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# Hazard Reduction in Nanotechnology

*Lucas Reijnders*

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solvent

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**Summary**

The release of hazardous substances is a matter of concern for nanotechnology. This may include some nanoparticles, reactants, by-products, and solvents. The use of low-hazard solvents may reduce the hazards from nanoparticle production and nanomaterial processing. The hazards of inorganic nanoparticles may be reduced by modifying their chemical composition, surface characteristics, or structure. In nanomedicine, optimizing the balance between persistence and excretion and preventing the release of toxic degradation products may reduce hazard. In applications of fixed inorganic nanoparticles, the focus should be on preventing the release of such particles and of hazardous compounds during the product life cycle. When, after exhaustion of known hazard reduction options, significant hazard remains, other approaches merit consideration.

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## Introduction

Hazard (the potential to cause harm) is a matter of concern for nanotechnology. Discussions about hazards of nanotechnology partly deal with the release of hazardous substances (Hoet et al. 2004; Royal Society and Royal Academy of Engineering 2004; Oberdörster et al. 2005; Maynard 2006). These may include some nanoparticles. Nanoparticles are defined here as particles that have at least one dimension between 1 and 100 nanometers (nm). Also, some hazardous reactants, by-products, and solvents may be released. Opportunities for releasing hazardous substances may be identified through application of a life cycle approach to nanotechnology products (Reijnders 2006; Sweet and Strohm 2006).<sup>1</sup> This covers products from “cradle to grave,” or, in case of recycling, from “cradle to cradle.”

Maynard and colleagues (2006) have called for the development of models to predict the potential impact of engineered nanomaterials on the environment and human health, as well as for the use of predictive models to engineer nanomaterials that are safe by design. Several ways to reduce the hazards to human health of substances linked to nanotechnology can already be suggested.

It seems likely that such health hazards will be similar in the case of mammals, but little can be said about hazards of nanomaterials to other kinds of environmentally relevant species, because few reliable data relevant to the impact of nanomaterials on such species are available (Borm et al. 2006). This article focuses on reducing human health hazards on the basis of the available research, although several references will be made to ecotoxicity, on the basis of laboratory experiments.

As to human health hazards of nanoparticles, the following can be noted. Inhalation exposure to inorganic nanoparticles may negatively affect lungs due to interactions between lung tissue and nanoparticles, including oxidative stress leading to pulmonary inflammation (Oberdörster et al. 2005; Borm et al. 2006; Kreyling et al. 2006; Maynard et al. 2006). Pulmonary inflammation may trigger systemic inflammation, which, in turn, may lead to cardiovascular disease (Kreyling

et al. 2006). Nanoparticles may also be translocated from the lungs to the circulatory system and thereby increase the risk of cardiovascular disease (Oberdörster et al. 2005; Borm et al. 2006; Maynard et al. 2006). Furthermore, nanoparticles may be translocated from the nasal region of the respiratory tract to the brain via the olfactory bulb (Oberdörster et al. 2005; Maynard 2007). Ingestion of some inorganic nanoparticles may negatively affect the intestines due to immune reactions and possible translocation from the intestines to other organs, carrying an inflammation hazard (Reijnders 2007). Dermal exposure to nanoparticles may be hazardous when such particles are photocatalytically active and can penetrate into the living part of the skin (Reijnders 2006; Maynard 2007).

The actual hazards of nanoparticles are variable, depending on characteristics of the specific nanoparticle. This article discusses the human health hazards of nanotechnology within two major areas where humans may be exposed to hazardous substances: the production of nanoparticles and processing of nanomaterials, and the application of nanoparticles in products.

