear, corrosive wear, and adhesive wear. Currently, there are several wear tests available through American Society for Testing and Materials (ASTM) Sub-committee G-02, with each test depending on the nature of the wear process involved. All ASTM tests define wear in terms of a volumetric loss of material, rather than a mass loss. For NPs, where particles of tiny volumes (~nm^3 to– μm^3) may be lost from the product sample, it is not clear that the standard wear test approach may be feasible in defining wear. Modification may be necessary to include a statistically significant sample for testing. Standard-setting organizations have been active in addressing the needs of the nanomaterials industry, but much work remains to be done in extending the current tribological tests to include NPs.

In terms of wear under normal operating conditions, it is common to divide the product's life into three distinct stages: primary or early stage, when the rates of wear can be high; secondary or mid-stage, when the rates of wear are relatively constant; and tertiary or final-stage, when rates

could be high, leading to failure of the product. The different wear processes mentioned above have different test methods, such as scratch tests (to determine abrasive wear) or peel tests (to determine adhesive wear characteristics). It may still be appropriate to use such test methods (in their current form as described by the standards) for situations such as nano-engineered coatings or other instances where a statistically significant sample is available and where the assumptions of the test method are still valid.

3.2.2 Reliability Testing

Reliability testing data will provide consumer use exposure data through accelerated testing. A nanocomposite material that begins to shed NPs during its lifetime would not be a viable product due to consumer safety concerns, and possibly performance issues. A nano-product that is designed to last 10 years will undergo accelerated testing regimes with known acceleration factors that predict exposure over the lifetime of the product. For any emerging technology, development of acceleration factors is required prior to product release as the acceleration factors and models are a function of the physics of failure of the specific product.

Reliability testing methods fall into two categories: shipping/handling and operational lifetime testing. Shipping/handling testing includes exposures to temperature extremes, relative humidity, mechanical shock, and vibration. The purpose of this testing is to assure the nanoproduct can survive transportation. Operational lifetime testing is designed to bring out the same failure mechanisms as would be seen in the use environment. Examples of this type of testing are leaching and weathering tests to evaluate chalking, peeling, and cracking. The environmental stressors involved in these failure mechanisms include temperature, relative humidity, ultraviolet exposure, thermal cycling, and unique use environment requirements. Monitoring of nanoparticle emission using techniques (see Section 3.1) must be included in these studies. Materials tests, such as tribology testing (Section 3.2.1), are also recommended initially and periodically throughout the reliability test regime, with a goal to correlate material degradation modes that result in nanoparticle emission. Failure modes and effects methodology is a valuable tool for a comprehensive reliability program.

3.2.3 Long-term Stability Tests

Evaluation of the long-term stability of chemical affinity between the nano-components and binders can be performed along with reliability testing. Nanomaterials should be studied for stability using test structures that simulate the product and processing history. Analytical testing such as high resolution scanning electron microscopy and transmission electron microscopy will provide data on the nano-component to matrix interfaces during and after long term stability testing. Nano-sized fillers require a strong interfacial bond with the matrix for enhanced mechanical properties [16]. Determination of the behavior of this binding mechanism over the life of the product can be obtained through long-term stability testing. Evaluation of the resistance to small molecules with regard to time-dependent chemical degradation of nanocomposites is one example of this form of empirical testing.

It is important to know when these materials will break down; thus, bringing the material to failure, even if it is at an extreme condition, will provide valuable information. Knowledge of the limits of the materials and design of the product well within the limits is critical for safe consumer products that contain nano-components.

4 DOSE-RESPONSE (TOXICITY) ASSESSMENT

With regard to toxicity, standard screening tests are currently under development for nanoscale particles, and elements of a screening strategy were recently proposed for NPs [17]. Considerable toxicity information is being generated on some of the most common types of nanomaterials in products or planned for products, such as certain metal oxides [*e.g.*, 18], fullerenes [*e.g.*, 19], and CNTs [*e.g.*, 20]. Research efforts are also being directed at developing expedient *in vitro* (cell and tissue cultures) and *in vivo* (in animals) tests that are predictive of the relative differences in toxicity of substances and potential for effects in humans [21,22].

