

Guidance Document for Research Work with Nanomaterials

Background

The purpose of this guidance document is to provide information to minimize occupational exposure to nanomaterials. Nanomaterials include, but are not limited to, ultrafine structures (engineered or extracted from natural components), devices and systems that have a length scale of roughly 1 to 100 nanometers in one dimension such as fullerenes, quantum dots, carbon nanotubes, nanowires, etc. Items that could be contaminated by these products include bench tops, clothing, gloves, etc.

Safety Issues

Clemson University works to provide a safe and healthy workplace for faculty, staff and students. Providing for a safe workplace involves the processes of hazard identification, risk assessment and risk management.

Hazards are identified by examining the nature of nanomaterials, the form of the nanomaterials (e.g. solid, powder, or liquid suspension), known toxicities, the manipulations to be performed in the research, and the potential routes of exposure (e.g. inhalation, ingestion, and dermal exposure).

The risk of working with nanomaterials is the potential exposure to ultrafine nanostructures, devices, and systems whose toxicity and health risks associated with nanoparticle exposure have not been defined.

Nanotechnology Research at Clemson University

Research with 1) recombinant DNA, 2) biological hazards, including but not limited to, a BSL2 agent or above, toxins, human blood and cell lines, and/or 3) chemicals that are defined as highly toxic, mutagenic, teratogenic, carcinogenic (confirmed or suspected), explosive or involving Schedule I or II drugs requires that an IBC application be submitted to the Office of Research Compliance for review by the Institutional Biosafety Committee (IBC).

For employees and students conducting research involving the creation, manipulation, or use of nanomaterials or devices not involving the materials listed in the previous paragraph, Clemson University recommends that researchers submit an IBC application.

When submitting an IBC application involving nanomaterials, Sections A, and a Hazard Acknowledgement Form, and Section B (for biological), Section C (for chemicals) and/or Section D (for recombinant DNA) should be completed if applicable to the work described in the application. Some of the items on the IBC application may not be applicable, and can be identified as such. The form can be obtained from the IBC website http://www.clemson.edu/research/orcSite/orcIBC_Forms.htm

The Office of Research Compliance (864-656-1525) can be contacted for information on submitting an IBC application.

Work Practices

In general, personal protective equipment (PPE) should include safety glasses or goggles, protective gloves such as latex, nitrile or a different glove-type, if necessary, lab coat or gown, and closed shoe. Work in some situations or locations may require the use of additional protective equipment. Activities in which aerosols or splashes may be created need to be conducted in a certified chemical and/or biological safety cabinet, or with other physical containment equipment or other personal protective equipment (e.g. face shields, respirators). Researchers should use professional judgment, personal experience and common sense and be adaptable and be cognizant of pertinent new information regarding the adverse health effects of exposure to nanomaterials.

Nanotechnology

Nanotechnology Definition

Nanotechnology is the study, design and manipulation of materials at the nanometer scale such that novel or enhanced properties emerge. Nanotechnology is somewhat loosely defined; in general terms it covers engineered structure, devices and systems that have a length scale of roughly 1 to 100 nanometers in one dimension (EPA 100/B-07/001, February 2007). At these length scales, materials begin to exhibit unique properties that affect physical, chemical and biological behavior differ from their bulk counterparts. Nanotechnology R&D is directed toward understanding and developing improved materials, devices, systems, and applications that exploit these new properties.

Safety Concerns

While the ability to develop nanomaterials and incorporate them into products is advancing rapidly, our understanding of the potential environmental, health, and safety effects of nanomaterials, and of the most effective ways to manage such effects has proceeded at a much slower pace. Given the enormous commercial and societal benefits that may potentially come from this technology, it is likely that nanomaterials, and the products and other applications containing them, will be widely produced and used. Therefore it is especially important to understand and minimize the potential risks.

The safety concerns regarding the use of nanotechnology have arisen from the recognition of unique attributes of nanomaterials:

- Low solubility ultrafine particles are more toxic than larger particles on a mass for mass basis.
- The ultrafine structure and size of nanomaterials permit the particles to penetrate through the skin, translocate from the respiratory system to other organs, or pass through the blood-brain barrier.