Production and processing, including the associated handling, packaging, transport, maintenance, and cleanup activities, may lead to the release of and exposure to nanoparticles. Inhalation is an important exposure route for workers, though ingestion and dermal exposure may also be relevant (Maynard 2006; Ostiguy et al. 2006; Sweet and Strohm 2006). Poor efficiencies in producing nanoparticles can result in releases of nonproduct nanoparticles (e.g., spills, waste, off-specification products, emissions). Moreover, hazardous solvents and reactants are applied in a variety of nanoparticle production and processing technologies (Vayssieres et al. 2002; Price et al. 2005; Shen et al. 2005).

Nanoparticles may also be hazardous in some product applications, especially those in which the nanoparticles are inherently dispersive, as those applications will inevitably lead to the exposure of nanoparticles to organisms (Maynard 2006; Reijnders 2006; Sweet and Strohm 2006). Such exposure may include inhalation, dermal contact, and ingestion. Inherently dispersive applications may include drugs, fuels, disinfectants, personal care products, lubricants, and

environmental remediation. Other applications use fixed nanoparticles. In these applications, hazard depends on what will happen to the nanoparticles during the product life cycle. For example, during attrition, cleaning, or recycling, hazardous nanoparticles and compounds may be released (Reijnders 2006).

### **Hazard Reduction During Nanoparticle Production and Processing**

A wide variety of processes exist for producing nanoparticles, including a variety of gas- and solvent-based processes.<sup>2</sup> Nanoparticles may be “grown” on templates or produced, for example, by grinding or the use of ultrasound (sonication). Depending on the process, nanoparticles, reactants, solvents, and gases may be released. Often, there is further processing (e.g., purification, functionalization, disaggregation, coating, and assembly) of nanomaterials, which may lead to additional releases of hazardous substances. End-of-pipe technologies aimed at treating waste streams to control emissions add to the cost of production and may still allow for substantial releases of nanoparticles (Maynard and Kuempel 2005; Ostiguy et al. 2006; Reijnders 2006; Kim et al. 2007).

Exposure of workers to airborne nanoparticles has been studied. One way to reduce such exposure is to isolate and enclose processes, workstations, and handling in rooms that are ventilated in a way that prevents contamination of other workplaces. This may be successful in reducing worker exposure and risk (Maynard and Kuempel 2005; Maynard et al. 2006). Exposure may still occur during packaging, maintenance, cleaning, waste handling, and recovery, however (Maynard et al. 2006). Thus, other options for hazard reduction should be considered, including options for lowering the hazard of released substances.

The hazard of released inorganic nanoparticles to human health depends on a number of characteristics, including persistence in the body, surface characteristics (area, charge, structure, and chemistry, including solubility of substances in water), shape and spatial (e.g., crystal) structure, aggregation, and porosity (Ding et al. 2005; Maynard and Kuempel 2005; Oberdörster et al.

2005; Borm et al. 2006; Kreyling et al. 2006; Magrez et al. 2006; Reijnders 2006; Sweet and Strohm 2006; Maynard 2007). The toxicity of degradation products may also influence the hazard. Wide variations in these characteristics suggest that there may be wide variations in the hazard of nanoparticles. Changes in these characteristics may reduce the hazard and will be discussed in the next section.

One way to reduce the risks of nanoparticle production and processing is to limit nonproduct outputs or wastes from such activities, which, in turn, limits the potential for releases. This has added importance when nonproduct outputs are more hazardous than products. This may, for instance, occur in arc-discharge synthesis of single-walled carbon nanotubes. For this type of synthesis, it has been shown that the smallest fractions produced, which are nonproduct outputs of the synthesis, were much more toxic to an estuarine meiobenthic copepod than the product output of the synthesis (Templeton et al. 2006). Also, there is evidence that high levels of iron in nonpurified single-walled carbon nanotubes leads to an increased human health hazard, when compared with purified nanotubes, which are characterized by a lower level of iron (Kagan et al. 2006).

