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HEALTH IMPACTS OF EXPOSURE TO NANOPARTICLES: ENVIRONMENTAL, HEALTH, AND SAFETY FACTORS TO TAKE INTO ACCOUNT WHILE EVALUATING RISKS AND DANGERS

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Abstract:

Research and development in material science is currently witnessing a dramatic expansion in the realm of nanotechnology. The majority of research efforts have been directed on applications; implications, or the effects on health and the environment, have received less attention. Ensuring the safety of products being produced from an environmental, health, and safety (EHS) perspective is crucial for the success of nanotechnology. Regarding this, research on pulmonary toxicity have previously indicated that as compared to bigger particles of same composition, lung exposures to ultrafine or nanoparticles—defined here as particles b 100 nm in one dimension—produce heightened unfavorable inflammatory responses. The toxicity of nanoparticles may be significantly influenced by surface characteristics, especially particle surface area, and the production of free radicals as a result of particle-cell interactions. Some of the most important elements for researching EHS risks and hazard effects associated with nanoparticle exposures are highlighted in this concise review. Hazard and exposure assessments lead to health and environmental risk assessments. The significance of particle characterization studies, the creation of a risk framework for nanomaterials, and corresponding hypothesis-driven, mechanistically-oriented investigations in tandem with base set hazard studies are the main points of discussion here. These studies clearly show that particle size is only one (and possibly a small) factor influencing the safety of nanomaterials.

Keywords: Nanoparticle, Exposure, Risk, Safety, Characterization.

Introduction:

partly comes from the Greek word "nano," which means "dwarf." From the perspective of material sciences, it is exciting to see new products being created with engineered nanomaterials because, as one reduces the particle size range below ~100 nm, one can observe that the

properties of the particles change. These properties can then be utilized to create products with more applications. As the particle size decreases within the nanoscale range, gold particles, for instance, can exhibit color changes to red or blue. Furthermore, at decreasing particle size ranges approaching 50 nm, pigment-grade titanium dioxide particles—which are typically in the 300–400 nm size range—lose their white hue and becoming colorless, or transparent. This property could be helpful for making sunscreens and other cosmetics, among other things. Certain kinds of particles that have been used for their electrical insulating qualities may turn conductive at the nanoscale, while compounds that are insoluble may become more soluble at sizes smaller than 100 nm. Changes in physical attributes therefore contribute to increased adaptability and effectiveness in product development, leading to more successful industrial and medical applications concurrent with the creation of more adaptable and effective goods (Colvin, 2003).

In general, particle types in the size range of 100 nanometers or less, in at least one dimension, have been defined as nanoparticles (also called ultrafine particles). Ten hydrogen atoms are about the breadth of a nanometer, or nm. In terms of particle size comparisons with biological and cellular endpoints, an erythrocyte's diameter is roughly 7 micrometers (μm), or 7000 nanometers. Certain viruses are known to have a size range of 60–100 nm, while the size of certain bacteria is frequently reported in the 1 μm (or 1000 nm) range. The phrases "nano" and "ultrafine" are commonly used synonymously, with the latter being thought to as a more modern term. This has caused some confusion because, although engineered nanoparticle types are frequently purposefully made to certain particle size ranges for particular applications, some investigators have used the word "ultrafine" to refer to particles generated via combustion sources.

It is reasonable to assume that the biological effects associated with exposure to nanoparticles may differ from those associated with bulk particles given the changes in physical and chemical properties that occur as particle sizes are decreased within the nanoscale range (and therefore take on different properties versus the “larger” fine-sized particle-types). As a result, a new field in toxicology, exposure assessment, and health risk evaluations is the study of possible health concerns associated with exposures to manufactured nanomaterials. As novel particles and materials are discovered, toxicity data sets and methods for aiding exposure evaluations for different types of nanoparticles are also being developed.

