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**Applications and implications of nanotechnologies for the food sector**

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**Abstract**

A review of the current and projected nanotechnology derived food ingredients, food additives, and food contact materials is presented in relation to potential implications for consumer safety and regulatory controls. Nanotechnology applications are expected to bring a range of benefits to the food sector, including new tastes, textures and sensations, less use of fat, enhanced absorption of nutrients, improved packaging, traceability and security of food products. The review has shown that nanotechnology derived food and health food products are set to grow worldwide, and a variety of food ingredients, additives, carriers for nutrients and supplements, and food contact materials is already available in some countries. The current level of applications in the European food sector is at an elementary stage, however, it is widely expected that more and more products will be available in the EU in the coming years. The toxicological nature of hazard, likelihood of exposure, and risk to consumers from nanotechnology derived food/ food packaging are largely unknown, and this review has highlighted major gaps in knowledge that require further research. A number of uncertainties and gaps in relevant regulatory frameworks have also been identified, and ways of addressing them proposed.

**Keywords:** Nanotechnology, Nanoparticles, Food, Food Additives, Food Packaging, Consumer Safety, Regulatory Frameworks

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## Introduction

Within the past few decades, the evolution of a number of new science disciplines and technologies has revolutionised the food sector. Most notable among these are biotechnology, cognitive sciences, information technology (IT), and more recently nanotechnology, which is a broad interdisciplinary area of research, development and industrial activity that involves the manufacture, processing, and application of materials that have one or more dimensions of the order of 100 nanometers (nm) or less (BSI 2005 [Internet]). Nanotechnology is an enabling technology that has opened up new avenues of R&D in a number of fields including medicine, cosmetics, agriculture and food; and is being used as a means to understand how physicochemical characteristics of nano-sized substances can change the structure, texture and quality of foodstuffs. Convergence of nanotechnology with other technologies is also leading to further innovations that are expected to make a major impact on production, processing, storage, transportation, traceability, safety and security of food. For example, integration of biotechnology, nanotechnology, and IT has opened up new opportunities for the development of nano biosensors for the detection of pathogens and contaminants in food. Such integration of technologies, combined with understanding of taste receptors and flavour perception, is leading to the development of 'electronic tongue' for describing the taste attributes of food. Indeed, the manipulation of substances so close to the molecular level has blurred the boundaries between a number of traditional food science disciplines, and opened up ways for the development of new food textures, tastes, and sensations.

The applications of nanotechnology in the food sector are only new emergent, but they are predicted to grow rapidly in the coming years. Many of the world's largest food companies are reported to have been actively exploring the potential of nanotechnology for use in food or food packaging (Cientifica 2006 [Internet]; The Sunday Telegraph 2006). Applications in this area already span development of improved tastes, colour, flavour, texture, and consistency of foodstuffs, increased absorption and bioavailability of nutrients and health supplements, new food packaging materials with improved mechanical, barrier and antimicrobial properties, and nano-sensors for traceability and monitoring the condition of food during transport and storage.

The rapid proliferation of nanotechnologies in a wide range of consumer products has also raised a number of safety, environmental, ethical, policy and regulatory issues (ETC Group report 2003 [Internet], Royal Society and Royal Academy of Engineering 2004 [Internet], Maynard et al. 2006). The main concerns stem from the lack of knowledge with regard to the interactions of nano-sized materials at the molecular or physiological levels, and their potential effects and impacts on consumer's health and the environment. The

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nanotechnology-derived foods are also new to consumers, and it remains unclear how public perception, attitudes, choice and acceptance will impact the future of such applications in the food sector. It is, however, well known that uncertainties and lack of knowledge of potential effects and impacts of new technologies, or the lack of a clear communication of risks and benefits, can raise concerns amongst the public. A recent example is the negative public reaction in the EU to GM crops and GM food. In this context, concerns have already been raised over application of nanotechnology for food (for example ETC Group Report 2004 [Internet]). It is, therefore, important that an appraisal of potential consumer safety and regulatory implications is carried out in the face of actual or potential applications of nanotechnology in the food sector. This paper is aimed at providing a state-of-the-art review of current and projected processes, products and applications of nanotechnology in the food sector, potential implications of such developments in relation to consumer safety, and whether the existing EU food laws and associated regulatory frameworks are adequate to control any such risks.

*Sources of information*

As part of this review, extensive searches for relevant information were carried out using a variety of sources for published literature, relevant company websites, and patent databases. The international inventory of nanotechnology consumer products developed by the Woodrow Wilson Institute [Internet] was accessed for information on the available consumer products in the food, drinks and related sectors. In addition, the CSL database of nanomaterials manufactured and used in the UK was also used for gathering information on relevant materials and applications (CSL Nanomaterials Database [Internet]). Other sources of information included key reports, such as from the Institute of Nanotechnology (Joseph and Morrison 2006 [Internet]), and the Institute of Food Technologists (Weiss et al. 2006), and a recent market analysis report from Cientifica (2006). Up-to-date information was also gathered at the first European International Workshop “*Nano and Micro Technologies in the Food and HealthFood Industries*’ (October 2006, Amsterdam); the “*Nanotoxicology Conference*”, (April 2007, Venice, Italy); the “*2007 CSL/JISFAN Joint Symposium on Food Safety and Nutrition – Nanotechnology in Foods and Cosmetics*” (June 2007, Greenbelt MD, USA); and the *Food Contact Plastics* Conferences (June 2006 and 2007, Brussels).