In contrast to the suggestion that the precision of nanotechnology is conducive to eliminating waste products (Myers 2006), processes for producing nanoparticles with narrow product specification often generate relatively large nanoparticulate nonproduct outputs. For instance, a gas-phase synthesis of nanoparticles claimed to be “tailor-made” generates particles with a size distribution spanning at least one order of magnitude (Gutsch et al. 2005). As to the production of semiconducting nanotubes, all current synthesis methods generate both semiconducting and metallic nanotubes (Yan et al. 2007). The synthesis of single- and multiwalled carbon nanotubes typically results in the production of amorphous carbon, fullerenes, graphite, and transition metal catalyst particles as well (Rao 2005; Vivekchand et al. 2005; Suzuki et al. 2006). These “impurities” necessitate purification, which tends to be a multistep procedure (Rao 2005; Vivekchand et al. 2005; Suzuki et al. 2006).

Increasing the efficiency of producing nanoparticles according to specification is

important in reducing hazardous nonproduct outputs. Some technologies may be better in this respect than others. For example, better control of nanofiber growth in gas-phase production is possible when catalytic chemical vapor deposition techniques are used (Melechko et al. 2005). Flow focusing<sup>3</sup> may better control the size distribution in the production of nanoparticles (Martin-Banderas et al. 2005). Hazards linked to further processing of synthesized nanofibers can, in part, be circumvented by the local synthesis of nanofibers (Englander et al. 2005). A catalyst-free method of producing single-walled carbon tubes might reduce the hazards linked to postsynthesis purification (Vivekchand et al. 2005).

It has also been suggested that solvent-based technologies for producing nanoparticles will result in lower nanoparticle releases than gas phase technologies or dry technologies in general (Gardea-Toresdy et al. 2002; Kinloch et al. 2003; Ostiguy et al. 2006). The alleged advantage of solvent-based processes, however, should be balanced against the hazards associated with production and processing inputs, such as solvents. This has given rise to the study of ways to reduce the use of hazardous solvents. Less hazardous approaches have been proposed in the context of metal, metal sulphide, and metal oxide nanoparticle production and the disaggregation of carbon-based nanoparticles.

First, approaches have been studied for synthesizing nanoparticles that contain metals using organisms such as bacteria, fungi, and plants (Gardea-Toresdy et al. 2002; Bansai et al. 2004; Bhattacharaya and Gupta 2005; Mandal et al. 2005; Gericke and Pinches 2006). Nanoparticles can be generated this way but tend to be characterized by limited uniformity of size and shape. Thus, many of the nanoparticles produced via organisms may be off-specification. This leads to relatively large nanoparticulate nonproduct outputs, which may be hazardous. There is some evidence that in subcellular systems, products may be more uniform in size and shape (Mao et al. 2004). This merits further research. Furthermore, some studies have focused on solvent replacements. Successful replacements studied so far are summarized in table 1.

## Hazard Reduction for Products With Inherently Dispersive Nanoparticles

Products with inherently dispersive nanoparticles will inevitably lead to organism exposure to nanoparticles. Such products usually contain ingredients other than nanoparticles. These ingredients may alter the hazard. Research on the penetration of quantum dots (a type of nanoparticle) into the skin has shown that penetration depends on whether the quantum dot is combined with polyethylene glycol, polyethylene glycolamine, or carboxylic acids (Ryman-Rasmussen et al. 2006). This suggests that the hazards of dispersive products may be reduced by judicious choice of ingredients.

To a considerable extent, the characteristics that make a nanoparticle useful may also make it hazardous. For instance, nanotubes have a number of useful applications, critically depending on their tubelike character, but a corollary thereof is that it may be more difficult for macrophages to safely engulf tubelike structures than, for example, amorphous carbon black nanoparticles (Lam et al. 2006). Nanosized silver is exploited for its bactericidal properties, and when the nanoparticles are released, those properties may be hazardous to benign bacteria. The performance of inorganic particles used as glidants in medicinal powders, cosmetics, and food products is better when these particles are smaller in size (Ohta et al. 2003; Meyer and Zimmermann 2004), and this limits the options for hazard reduction, because reduced size of glidants tends to increase hazard (Reijnders 2007).

