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Environment, Health and Safety Committee
Note on:
WHY DO WE WORRY ABOUT NANO-MATERIALS?

Concerns have been raised about potential risks to the health of workers, consumers and the environment with the increase in manufacture of nano-materials. These concerns generally relate to the size of nano-particles which may be able to cross biological membranes and enter cells, tissues and organs more easily than larger particles. Furthermore, fears exist that their potential adverse effects may be enhanced by their greater reactivity, a property related to their high surface area to size ratio. In addition, concerns have been expressed that some nano-materials, for example carbon nano-tubes appear to have similarities with asbestos and this raises questions as to whether these may give rise to similar pathological effects. This Note aims to provide some insight into our current understanding of the risks associated with nano-particles and nano-materials.

WHAT ARE NANO-MATERIALS?

Nano-materials have been around for a very long time but only recently have they been defined as such. Nano-material is a generic term that covers materials with one or more external dimensions, or an internal structure, on the nanoscale. These materials may exhibit novel characteristics compared with the same material without nanoscale features. Nano-particles are defined in terms of their size and unique properties which may be different from the bulk material.

The SI prefix nano- (symbol n) is derived from the Greek nanos (νανος) meaning dwarf. It denotes a factor of 10^{-9} and is used in science to prefix units of mass, time and length. When used as a prefix for something other than a unit of measure, as in 'nano-material', 'nano-particulate', nanotechnology it relates the root word to a scale of nanometres (1 nm = 1/1,000,000,000 of a metre). Convention limits nano-particles and nano-materials to be less than 100 nm. More precisely, nano-materials / particles are those smaller than 100 nm in at least one dimension. By way of comparison, the wavelength of visible light is 400–700 nm and a human hair is approximately 70,000 – 80,000 nm thick.

Using examples from chemistry and biology, the range extends from the 'flu virus (100 nm) to the DNA molecule (2-3 nm in diameter) to C60 fullerene, a molecule composed of 60 carbon atoms, the van der Waals diameter (molecular diameter) of which is about 1 nm. A gold atom is 0.32 nm in diameter but spheres of monodisperse colloidal gold, also known as "nano-gold" (originally used as a method of staining glass), may be 10-20 nm in diameter and are a suspension (or colloid) of sub-micrometre-sized particles of gold, usually in water.

Nano-particles occur naturally, as in smoke. Nano-particles are also produced when some food is fried, are present in car exhaust fumes, incinerators and forest fires as well as during industrial processes such as arc welding. 'Soft' nano-particles occur in milk as casein micelles (aggregates of several thousand protein molecules) or as oil globules in mayonnaise. Meat is another complex material containing nano-structures.

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Nano-particulate gold and silver have been used in glass making since Roman times. However, it is only recently that nano-materials have been deliberately manufactured.

Man-made nano-materials range from the well-established multi-ton production of carbon black and fumed silica, for applications as fillers in plastic, and in car tyres to microgram quantities of many exotic products such as the semi-conductor fluorescent quantum dots used as markers in biological imaging. Nano-materials in products can be free (e.g. the nano-particulate titanium or zinc oxides in sunscreens) or bound (e.g. nano-particulate titanium dioxide on the surface of self-cleaning glass).

The term nanotechnology is often used to describe the methods used to manufacture nano-materials. Strictly this is incorrect and the word should be used for the study of controlling nano-sized matter. More precisely: nanotechnology is the engineering of functional systems at the molecular scale. In its original sense, 'nanotechnology' referred to the projected ability to construct items through molecular self-assembly, the 'bottom-up' approach, or construction of 'nano-objects' from larger entities without atomic-level control, the 'top-down' approach. Nanotechnology now includes many areas of physics, such as nano-electronics, nano-mechanics and nano-photonics and chemistry which now includes molecular nanotechnology in which materials and devices are built from molecular components which assemble themselves through the rules of molecular recognition.

WHAT ARE THE PROPERTIES OF NANO-MATERIALS?

This question can be answered by looking at the two key properties of nano-particles. Firstly, anything smaller than 50 nm is subject to the laws of quantum physics and chemistry which can give them optical, magnetic or electrical properties which are different from the bulk form of the material. Secondly, the smaller the particle the more reactive it is. Also, nanoscale particles entering the body may be more readily absorbed.