- The greater surface area and surface chemistry conferred on these nanomaterials promote greater interactions with biological systems thus could induce stronger tissue responses.

Knowledge Gaps

The National Institute for Occupational Safety and Health (NIOSH) has identified the current knowledge gaps regarding the toxicity and health risks associated with nanoparticle exposure (Texas A&M, 2005).

1. *The nanoparticle nomenclature is not sufficiently well described or agreed*

Currently there are no agreed definitions for nanoparticles, nanoparticle aerosols, or for the various types of nanoparticles which are produced. Definitions proposed need to define a size interval to take account of the distribution in sizes likely to be present, to consider whether the definition should be based on physical dimensions (e.g. length, diameter, surface area) or on some behavioral property such as diffusivity and take account of agglomerated aerosols. Progress on nomenclature issues is usually best achieved based on consensus.

Notes:

An agglomerate is a group of particles held together by relatively weak forces, including van der Waals forces, electrostatic forces and surface tension.

An aggregate is a heterogeneous particle in which the various components are held together by relatively strong forces, and thus not easily broken apart.

2. *There are no convenient methods by which exposures to nanoparticles in the workplace can be measured or assessed*

For inhalation, the most appropriate metric for assessment of exposure to most nanoparticles is particle surface area. Currently there are no effective methods available by which particle surface area can be assessed in the workplace. There is a need for more research into the development of new improved methods, combinations and strategies to provide reliable assessments of exposure to nanoparticles and nanoparticle aerosols. Development of appropriate methods to evaluate dermal and ingestion exposure is also necessary.

Notes:

The route of exposure to nanomaterials could include inhalation, oral ingestion, or exposure to the eyes and skin. *In vitro* and *in vivo* exposure sensitivity studies should be conducted to investigate cellular and tissue-level responses for each of these routes of exposure.

3. *Insufficient knowledge concerning nanoparticle exposure is available*

Much more information is needed regarding the exposure of workers involved in the production of all of the various types of nanoparticles via all of the production processes. In the absence of suitable measurements systems, coherent approaches as described above should be adopted. At this stage there is insufficient evidence to judge whether exposure to the various forms of nanoparticles is occurring at significant levels in nanoparticle production processes.

4. *The effectiveness of control approaches has not been evaluated*

Better understanding is required relating to the effectiveness of control of nanoparticles. This will be better informed given the development of appropriate methods for assessment of

exposure to nanoparticles and a better understanding on the levels of exposure that may be acceptable. This is true for inhalation, dermal and ingestion risks.

5. *Knowledge concerning nanoparticle risks is inadequate for risk assessments*

Current knowledge is inadequate for risk assessment. Risk assessment approaches will have to consider how best to use information which is currently available, and plan to collect new information. An effective strategy for collecting, storing and disseminating this information is also necessary. Development of appropriate databases, and other information resources that can be used to collect and disseminate information on studies to investigate exposure or toxicological assessment of nanoparticles is a key element in this. Researchers must document, collate, maintain and disseminate information relevant to nanoparticle risk issues.

Notes:

A document entitled a “Nano Risk Framework” (Environmental Defense – DuPont Nano Partnership, June 2007) — a joint effort by Environmental Defense and DuPont — for ensuring the responsible development of nanoscale materials. It establishes a process that can be widely used by companies and other organizations.

Reasonable Control Strategies for Working with Nanoparticles

Strategies to control exposure to nanoparticles could include:

- Total enclosure of the process
- Storage of all nano-materials in total enclosure
- Local exhaust ventilation, with HEPA filtration
- General ventilation
- Limitation of numbers of workers and exclusion of others
- Reduction in periods of exposure, via SOP’s and personnel training
- Regular cleaning of wall and other surfaces; documented cleaning schedule
- Use of appropriate personal protective equipment
- Prohibition of eating and drinking in laboratories and controlled areas
- Transport of nano-materials within secondary containment device
- Immediate cleanup of all spills & discharges
- Collection of all nanoparticle waste materials for disposal in compliance with the Clemson University Hazardous Waste Management Plan.

