Nanomaterials: health effects and legislation

Efectos de los nanomateriales en la salud y su normatividad

Hugo Ricardo **Zea**[1]

RESUMEN

La forma como los materiales nanométricos interactúan con sistemas biológicos es poco conocida, y aunque los beneficios de algunos nanomateriales son evidentes también existe la posibilidad de que algunos puedan ser nocivos para la salud y el medio ambiente; sin embargo, la información científica sobre los efectos de los nanomateriales en estos ámbitos es escasa. Este documento hace una breve descripción de los efectos en la salud de los nanomateriales y los desarrollos legislativos concernientes a su regulación.

Palabras clave: nanomateriales, efectos sobre la salud, legislación.

ABSTRACT

The mechanisms by which nanomaterials interact with biological systems is not well understood and although the benefits of some nanomaterials are evident, some offset effects on health and the environment may occur; however, scientific information is scarce. This document gives a brief description of the effects of nanomaterials on health and the current tendencies in developing the pertinent regulations.

Keywords: Nanomaterials, health effects, legislation.

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Introduction

The International Organization for Standardization (ISO) defines a nanoobject as being a material having at least one of its three external dimensions in the nanoscale order (from 1 to 100 nm); many products making use of nanomaterials' properties are already available on the market, therefore being in direct contact with and manipulation by consumers. A mass entrance onto the market of products which include nanomaterials in their formulation is expected in the coming years (pharmaceutical products, elements for diagnosis, electronics, production and energy storage) (Lu *et al*., 2009; Sahaym and Norton, 2008). These new advances' economic impact has been considered in billions of dollars; such impact is estimated at being around 450 billion dollars for 2015 just in the electronics industry (Hullmann, 2007; Kobayashi, 2004; Losch, 2006; Luther *et al*, 2005). A common challenge for all emerging technologies is to identify potential risks during the early development stages and not at more advanced stages when remediation efforts prevail over prevention procedures.

The mechanisms by which nanometric materials interact with biological systems are not well understood and, although the benefits of some nanomaterials are evident, some of them could be dangerous and risky to human health. Existing knowledge about nanomaterials' toxicity is limited; some studies have been performed to understand potential health risks according to nanomaterials' exposure route (inhalation, skin contact, ingestion), for example, it has been determined that certain types of carbon nanotubes can cause lung cancer if inhaled (Muller *et al*., 2005); nevertheless, most of the health risks which nanomaterials could cause are subject to current investigation (Table 1 summarises some of the results).

Inhalation

Inhalation is the most frequent route for exposure to nanomaterials and the resulting effects are closely related to inhaled material particle size; dispersed particles having an average size smaller than 100 nm have greater toxicity than aggregates of the same nanomaterial (300 to 700 nm) (Canoe *et al*., 2004; Shvedova *et al.*, 2006). Available information indicates that the percentage of nanometric particles in the 10 to 90 nm range deposited in the pulmonary alveoli increases from 26% to 47% whilst percentage decrease for particles bigger than 100 nm; in terms of particle deposition in the bronchial zone, this percentage decays continuously with increased particle size (Oberdorster *et al*., 1994). Other studies have established that the effect of inhaled particles not only depends on the amount of inhaled particles but also on their surface area (Driscoll *et al.*, 1997; Oberdorster and Yu, 1999). Human exposure-related literature is scarce due to restrictions on carrying out experimental studies; an important source of information regarding the effects of nanomaterials in human health can be obtained from production units and factories' occupational health reports; e.g. printer ink cartridge factory workers developed severe damage in their lungs by inhaling nanoparticles; analysis of samples taken from the workers' lungs showed pleural granulomas, fluid accumulation and the deposition of particles of about 30 nm, both in pleural membranes and in fluid extracted from lungs.