When compared to larger-sized particles of similar or identical composition at equivalent doses/mass concentrations, lung exposures to ultrafine or nanoparticles cause greater adverse inflammatory and fibrotic responses, according to the few pulmonary toxicity studies with ultrafine particles in the rat model that date back to the mid-1990s. Rats are a known sensitive species, and almost all of these particle investigations have been carried out under high dose particle overload scenarios. The high size-specific deposition of nanoparticles when inhaled as monodispersed rather than aggregated particles is one factor contributing to these effects. According to some data, inhaled ultrafine or nanoparticles that deposit in the lung may be more likely to evade the regular clearance processes of alveolar macrophages and enter other

anatomical regions of the respiratory system, such as the pulmonary interstitium and the systemic vasculature. The belief that all nanoparticles are probably more harmful than fine-sized particulates has been reinforced by data from the small toxicological database (Oberdorster, 2000; Donaldson, Stone, Clouter, Renwick, & MacNee, 2001).

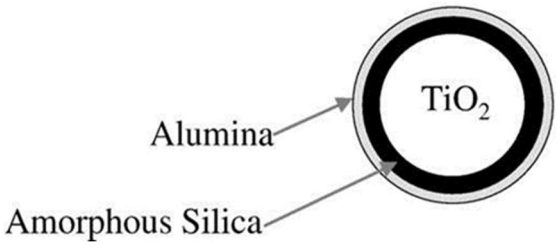
This concise analysis aims to enumerate and pinpoint some essential elements and concerns that could potentially impact environmental threats to one's health and safety from nanomaterial exposure. The aim of the study is not to provide an exhaustive overview of nanotechnology; instead, it will concentrate on certain significant and current areas related to evaluations of the impacts on health. These include the following:1) the significance of studies on particle characterization;2) the creation of a Nano Risk Framework and related base set hazard studies;3) an instance of a mechanistic bioassay study on pulmonary toxicity using nanoquartz particles;4) research on the creation of in vitro screening assays for pulmonary toxicity to particle types; and5) concerns about safe handling of nanomaterials in laboratory settings.

The significance of carrying out physicochemical characterizations research on several kinds of nanoparticles :

The creation of a safety database for nanoscale particles is changing in tandem with the development of new particles, materials, and exposure techniques, as was covered in the Introduction section. When compared to fine-sized (bulk) particle types of similar chemical composition, exposure to ultrafine/nanoparticles (defined as b 100 nm in one dimension) may produce enhanced toxicity, according to data from some pulmonary toxicity studies conducted on rats (Donald- son et al., 2001; Oberdorster, 2000). It has been hypothesized that the development of lung toxicity associated with nanoparticles is significantly influenced by the measurement of particle surface area and particle number. A closer examination of these studies reveals that a number of other physicochemical characteristics, such as crystal structure, aggregation potential, and surface coatings, were different in the various particle-types that were being compared. The assumptions made from these studies were that the only differences (i.e., variables) between the ultrafine and fine-sized particle-types were the particle sizes. Furthermore, results from additional recent studies using nanoquartz and ultrafine titanium dioxide particle types show that some nanoparticle types' toxicity may be largely related to their surface reactivity in terms of influencing the development of cytotoxic and inflammatory responses in the lung (Warheit, Webb, Colvin, Reed, & Sayes, 2007a; Warheit, Webb, Reed, Frerichs, & Sayes, 2007b).