With decreasing size the ratio between mass and surface area changes. Nano-particles have a very high surface area-to-mass ratio and the number of surface molecules increases exponentially when particle size is below 100 nm. These surface molecules characterise the whole particle not just the surface, a property which becomes insignificant for particles larger than 10^{-6}m (1000nm). In some cases, surface energy (a measure of the energy needed to disrupt intermolecular bonds when a surface is created) may be similar to the bulk energy of a particle. This has obvious advantages in catalysis where the size of nano-particles may be only one or two orders of magnitude greater than the size of the constituent atoms or molecules they contain. A nano-particulate metal (M), for example, may have particles in the 5 nm range with approximately 3600 atoms (represented as M_{3600}), at 2 nm about 200 atoms and at 1 nm, about 30 atoms. At 1 nm about 90% of the atoms are on the surface.

For some materials, there are changes in physical properties with decreasing particle size. One difference is depression of the melting point with particle size, a phenomenon that has been known for one hundred years. Bulk gold melts at 1063ºC but nano-particulate gold melts several hundred degrees lower. Particles in the 5 nm size range melt at about 830°C; particles of about 2 nm melt at 350°C. This occurs because surface energy is always lower in the liquid phase than the solid phase. The smaller the nano-particle, the larger the contribution made by the surface energy to the overall energy of the system and thus the more dramatic the melting temperature depression.

Other differences include the absorption of solar radiation in photovoltaic cells, which is much higher in materials composed of nano-particles than it is in thin films of material. Also, copper nano-particles smaller than 50 nm are not malleable or ductile like the bulk material and are considered to be 'super hard'.

USES AND BENEFITS OF NANO-MATERIALS

There are a growing number of applications of man-made nano-materials which are being incorporated into a wide variety of technologies and products including: the manufacture of polythene; paints, varnishes, coatings; information and communication technology; biomedical applications; environmental remediation technology; energy capture and storage; food technology; and military technologies.

Carbon nano-tubes (CNTs) are an increasingly cited example of a manufactured nano-particle. CNTs have high conductivity, high surface area/mass, unique electronic properties, and potentially high molecular adsorption capacity. These properties make them suitable for many purposes, for example as additives to strengthen other materials, from concrete to protective clothing; hydrogen storage; conductive plastics for car body panels that will facilitate electrostatic spray painting; electromagnetic shielding; electron field emitters (flat panel displays); super capacitors; new types of batteries that could hold more energy than conventional batteries.

In the widest sense, nanotechnology and nano-materials are a natural part of food processing and conventional foods, because many foods contain nanostructures, for example meat, or nano-sized components, for example emulsions. However, recent technological developments may allow manufactured nano-particles to be added to food. These could be finely divided forms of existing ingredients, free or encapsulated, or completely novel chemical structures.

Food packaging is already being developed using nanotechnology. Packaging can contain antibodies attached to fluorescent nano-particles to detect chemicals or pathogens in the food. Other types of nano-sensors in plastic packaging can detect gases given off by food when it spoils and the packaging itself will change colour to signal that the food has gone bad. Packaging can contain oxygen scavengers or UV absorbing materials such as nano-particulate TiO_2. Packaging can be made with antimicrobial and antifungal surface coatings containing the nano-particulate metals; silver, magnesium or zinc. Nanotechnology is also used to produce anti-microbial food contact materials in packaging or as coatings for food containers, chopping boards and refrigerators.

Pharmaceutical use of nano-particles (nano-pharmaceuticals, not to be confused with nanoceuticals – see below) is increasingly diverse. Therapeutic applications have existed for some years and this is still a rapidly growing field. Biomedical imaging is newer: one example is the use of quantum dots which can fluoresce under laser light. More recently, nano-particles have been used in medical applications as well. For example, it has been shown that it is possible to transfer light to quantum dots from a bioluminescent protein such as luciferase. These composite dots produce light without an external source of illumination. As a result, it is possible to visualise targets deeper in tissue sections or living animals and to identify multiple targets at the same time with a wider variety of detection devices.