Concerns associated with the toxicity of NPs include their potential to become airborne and their ability to cross biological membranes and barriers. Other concerns are that even relatively inert substances may become more reactive, and thus toxic, by virtue of their small size and higher relative surface area. Although the understanding of the toxicity of nanoscale particles, and particularly novel NPs, is far from complete, some initial trends are emerging that may be helpful for assessing factors that influence the relative toxicity of different types of materials depending on their properties [3]. For example, toxicity is not simply as a function of size, but depends on many other factors such as chemical composition, particle shape, structure, and surface properties or coatings [3,18,21]. In addition, the wealth of information on more well studied small-scale materials (*e.g.*, UFPs, metal fumes, mineral fibers) can be used to aid our understanding of potential effects and research directions for NPs [*e.g.*, 5,11]. For example, as shown for UFPs from air pollution [5], airborne exposures to several types of insoluble nanoparticles are showing both respiratory and cardiovascular effects (*e.g.*, CNTs [8], inert metal oxides [22]).

Among NPs tested (largely by *in vitro* testing, *in vivo* instillation in the trachea of rodents or in aquatic toxicity tests), the general trend in toxicity seems to indicate quartz, fullerenes, and CNTs as more toxic than metal oxides (*e.g.*, TiO_2, ZnO, CeO, AgO). Higher toxicity of more soluble metals (Zn or Fe) relative to less soluble metals [23] should be considered within the context of the whole animal at environmentally relevant doses. At low doses, essential metals in solution would be readily handled by physiological mechanisms. In assessing the potential toxicity associated with exposure to NPs in consumer products, the magnitude of dose and conditions of toxicity tests should be considered. For example, one of the most well-studied nano-scale TiO_2 forms is P25 (80% anatase, 20% rutile). The form used in products, however, may be very different (*e.g.*, pigmentary TiO_2 is mostly rutile) or presence of coatings (*e.g.*, alumina and silica) may reduce toxicity [18,21,24].

Given the early stages of this research, toxicity studies of nanomaterials typically use worst-case applications at very high doses. In assessing potential toxicity, one must consider all aspects of exposure (e.g., dermal penetration, potential for agglomeration) and resulting toxic effects, particularly at lower concentrations that would occur in real life.

5 RISK CHARACTERIZATION

An approach for evaluating health risk of consumer products is shown in Figure 2.

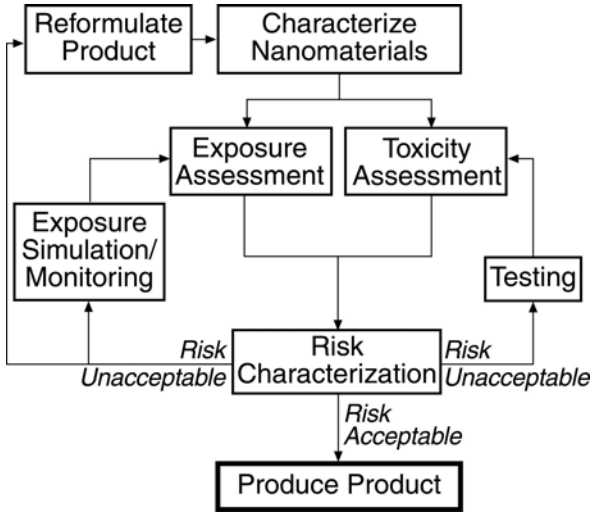

Figure 2. Health risk assessment of consumer products containing nano-engineered materials.

This approach incorporates both the exposure and toxicity information using an iterative process to determine whether risk might be acceptable or manageable, and to aid in engineering safety into products prior to manufacturing and production.

6 CONCLUSIONS

Although there are several data gaps in the exposure and toxicity data, information on well-studied particles can be used to better understand factors affecting these issues. In addition, materials science analysis and simple testing can be done early in a product's life to minimize exposures both during the manufacturing setting and in consumer use, as well as possibly in the environment. Assessment of properties and behavior of NPs over the operational environment will enhance successful prediction of exposure potential. For consumers, the vast majority of NPs are encapsulated within the product, thereby minimizing or eliminating exposure. Product durability will be necessary over the life cycle of the products to ensure their safety.

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