Particle interactions and surfaces are crucial elements of materials at the nanoscale. The fraction of atoms at the particle's surface increases in relation to the amount inside its volume as the particle size decreases. As a result, certain types of nanoscale particles are produced that are likely to become more reactive, producing catalysts that are more effective in a range of applications. Reactive groups on the surface of particles, as opposed to nonreactive surfaces or

surface coatings that tend to passivate, are likely to also influence the biological (perhaps toxicological) effects when taking into account the possible health implications. Consequently, changes in the surface chemistry that form the “shell” on a kind of (core) nanoparticle may be significant and pertinent to the health impacts that follow exposures (refer to Fig. 1). Additionally, surface coatings can be used to modify the surface characteristics of nanoparticles to stop them from aggregating or agglomerating with other types of particles, or they can be used to "passivate" the type of particle to lessen the impact of reactive oxidants produced by UV light. It's fascinating to



Think about how surface coatings, which work to prevent aggregation while promoting particle dispersion, can increase the effectiveness of the type of particle in the intended application. However, they can also make it easier for nanoparticles to move from the respiratory tract to the systemic circulation, which would greatly increase the distribution and exposure of nanoparticles to different parts of the body (perhaps a double-edged sword?). (Oberdorster et al., 2005; Borm et al., 2006). In summary, two distinct types of nanoparticles with titanium dioxide as their "core" may not have identical or even comparable hazard potentials from a toxicological standpoint. This highlights the significance of nanoparticle core-shell dynamics for biological effects. Crystal structures (rutile versus anatase), surface coatings (passivation and neutralization), aggregation status, particle size distribution, surface area, and surface reactivity can all differ. Despite having a comparable "core," these variations in the physicochemical particle properties could lead to relative variations in the potencies of pulmonary inflammatory and cytotoxic endpoints, which could have benign to more moderate health effects (Warheit et al., 2007b).

Researchers should thoroughly characterize the physicochemical features of the nanoparticle kinds that are being evaluated for toxicity testing, according to numerous scientific organizations and task committees. Unfortunately, all too frequently, this advice turns into a long, non-prioritized laundry list of material attributes. Therefore, before conducting hazard studies with nanoparticle-types, we have previously recommended that, at the very least, experimentalists should characterize the following (prioritized) physicochemical properties in order to adequately describe the physical characteristics of the nanoparticle-type being evaluated:

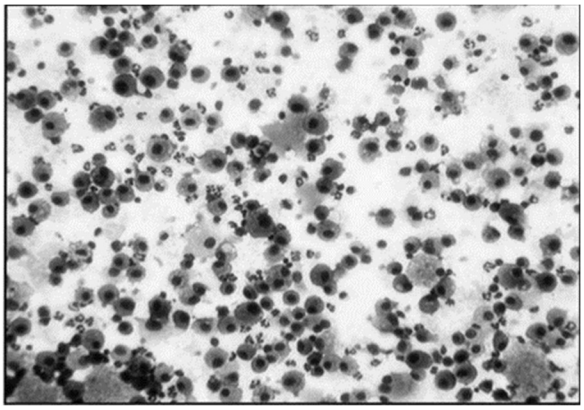
- Depending on the exposure route, particle size and size distribution (wet state) and surface area (dry state) in the pertinent media being used;
- Crystallinity and crystal structure;

- Status of aggregation in the pertinent media;
- Surface coatings and composition;
- Reactivity of the surface;
- The process for synthesizing and/or preparing nanomaterials, including any post-synthesis adjustments (such neutralizing ultrafine TiO2 particle kinds);
- Sample purity; (Warheit, 2008).