CONTROL OF EXPOSURE BY INHALATION

Engineering control

For air velocities prevailing in workplaces, airborne nanoparticles can be considered as having no inertia. They will therefore behave in a similar way to a gas and if not fully enclosed will diffuse rapidly and will remain airborne for a long time. Because of their high diffusion velocity, these particles will readily find leakage paths in systems in which the containment is not complete. Engineering control systems designed for use to control nanoparticles such as enclosures, local exhaust ventilation (LEV), fume hoods and general ventilation therefore need to be of similar quality and specification to that which is normally

used for gases rather than for particulate challenges. These systems do exist and are in common use in the chemical and other industry. Like all such systems effective performance of these systems will be highly dependent on appropriate use and maintenance.

Engineering controls are widely used to reduce exposure to welding fume. A variety of methods are recommended including general ventilation, LEV, fume hoods and on-gun extraction (HSE, 1990). The level of protection provided by these methods is considered to be quite variable and dependent on issues previously mentioned such as maintenance and worker behavior. Engineering controls of this type are also used in the carbon black industry but as indicated earlier, significant exposure in this industry still occurs.

Filtration

Filtration plays an important role in the control of exposure to airborne particles. High Efficiency Particulate Arrester (HEPA) filters are used in engineering control systems to clean the air before returning it to the workplace. These filters are usually referred to as mechanical filters.

Filtration theory is well understood and has been extensively described by several authors (e.g. Brown, 1992). As an aerosol penetrates through a filter, the trajectories of the particles deviate from the streamline due to various well-understood mechanisms. As a result, particles may collide with the filter elements (fibers) and become deposited on them. The mechanisms include diffusion, interception, initial impaction and gravitational settling. Electrostatic forces can also play a role in some filter types.

For particles less than 100nm, Brownian diffusion is the dominant mechanism (Lee and Mukund, 2001). Filtration efficiency due to Brownian diffusion increases as particle size decreases. Brownian diffusion is caused by collisions between particles and the air molecules to create random paths that the particles follow. The random motion increases the probability of a particle contacting one of the filter elements. Once the particle is collected onto a surface it will adhere to it due to the Van der Waals forces. Therefore filters are likely to be good collectors of nanoparticles.

Current methods for certification of HEPA filters and for respirator filters do not routinely require testing at particle sizes in the nanometer size range. Internationally recognized standards for HEPA filters (DOE, 1998) require that the filter is challenged with an aerosol with a mass median diameter of 300nm and that the particle collection efficiency is greater than 99.97%. Three hundred nanometers is considered to be a much more penetrating aerosol for these filters than nanometer size particles due to the decrease of Brownian diffusion at this particle size. Similarly European Standards for respirator filter cartridges (CEN, 2001a) and for filtering face pieces (CEN, 2001b) require that these systems are tested against sodium chloride aerosols with a mass median diameter of 300nm. Again this is based on an expectation that this would be the most penetrating size.

Little work has been done to quantify the performance of filters against particles in the nanometer size range. It is still widely accepted, that with diffusion the dominant mechanism and the efficiency of filters will be high.

Use of Personal Protective Equipment (PPE)

Use of PPE such as respirators and air fed devices may be used (as a final option) as a method of control for any airborne hazard. All of these devices depend on filtration as a means

of cleaning the air prior to it being breathed by the worker. The discussion relating to filtration applies equally here. It is probable, for all but the smallest nanoparticles (<2nm) that the filtration efficiency will be high. It was not possible to identify any relevant research that has demonstrated this.

Air-purifying respirators are widely used in diverse workplaces, and thanks to decades of research and experience, occupational health professionals have confidence that a NIOSH-certified device with the correct filter, and properly fit-tested, will provide appropriate protection against silica dust and other traditional airborne contaminants.