The first nano-pharmaceuticals for therapeutic application were based on liposomes. These are uni- or multi-lamellar bilayers of natural phospholipids and cholesterol that form spherically concentric structures. They have the ability to entrap both water soluble and insoluble substances and, because they are nanoparticulates, deliver them to places which would be inaccessible to the parent compound in bulk form. Recently, a new generation of liposomes called ‘stealth liposomes’ have been developed that have the ability to evade interception by the immune system. There are also other carriers using polymers conjugated with drugs that have been developed particularly for cancer treatment. Polymer–drug conjugation promotes tumour targeting through enhanced permeability and retention through endocytic capture by cells.

Nano-particulate elemental silver is a powerful bactericide that can be impregnated into a variety of products, e.g., wound dressings, odour-free socks, children’s toys, air filters, refrigerators, etc.

Nanoceuticals are nutritional supplements that have been reduced by nanotechnology to the nano-scale. The process does not change the chemical structure of the nutrient but it does change how it acts, primarily by making it more bioavailable. The safety of these products has been questioned but because they are dietary supplements it is uncertain who should assess this.

RISKS ASSOCIATED WITH NANO-MATERIALS

Mankind is continually exposed to a variety of naturally occurring and man-made nano-particles and materials. To date, there is little evidence of adverse health effects as a result of exposure to manufactured nano-particles but that does not mean that their health effects are fully understood. Nor can it be assumed that all nano-particles are ‘safe’ e.g. exhaust fumes from vehicles. As novel materials developed from nanotechnology are moved from the laboratory into commercial production, the potential for occupational and public exposure to manufactured nano-particles may increase dramatically in the future.

Nano-particles are usually bound in a matrix in manufactured nano-materials, e.g. ‘self-cleaning’ glass, but may be unbound in some products such as cosmetics. However, because of their highly reactive properties, nano-particles tend to clump together (agglomerate) to form larger particles in the environment. Even so, the potential to be exposed to manufactured nano-particles exists when the materials in which they are bound break down, for example, at the end of their useful lives.

There are some concerns that because of their reduced size, nano-particles may be able to penetrate biological membranes or be absorbed more easily than larger particles. Generally, it appears that the highest risk of exposure to ‘free’ nano-particles and materials, as is the case for many hazardous substances, is in an uncontrolled manufacturing environment.

Toxicology is the study of the adverse effects of chemical and physical agents on living organisms. This includes the effects of nano-materials on human health as well as their effects on other biological systems. The basic rule of toxicology that 'dose matters' also applies to nano-toxicology. The most significant factor is the route of exposure. In humans, this may be by inspiration into the respiratory system, ingestion, penetration through the skin, or, in special circumstances, injection into the body. The final consideration is the fate of the material after exposure. In addition to the possibility of occupational exposure, the risk of exposure to nano-materials may be most significant in food and increasingly in pharmaceuticals. A related topic, which is attracting considerable interest, but is not addressed in this Note, is the environmental impact of nano-materials both from industrial and domestic waste, and in sewage.

Of particular concern are nano-particles which can be respired deep into the lungs or which enter the nasal cavity. The nano-materials known as single-walled carbon nano-tubes have comparable dimensions to amphibole asbestos fibres, are biologically stable and so could induce mesothelioma in exposed people. Other respirable particles have been shown to pass rapidly from the lungs into the systemic circulation concentrating in organs such as the liver. Nano-particles deposited on the olfactory mucosa have been shown to pass along axons of the olfactory nerve into the CNS. Nano-TiO_2 instilled into the nasal cavity of mice has been shown to travel via the olfactory nerves into the brain, by-passing the blood-brain barrier. Most of the material remains in the olfactory bulb but some is transported to other brain areas.