It may be possible to lower specific human health hazards while meeting product requirements and using nanoparticles. In some cases, inherently dispersive inorganic nanoparticles may be replaced by fixed nanoparticles. A case in point is the dispersion of titanium dioxide ( $\text{TiO}_2$ ) nanoparticles to degrade hazardous substances in contaminated water. The immobilization of  $\text{TiO}_2$  nanoparticles on large inorganic supports that are not vulnerable to photocatalytic degradation reduces the potential hazard while enabling the  $\text{TiO}_2$  nanoparticles to effectively degrade hazardous substances (Reijnders 2008).

**Table I** Hazard reduction by solvent substitution

<i>Solvent substitute</i>	<i>Synthesis of nanoparticles containing metals</i>	<i>Disaggregation and derivatization of nanoparticles containing carbon</i>	<i>Reference</i>
Less hazardous organic solvents	Yes	No	Shen et al. 2005
Supercritical CO <sub>2</sub>	Yes	No	Matsuyama et al. 2003; Sui et al. 2006
Ionic liquids	Yes	Yes	Jiang and Zhu 2005; Z. Li et al. 2005; Price et al. 2005
Aqueous solutions in the presence of sugars and/or polysaccharides	Yes	No	Raveendran et al. 2003; Huang and Yang 2004; Sun et al. 2004; Sakai and Alexandridis 2005; Raveendran et al. 2006

When the dispersive nature of the application is maintained, there may still be scope for hazard reduction. For example, changing the crystal structure and chemical nature of glidants of a specific particle size may result in hazard reduction (Hussain et al. 2005; Sayes et al. 2006b). In the case of nanoparticles for medical applications, scientists can reduce hazard by optimizing the balance of persistence in the body (long enough to have the intended effects) and excretion (to limit unintended effects) and by preventing the release of toxic degradation products (Reijnders 2006). Also for nanomedicine, it has been found that hydrophilicity and neutral charge are conducive to low cytotoxicity and reduced inflammation (Vonarbourg et al. 2006).

Surface modification of inorganic nanoparticles has shown promise for hazard reduction in products that inevitably lead to exposure. Maintaining the surface modifications during the time when exposure may occur is crucial to achieving hazard reduction. A few examples illustrate the potential for hazard reduction by surface modification. The inflammation response to quartz can be much reduced when the quartz surface is modified with aluminum lactate (Duffin et al. 2002). Cytotoxicity of carbon nanotubes and fullerenes can be reduced by the introduction or removal of specific functional groups (Sayes et al. 2004; Dumortier et al. 2006; Magrez et al. 2006; Sayes et al. 2006a). As to cadmium selenide (CdSe) quantum dots, which may be used

for imaging, surface coatings (e.g., zinc sulfide [ZnS] and a variety of organic compounds) have been shown to significantly reduce cytotoxicity (Derfus et al. 2004; Hoshino et al. 2004; Hardman 2006) and endocytosis (Chang et al. 2006), whereas usefulness for imaging is maintained. Triethoxyoctylsilane coatings on pigment-grade titanium dioxide nanoparticles reduced the pulmonary toxicity of these particles to rats (Warheit et al. 2003). In sunscreens, TiO<sub>2</sub> and zinc oxide (ZnO) nanoparticles are applied in preference to larger particles of the same compounds, as the latter produce a white color, whereas nanoparticles are apparently transparent. TiO<sub>2</sub> and ZnO nanoparticles are photocatalytically active, however, which may cause damage to DNA and several other components in skin cells when the skin is not intact and may also be associated with relatively high ecotoxicity (Adams et al. 2006; Fond and Meyer 2006; Maynard 2006; Reijnders 2006). The photocatalytic characteristic, however, can be counteracted if the TiO<sub>2</sub> and ZnO nanoparticles are coated with silica or aluminum oxide. Experiments show that depending on the completeness of the coating, the photocatalytic activity of TiO<sub>2</sub> and ZnO can be reduced and the transparency of sunscreens retained (Q. Y. Li et al., 2005; El-Toni et al. 2006; Hong et al. 2006). Another approach to hazard reduction is the incorporation of dopant ions in photocatalytically active particles. The incorporation of manganese and vanadium ions

in titania nanoparticles at levels below 1 atom percentage has been shown to strongly reduce the capacity to damage DNA (Wakefield et al. 2004).