Conventional knowledge, based on a substantial body of evidence, holds that airborne particles 0.3 micrometers in size are more likely to penetrate a filter than particles of other sizes. Particles larger than 0.3 μm will be blocked by filter fibers. Those smaller than 0.3 μm will be stuck on and among the fibers through a process called "diffusional capture." Consequently, if a filter captures particles 0.3 μm in size, scientists could be confident that the filter would capture particles of any size.

It is well recognized in the science of Industrial Hygiene, however, that the determining factor governing the effectiveness of respiratory protection equipment (RPE) against particulate challenges is not absolute penetration through the filter, but rather face-seal leakage that bypasses the device. Face seal leakage is dependent on many factors including the fit of the mask to the face, duration of wearing, work activity etc. Since it is expected that nanoparticle aerosols will have high mobility, it is possible that enhanced leakage will occur although no more than might be expected for a gas. No relevant research to quantify this has been identified.

CONTROLS FOR DERMAL EXPOSURE

Issues relating to dermal exposure have only relatively recently come to prominence in occupational hygiene. Based on our understanding of the various processes by which nanoparticles can be synthesized there seems to be a strong possibility of dermal exposure occurring, most likely in the later stages of the process i.e. recovery or resulting from surface contamination. There is some evidence that dermal exposure to nanoparticles may lead to direct penetration of nanoparticles into the epidermis and possibly beyond into the blood stream. Therefore, it may be necessary to introduce control to exclude or limit the level of dermal exposure likely to occur. As for inhalation exposure, COSHH provides a framework by which a strategy to prevent or control dermal exposure can be developed. However, it is acknowledged that prevention of dermal exposure is not covered so well in the guidance associated with COSHH.

As with control of exposure by inhalation, the first approach is enclosure of the process. This should certainly be achievable as powder-handling processes can be enclosed successfully. However in practice, particularly with products or processes that are in development, the main emphasis is on investment and expenditure at the synthesis end of the process. This is likely to limit the expenditure on sophisticated control and automation processes to deal with what will be perceived as relatively mundane tasks such as harvesting and packing of nanomaterials.

In any case even where such processes are in place, the requirements for attention to breakdowns, maintenance etc means that the possibility of dermal exposure cannot be excluded

at all times. In these and other instances protection against dermal exposure typically consists of the use of Skin Protective Equipment (SPE) i.e. suits, gloves and other items of protective clothing.

Even for powders in the macro scale, it is recognized that SPE is very limited in its effectiveness to reduce or control dermal exposure. Based on current understanding (Schnieder et al; 2000) multiple processes contribute to dermal exposure, and the relative ineffectiveness of SPE. In addition to the classical view that the failure of SPE results from direct penetration or permeation of an agent through the material from which the equipment is constructed, other process include transfer of substances by direct contact between surface, skin and outer respectively inner clothing or gloves, and redistribution of substances between compartments of the same type, e.g. redistribution of contaminants from one part of the skin contaminant layer to another as a result of touching the face with contaminated fingers.

Current European testing for certification of PPE against dermal exposure only takes account of permeation or penetration. Although recently, new tests have been proposed which take account of the other human factors based on simulations (Brouwer et al; 2005). Since it is likely that nanoparticles which escape into the workplace will become widely dispersed and will have high surface area, it is likely that the human factor element will be even more critical than for macrosized particles. In this case, it is quite likely that SPE will be less effective against nanoparticles than against macro size particles. It is also quite likely that direct penetration of nanoparticles through the material from which the protective clothing is made will be higher than for macro-sized particles.

CONTROLS FOR INGESTION EXPOSURE

Understanding about exposure by ingestion in the workplace is not currently well developed. It is considered that ingestion exposure in the workplace results primarily from hand-to-mouth contact. It follows that strategies that tend to reduce dermal exposure in the workplace will also tend to reduce exposure by ingestion. The converse of this is also true. At this point in time we have identified no relevant research that has successfully quantified exposure to nanoparticles by ingestion in the workplace or the effectiveness of strategies to reduce this exposure.

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