Studies on rats led to determining that nanoparticles having around 40 nm diameter may lodge in lung walls and migrate to the circulatory system; such particles deposited on the nasal inner tissue

[1] Chemical Engineer, Universidad de América, Colombia. MSc in Chemical Engineering, Universidad Nacional de Colombia, Colombia. PhD in Chemical Engineering, University of New Mexico. Associated Professor Universidad Nacional de Colombia. E-mail: hrzear@unal.edu.co

Material	Exposure	Effect	Reference
Titanium dioxide	Inhalation	Lung membrane inflammation	Sager et al., 2008, Warheit et al., 2007 Warheit et al., 2009
SWCNT	Inhalation	Lung membrane inflammation, breathing deficiency, reduction of immunologic capacity	Mercer et al., 2008 Shvedova, et al., 2005 Shvedova et al., 2003
CNT	Inhalation	Lung membrane inflammation, development of malignant cells in lungs walls	Poland et al., 2008 Takagi et al., 2008
Fullerenes	Inhalation	No reported effects	Baker et al., 2008
Iron oxide	Inhalation	Accumulation in the olfactory bulb	Saba et al., 2010
Nickel	Inhalation	Lung membrane inflammation, accumulation in some organs beyond the respiratory system	Ispas, et al., 2009 Kang, et al., 2011
Quantum dot Qdot 655	Skin contact	Epidermis penetration, inflammation of subcutaneous layers	Ryman-Rasmussen et al., 2006)
Quantum dot Qdot 566	Skin contact	Epidermis penetration	Ryman-Rasmussen et al., 2006
CNT	Skin contact	Epidermis inflammation, penetration of cell membrane	Monteiro-Riviere et al., 2005 Murray et al., 2007 Shvedova, et al., 2003
Nickel	Skin contact	Penetration of cell membrane	Ispas et al., 2009
Titanium dioxide	Ingestion	Cytotoxic effects on digestive system cells, modifying DNA molecular structure, damaging effects to liver and small intestine walls	Dybdahl et al., 2003 Moos et al., 2010 Trouiller et al., 2009 Wang et al., 2006 Wang et al., 2007
Zinc oxide	Ingestion	Cytotoxic effect on digestive system cells, modification of DNA molecular structure, growth delay, renal injury and anaemia	Dybdahl et al., 2003 Moos et al., 2010 Trouiller et al., 2009 Wang,et al., 2006, Wang et al., 2007
Vanadium oxide	Ingestion	Cytotoxic effect on digestive system cells, modification of DNA molecular structure	Dybdahl et al., 2003 Moos et al., 2010 Trouiller et al., 2009 Wang et al., 2006 Wang et al., 2007

migrate directly into the brain through the olfactory nerve (Aust *et al*., 2009; Geyser *et al*., 2005; Harder *et al*., 2005; Warheit *et al*., 2009). Experimental studies on mice have demonstrated that insoluble doses of nanoparticles have a bigger impact on health than equivalent doses of the same material aggregate in larger diameter particles causing pulmonary inflammation, pulmonary membrane damage and tumours (Barlow *et al*., 2005; Heinrich *et al*., 1995; Lee *et al*., 1985; Oberdorster *et al*., 1992; Oberdorster *et al*., 1994; Oberdorster and Yu, 1990; Renwick *et al*., 2004).
Ultra-fine TiO_2 (anatase) particles have been shown to be highly active in terms of pulmonary membrane inflammation; nevertheless, the effect of particles smaller than 2 μm was not established, given individual ultra-fine particles' tendency to become aggregated in the pulmonary membrane (Sager *et al*., 2008); other reports have concluded that the main incidence for pulmonary tumours caused by inhaling 20 to 300 nm TiO_2 particles has been observed for 20 nm particles (10 mg/m3 concentration) even if 300 nm particle concentration were 25 times bigger (250 mg/m^3) (Heinrich *et al*., 1989; Lee *et al*., 1986).