It may be that after exhaustion of known hazard reduction options, a significant hazard remains. In such cases, alternative approaches deserve consideration. For instance, in the case of nanoparticulate glidants, there are alternative glidants based on magnesium stearate and sodiumstearylfumarate (Ahmed 2005; Khanam and Nanda 2005).

### **Hazard Reduction When Nanoparticles Are Fixed in Products**

When nanoparticles are fixed in products, the possibility that hazardous substances may be released during attrition (i.e., wear, tear, and corrosion), product modification, recycling (e.g., grinding), or maintenance (e.g., cleaning) merits consideration.

Only limited information is available on losses of hazardous substances from products in which fixed nanoparticles are applied. A study on the application of nanosized bactericidal silver in textile fabrics did show that 60% of nanoparticle-linked bactericidal activity was lost after 20 washing cycles (Lee et al. 2003). It seems likely in this case that silver nanoparticles have been released. Hsu and Chein (2007) found a substantial release of TiO<sub>2</sub> nanoparticles from tiles and synthetic polymers coated with TiO<sub>2</sub> nanopowders when the products were subjected to conditions simulating sunlight, wind, and human contact. Automotive catalytic converters apply nanoscale platinum-group (Pt-group) metal particles (Lloyd et al. 2005), which may be emitted from catalytic converters during their use. In this case, Pt-group nanoparticles are often bound to micrometer-sized support particles (Merget and Rosner 2001; Ek et al. 2004; Ravindra et al. 2004; Dahlheimer et al. 2007). The extent to which Pt is soluble seems to be an important determinant of hazard of Pt particles, however, and there is some evidence that solubility may increase when the size of Pt nanoparticles in emitted micrometer-sized particles decreases (Ek et al. 2004). It also seems possible that part of the Pt emitted from

catalytic converters is emitted as nanoparticles (Merget and Rosner 2001; Ravindra et al. 2004). A final example is the use of TiO<sub>2</sub> nanoparticles in "transparent" paints. In this case, there is no evidence of hazard when TiO<sub>2</sub> nanoparticles are contained in a hardened layer, but the hazard might be significant when such a layer is sanded (Overbeke 2007).

From these examples, it seems that hazard reduction efforts should focus on reducing the release of inorganic nanoparticles and hazardous compounds during a product life cycle. Again, when, after exhaustion of known hazard reduction options, significant hazard remains, alternative approaches merit consideration.

### **Concluding Remarks**

Available research shows a number of useful approaches for hazard reduction. More research is necessary to fully understand the potential for hazard reduction and to keep up with the rapid increase in nanotechnology applications, however. Hazard reduction may be constrained by application requirements, which drive the development and use of nanoparticles. It may be that after exhaustion of known hazard reduction options, significant hazard remains.

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### **Notes**

1. Editor's note: For discussions of the application of life cycle assessment (LCA) to nanotechnology, see the contributions by Seager and Linkov (2008) and Shatkin (2008) in this issue.
2. Editor's note: A review of nanomanufacturing methods and some of their environmental impacts can be found in an article by Şengül and colleagues (2008) in this issue.
3. Flow focusing combines hydrodynamic forces and specific geometry to force a fluid stream to flow through a small orifice. As the jet exits the orifice, it breaks up into homogeneous droplets in the micro and nanometer range (Martin-Banderas et al. 2005).

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