In order to facilitate a methodical process for identifying environmental health and safety (EHS) risks associated with exposures to newly developed products containing engineered nanoscale materials, Environmental Defense and the DuPont Company jointly developed and promul- gated the Nano Risk Framework (2007). First and foremost, knowledge of exposure and hazard assessments is necessary for determining health or environmental concerns. Furthermore, there are numerous situations in which the exposure assessment or potential cannot be measured because of technological limits in assessing nanoparticle exposures in the workplace or limitations in measurement (methodologies) in the environmental context. As a result, it is frequently necessary to estimate exposure evaluations using rational and knowledgeable product lifecycle considerations. Furthermore, a foundational set of hazard studies that would offer a rational and practical evaluation of the nanoparticulate-type's toxicity for human health and environmental concerns may be incorporated into the EHS framework. The Nano Risk Framework is an interactive approach with six fundamental components that match different stages of development. You can obtain this framework from the following website: www. the nanoriskframework.com. The six steps are summarized as follows in brief: Phase 1. Explain the Substance and Step 2 of the Application. Profile Lifecycle(s) The Nanomaterial's Properties 2B. The Nanomaterial's Hazards 2C. The Nanomaterial's Exposures Step 3. Assess the Risks Section 4. Evaluate Risk Management, Step 5. Choose, Record, and Take Action Step # 6. Evaluate and Modify Steps 2A, 2B, and 2C are undoubtedly the most demanding parts of the nanorisk framework for the user. The purpose of Step 2A is to identify and describe the nanomaterial's chemical and physical characteristics. The possible safety, health, and environmental risks associated with the nanomaterial are identified and the hazard profile is characterized in Step 2B. An illustration of how the Framework methodology is being used to evaluate the risks associated with a recently created ultrafine TiO2 material is outlined below. The purpose of Step 2C is to identify and assess the possibility of exposure to the nanomaterial by humans or the environment. This includes exposures resulting from the product's intended usage as well as unintentional releases that may occur over the product's lifetime. The framework's lifetime feature strongly advises the user to think about how the physicochemical characteristics, risks, and/or exposure

Certainties could change at any point in the material's lifecycle, such as after the product's typical lifespan and possibly even after disposal. Regarding the application of the Framework's hazard component to a novel material, the toxicity outcomes of a foundational series of hazard tests conducted on a recently created, thoroughly examined, ultrafine rutile TiO2 (uf-TiO2)

particle-type have already been published (Warheit Studies on pulmonary bioassay toxicity of α-quartz particle types at the fine and nanoscales Prior research has shown that, in comparison to particle properties, surface features of nanoparticles, such as surface reactivity, may have an equal or greater impact on pulmonary toxicity.



Linking Research

When evaluating the safety of compounds in commercial development or when modifying already-existing goods, such as changing the particle size of particulates, pulmonary bridging studies can be used to give pertinent and accurate screening hazard data. Having reliable inhalation toxicity data for comparisons with data derived from instillation trials is essential to the bridging strategy's potency. The materials for which inhalation data are available can then be compared to the results of the pulmonary bioassay (i.e., intratracheal instillation mode of exposure) as reference particle types. The effects of the implanted materials are therefore used as a reference (known) particle-type in the description of the basic bridging concept, and they are subsequently "bridged" or benchmarked to the inhalation toxicity data for that particle-type, concurrent with the testing of novel compounds. Because the injected or inhaled control material consistently elicits the same reactions as the newly tested particle-type, the results of bridging studies in rats are then valuable as preliminary pulmonary toxicity screening (i.e., hazard) data. In this instance, the outcomes of short-term inhalation trials using Min-U-Sil quartz particles were comparable to those of earlier pulmonary bioassay instillation investigations. As a result, using Min-U-Sil quartz particles, the nanoquartz investigations can be connected to the inhalation and instillation pulmonary bioassay research.

Attempts to replace in vivo pulmonary investigations with in vivo screening studies

toxicity tests using types of fine and nanoscale particles There has been very little correlation found in published reports between the effects of pulmonary toxicity following in vivo intratracheal particle instillation and in vitro cell culture exposures, despite previous

attempts by other investigators to develop in vitro models as predictive screens for pulmonary toxicity to particles. We recently evaluated the ability of in vitro screening studies to forecast the lung toxicity of various fine or nanoparticle kinds in rats when they are present in vivo. Rats were administered two distinct doses of the following particle types via intratracheal instillation throughout the in vivo portion of the study: carbonyl iron, crystalline silica, amorphous silica, nano zinc oxide, or fine zinc oxide. Lung inflammation and cytotoxic indicators were assessed 24 hours, 1 week, 1 month, and 3 months after exposure. Three distinct culture settings were used for the study's in vitro portion, which used the same test particle types as those covered in the in vivo investigations. The same particle types as mentioned above were incubated with cultures of rat lung epithelial cells, primary alveolar macrophages from lavaged rats, and alveolar macrophage/L2 lung epithelial cell co-cultures at 1 h, 4 h, 24 h, or 48 h.