Carbon nanotubes (CNT) represent another substance requiring special attention given their large number of applications. Scientific publications have reported granuloma formation and pleural inflammation in rats and mice exposed to CNT-contaminated atmospheres; these results also indicated that once CNT have reached the lungs, their toxicity is higher than that of comparable materials like charcoal and quartz (Lam *et al*., 2004; Service, 2003; Warheit *et al*., 2004). Special types of CNT are those constituted by a single wall (SWCNT) which when supplied to mice by inhalation in doses varying from 0.5-2 mg/kg had a high incidence regarding pulmonary membrane inflation, respiratory deficiency, reduced immunological capacity and some cases of pleural fibrosis during the first 7 days' exposure (Mercer *et al*., 2008; Shvedova *et al*., 2005). The same studies led to concluding that SWCNT particles having an average 100 nm diameter did not behave as asbestos particles, as has been hypothesised previously (Takagi *et al*., 2008); studies published by the US National Institute for Occupational Health and Safety (NIOSH) established that only a small fraction of the CNT present in air are in fact inhaled during breathing (Maynard *et al*., 2004).

Skin contact

Skin exposure to nanomaterials essentially takes place during handling and manipulating consumer products formulate to be applied directly to the skin (cosmetics, sun block, topical medicine). The skin is constituted by three layers: the epidermis, dermis and subcutaneous layer. There is also an external layer of dead cells constituting the uppermost section of the epidermis called "*stratum corneum*" (SC); these dead cells become the skin's first barrier and protection against external agents. Most of the available literature regarding nanomaterials interaction with the skin has been focused on determining whether pharmacological formulations are able to penetrate through the skin. TiO_2 particles are a main component of solar radiation protection products; several studies have demonstrate that TiO_2 micron size particles are able to penetrate the SC but do not cross into the dermis' most inner layers (Lademann *et al*., 1999); however, particles of the same material in sizes ranging from 5-20 nanometers penetrate all the skin's layers and interact with the immunological system (Hosmer *et al*.).

Additional factors besides those inherent in the properties of nanomaterials in contact with the skin (dose, vehicle, reactivity)

have been considered important variables in determining their effects (skin age, anatomical exposure site, wounds or exposed lacerations, etc.). Experimental evidence has proved that wounded skin facilitates nanomaterial migration into the inner layers, especially at sites of the body where the skin tends to be thin (Hostynek 2003); smaller nanomaterials penetrate deeper into the skin's layer than bigger particles (Mossman and Sesko, 1990). Some studies have suggested that nanomaterials could penetrate the skin during prolonged occupational exposure (Hoet *et al*., 1999). There is no certainty whether nanomaterial penetration through skin causes detrimental health effects; however, specific studies on mice regarding the application of topical formulations containing SWCNT have caused skin irritation (Fischer *et al*., 2003). *In vitro* studies using human epithelial cells have demonstrated that both CNT and SWCNT penetrate and damage the cell membrane (Morgan *et al*., 1988).

Ingestion

Determining nanomaterials' effects on health regarding the digestive system has become an important issue lately as many processed food products contain nanoscale ingredients in their preparation, besides food becoming contaminated with nanomaterials by coming into contact with surfaces containing them (packaging material, kitchen utensils, etc.). Such nanoparticle materials might be able to accumulate in organs like the kidneys and the liver. Although nanoparticle absorption in the gastrointestinal apparatus is apparently low, health risks due to ingested nanomaterials have still not been clearly determined and are extremely dependent on nanomaterial's inherent characteristics (size, surface structure, chemical composition). Little data is available regarding nanomaterials' toxic or inflammatory potential; it has been reported that vanadium nanometric oxide particles have cytotoxic effects on digestive system cells; similar effects have been reported for zinc oxide nanometric particles (Moos *et al*., 2010). Some studies on rats and mice have demonstrated damage to DNA molecular structure and high nanoparticle toxicity for several types of materials; the most affected organs have been the liver and small intestine inner walls (Dybdahl *et al*., 2003). The oral administration of high doses (5 g Zn/kg) of ZnO nanoparticles has caused growth delay during the first days of treatment, accompanied by collateral effects such as renal damage, anaemia and the death of two of the case studies (Wang *et al*., 2006); the same authors have reported hepatic and renal injuries when oral administration was replicated using TiO_2 nanoparticles (Trouiller *et al*., 2009; Wang *et al*., 2007).