While this neuronal uptake mechanism has been described particularly for the respiratory tract, it is not known whether it exists for other exposure routes as well. The same or similar translocation mechanisms may also apply to dermal and intestinal exposures once penetration across the epidermis or across intestinal epithelium has occurred, while such penetration may well be much more rapid with nanoparticles. High daily absorption of nano-particles occurs through the digestive tract. This has been estimated for sub-micron particles at 10^{12} - 10^{14} particles ingested per day with an estimated mucosal uptake of 0.1 – 1% (i.e. 10^9 –10^{12}/d). These particles are mainly titanium dioxide (TiO_2) and particulate silicates (including aluminosilicates) from food and toothpaste. Many studies have examined whether nano-particulate materials can penetrate the skin. This is of particular interest in sunscreens, which commonly contain nanosized ZnO or TiO_2. Since the size of these particles is less than that of the wavelength of light they are effectively invisible which is seen as a cosmetic asset. Current knowledge indicates that while it is fairly well established that there is no percutaneous translocation of either oxide through intact skin there is doubt about abraded or sun-burnt skin.

There is also doubt about some other nano-particles, particularly those which will only be experienced through occupational exposure. The potential for exposure varies according to its stage in a product’s life cycle. Although the potential for exposure is greatest during manufacture this stage is the most controllable. It is harder to control exposure during product use, however, as mentioned most nano-particles will be fixed in a matrix making exposure unlikely. There may well be issues at end-of-life when products are recovered or sent for disposal.

CONTROL MEASURES

There are no existing or proposed regulations specifically aimed at controlling nano-materials anywhere in the world. Nonetheless, the control of nano-materials is subject to the provisions of the following European Union directives and regulations, (which are subject to periodic amendment):

- Biocidal Products Directive 98/8/EC
- General Product Safety Directive 2001/95/EC
- Cosmetic Products (Safety) Regulations 2004 (as amended)[1]
- Directives 2001/83/EC, 2003/63/EC, 2004/27/EC which relate to the manufacture, sale, supply and importation of medical products
- EU General Food law Regulation
- EU Novel Foods Regulation 258/97

[1] A new European Regulation, approved on 20 November 2009, and which will come into force in three and a half years, will require cosmetics manufacturers to list any nano-particles in products marketed in the EU. The Regulation defines a nano-material as ‘an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100nm’.

- The Chemical Agents Directive – COSHH and DSEAR in the UK.
- REACH REGULATION (EC) No 1907/2006 of the European Parliament and of the Council (corrected version published in the Official Journal of the EU, 29 May 2007).

In the UK, the airborne 'workplace exposure limits' under COSHH still refer to the mass of substance in a volume of air. Unfortunately, mass may not be the best indicator of the risk from nano-particles because of the potential high reactivity of disaggregated nano-particles. According to the UK Health and Safety Executive there are no effective methods or technologies currently available by which particle surface area can be assessed in the workplace.

UNCERTAINTIES

The Royal Society/Royal Academy of Engineering report "noted that understanding the fate and behaviour of manufactured nano-materials in the environment is crucial for predicting the potential ecotoxic effects in various environmental species. Furthermore, the report recommended that carbon nano-tubes should be treated as 'new substances' under UK and European Health, Safety and Environment legislation and undergo extra safety checks before they are placed on the market to ensure they do not pose a threat to human health. However, this would trigger a raft of hazard testing, perhaps much of it on animals. The Royal Society / Royal Academy of Engineering report does not recommend a ban, noting that "sensible, pragmatic steps can be taken now by regulators to control possible risks from new manufactured nano-particles without (the need to) stop development activity".

A UK Government response to the Royal Commission for Environmental Pollution (RCEP) report "Novel materials in the Environment" 27th Report (2008) accepts the RCEP view that no evidence exists of actual harm but accepts this is a possibility. In particular, concerns were expressed about nano-silver effects on microbial communities and sediment feeding organisms, and about carbon nano-tubes and fullerenes which may have asbestos-like pathological effects.

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (2009) notes that "Experts are of the unanimous opinion that the adverse effects of nano-particles cannot be predicted (or derived) from the known toxicity of material of macroscopic size, which obey the laws of classical physics." This is important because the next generation of nano-materials may be even more reactive due to their enhanced properties. For example, proposed drug delivery agents which are functionalised to cross biological boundaries to reach specific target sites within the body.

Information also needs to be gathered about the fate of nano-particles in nano-enabled products at the end of product life as well as about the potential explosive properties of nano-particles. This may present a risk in cases where production amounts of such materials are scaled up for commercial purposes.

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