The culture fluids were assessed for cytotoxicity endpoints and inflammatory cytokines at multiple time points, in line with the in vivo studies. The in vivo lung toxicity experiments' data showed that the amount of toxicity caused by carbonyl iron particles was little. Exposure to crystalline quartz silica particles resulted in cytotoxic effects and persistent inflammation. After one week, exposure to amorphous silica particles caused brief inflammatory reactions that could be reversed. Lastly, intratracheal injection of nano- or fine-sized zinc oxide particles resulted in strong, momentary cytotoxic and inflammatory effects that were remedied by a month after the initial exposure. Findings from the in vitro pulmonary Studies on the cytotoxicity of various particle types revealed a range of uneven reactions.

Managing nanomaterials safely in the lab

A sensible product stewardship tool/safe-handling approach for nanotechnology would start with the general idea that health risk is a function of both hazard assessment and exposure evaluations, given the relative paucity of safety data on health concerns connected to exposures to nanoparticles. Additionally, staff members must to handle any novel nanomaterials with caution as a general rule. When scientific information about the dangers of nanomaterials is available, it should be handled consistently with the risks that have been identified. A successful risk management procedure would recognize and describe the dangers that the nanomaterial and its intended use present, as well as its kind, extent, and likelihood. Some of the first queries that need to be answered in relation to the hazard assessment tool are the following: 1) Are nanomaterials produced throughout the process, and where are the possible exposure points along the handling life cycle? 2) The substance should be thoroughly characterized, with the following inquiries addressed: is the material in a solid or liquid form, is it dusty, what is the size distribution, and is it soluble in water? 3) What is thought to have been exposed? The respiratory tract (i.e., inhalation exposure), the skin, the eyes, and the gastrointestinal tract (by oral or inhalation exposures) are the four main pathways of occupational exposure. 4) Which exposure route is most common? — this is an principal issue. An action plan is recommended by a risk

management assessment process, which assesses the choices for risk management (see Table 3). Potential exposures should be contained and controlled using sensible safety procedures that are suitable for the activity at hand and in line with the hierarchy of controls. It is important to take these steps to limit exposures as much as is practically possible. The hierarchy of control measures consists of the following: engineering control, procedural control, enclosure, replacement, elimination, and personal protective equipment (PPE). The tolerable amount of risk will determine which controls are chosen. PPE, as a last resort for control, such as High Efficiency Particulate Air (HEPA) filter respiratory protection and personal protective equipment, can frequently avoid cutaneous and ocular exposures. Engineering controls are useful where airborne nanoparticles are created. If sufficient toxicological information regarding the desired nanoparticle type is lacking.

Conclusion:

In summary, the purpose of this brief overview is to highlight some of the key concerns that affect the evaluation of the hazards to environmental health and safety associated with nanomaterial exposures. We have concentrated on the crucial topic of particle characterization research, which is a necessary precondition for investigating the effects of nanomaterials on human health and the environment. Furthermore, a careful framework for a risk management model has been built to detect any dangers associated with exposure to nanomaterials. Exposures and hazards combine to provide dangers to one's health and the environment. All too frequently, the idea of health risk is confounded with hazard data from a toxicity study. It should be highlighted that exposure plays a crucial role in this calculation. An occupational safety and health program that is built on the identification of nanomaterial risks, assessment of exposure potentials, and implementation of risk-reduction controls ought to include risk management as a fundamental component. Lastly, a description of some mechanistic pulmonary toxicity experiments using nanoparticles is given. Research is being conducted to create in vitro models that can be used to predict the pulmonary effects of nanomaterials; however, additional research and validation are necessary.

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