Legislation

The efficacy of any effort to regulate chemical substances is based upon a solid knowledge of the materials covered by such regulation; unfortunately, there is still great uncertainty regarding nanomaterials concerning these materials' potential risks, mainly due to the absence of appropriate standardised tests and procedures for determining such risks. Despite the lack of such knowledge, a lack of specific regulation for characterising the risks involved, health consequences and effects on the environment, some authors have identified three fundamental challenges in creating legislation for regulating nanomaterials: obtaining agreement for defining nanomaterial, determining whether current legislation can be adapted or whether a new regulatory framework must be created and defining whether nanomaterials should be considered as different material from their macroscopic counterpart having the same molecular structure (Chaundry *et al*., 2006).

Regarding the first challenge, the European organisation in charge of registering, evaluating, authorising and regulating chemical materials (REACH) defines nanomaterial as an insoluble or biopersistent material, intentionally manufactured with one or more of its external dimensions (or incorporated in its internal structure) in the 1 to 100 nm scale (Monica, 2008.). The USA initiative for nanotechnology shares the same definition proposed by REACH; however, it also includes nanomaterials available in nature besides intentionally manufactured ones. Organisations such as the American Chemical Society (ACS) and the International Organisation for Standardisation (ISO) have proposed their own definitions which sometimes come into conflict and emphasise the need for obtaining consensus on a definition leading to creating and implementing appropriate and effective regulation (Boxall *et al*., 2008; Monica, 2008).

The second challenge is related to determining whether existing regulation can be adapted to nanomaterials' unique characteristics; an important group of regulatory organisations have adopted an incremental approach, assuming that current chemical substances' regulation can be adapted and, in some specific cases, modified to include nanomaterials; nevertheless, some authors have argued that nanomaterials' special characteristics demand new and specific regulation. A possible complication arising from the use of such incremental approach would be the constant implementation and/or regulatory adaptation of addenda, which could make its application troublesome and confusing.

The third challenge concerns defining whether nanomaterials' physical-chemical and toxicological characteristics are equivalent to those of material having the same chemical composition but above the scale defined for nanomaterials. This definition would have a fundamental impact on producers and manufactures fulfilling requirements before marketing any nanomaterial (Chaundry *et al*., 2006). If nanomaterial is classified as being a substance different from its macroscopic counterpart having the same molecular structure in the USA, then current regulation would require that a producer has a pre-manufacture note (PMN) which must be sent to the Environmental Protection Agency (EPA) before such material is produced in any amount different to that intended for research and development; this PMN must include information about environmental impact and toxicity (Hansen *et al*., 2008; Hansen SF, 2008). The European Community has decided to assume that nanomaterials are covered by the definition of chemical substances currently approved by REACH, with the following reservation that when an existing chemical substance already being marketed in bulk is introduced on the market in the form of nanomaterial, then the material safety data sheet (MSDS) must be modified to include the specific characteristics of such substance as nanomaterial (Hansen *et al*., 2008).

Any new regulation must be based upon fundamental principles such as health and environmental protection, innovation and high level of participation of the bodies involved (regulating agencies, research entities, producers, consumers). Toxicological test results must contain degradation, accumulation, as well as recommendations about labour and environmental exposure as minimum information regarding physical-chemical characteristics to ensure the protection of health and the environment. The need to make manufacturers and producers responsible for nanomaterial throughout its whole life-cycle also becomes clear (Hansen and Tickner, 2008).

Conclusions

Although information related to nanomaterials' effects on health is scarce, an important increase in related scientific literature has been identified. It is clear that nanomaterials can penetrate most of the body's protective membranes and accumulate in diverse organs. Inhalation has been the most studied exposure route whilst the effects of skin contact and ingestion have not received the same detailed research. Overall effects can vary from simple irritation to tumour formation and DNA molecular modification. A special characteristic of nanomaterials is that their toxicity seems to be closely related to their surface area. Future work must concentrate on obtaining a definition of nanomaterial. It must be determined whether current legislation can be adapted or whether a new regulatory framework must be created, and it must be defined whether nanomaterials should be consider as different material from their macroscopic counterparts having the same molecular structure (Chaundry *et al*., 2006).

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