*Market drivers for nanotechnology applications*

For centuries, foods have been processed to enhance storage (preservation), texture, flavour, taste, and nutritional value, and to ensure microbiological safety. Most modern-day

foods undergo a variety of industrial and domestic processes before being eaten, e.g. heat-treatment, fermentation, acid-hydrolysis, kilning, curing, smoking and drying. The food industry is ultimately driven by profitability, which is consequent on gaining consumer acceptance by offering added-value in terms of quality, freshness, new tastes, flavours, textures, safety or reduced cost. The food industry is also looking out for new technologies to improve the nutritional value, shelf-life, and traceability of their food products. They are also aiming to develop improved tastes, reduce the amount of salt, sugar, fat and preservatives, address food-related illnesses (e.g. obesity and diabetes), develop targeted nutrition for different lifestyles and aging population, and maintain sustainability of food production, processing, and food safety (Cientifica 2006 [Internet]). A number of new processes and materials derived from nanotechnology can provide answers to many of these needs, as they offer the ability to control and manipulate properties of substances close to molecular level. For example, in terms of increasing the absorption of nano-sized nutrients and supplements and therefore enhancing the nutritional value of food, development of new tastes and sensations, and creamier textures through nanostructuring of food ingredients with less (or no additional) fat. It is therefore not surprising that one of the fastest moving sectors to embrace new technologies, such as nanotechnology, to realise the potential benefits is the food industry.

Many of the current nanotechnology applications in the food sector appear to have emerged from related sectors, such as pharmaceutical, cosmetics and nutraceuticals. The boundaries between food, medicine and cosmetics, are already obscure, and the advent of nanomaterials, which can interact with biological entities at a near-molecular level, is likely to further blur these boundaries. Some food and cosmetic companies are known to be collaborating to develop cosmetic nutritional supplements (Cientifica 2006 [Internet]).

Nanotechnology in recent years has developed into a wide-ranging, multibillion-dollar global industry. The global market impact of nanotechnology is widely expected to reach 1 trillion US\$ by 2015, with around 2 million workers (Roco and Bainbridge 2001). It is also clear from a number of reports, reviews, patent applications, and company products that applications of nanotechnology have also started to make an impact on different aspects of the food and associated industries (Chen et al. 2006). The nanofood sector (the term refers to the use of nanotechnology techniques, materials or tools for production, processing, or packaging of food) is currently led by USA, followed by Japan and China. However, Asian countries (led by China) are expected to be the biggest market for nanofood by 2010 (Helmut Kaiser Consultancy report 2004 [Internet]).

Estimates of the current global market size and the number of companies involved in the nanofood sector are varied. This reflects the difficulty in obtaining the exact information due

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to commercial and environmental sensitivities. Such sensitivities have led to a number of major food corporations, who had been until a few years ago at the forefront of food nanotechnology R&D, to disassociate themselves from publicity in this field, and becoming very protective of their activities in this area. Furthermore, a lot of the currently available information is aimed at projecting the 'magical potential' of nanotechnologies when applied to food or food packaging, rather than 'real' products and applications that are available now or in a few years time. This review has, therefore, scrutinised the information objectively with the aim of separating fact from fiction, and considered those products and applications that are identifiable, i.e. either currently available or in the R&D pipeline.

A recent report by Helmut Kaiser Consultancy has estimated that the nanofood market would have grown to US\$7 billion in 2006, and would reach US\$20.4 billion by 2010 (Helmut Kaiser Consultancy 2004 [Internet]). Another report, by the consulting firm Cientifica (2006), has valued food applications of nanotechnologies at around US\$410m (food processing \$100m, food ingredients \$100m, and food packaging \$210m). According to the report, the current applications are mainly for food packaging (improved barrier properties etc), with some applications for delivery systems for nutraceuticals. The report estimated that by 2012 the overall market value would reach \$5.8 billion (food processing \$1303m, food ingredients \$1475m, and food safety \$97m, and food packaging \$2930m).

It has been suggested that the number of companies currently applying nanotechnologies to food could be as high as 400 (Cientifica 2006 [Internet]). A number of major food and beverage companies are reported to have (or have had) an interest in nanotechnology. These include Altria, Nestle, Kraft, Heinz, and Unilever, as well as small nanotech start-up companies (Cientifica 2006 [Internet]). It is also widely anticipated that the number of companies applying nanotechnologies to food will increase dramatically in the near future. Considering such rapid developments in this field, and the global setup of international food companies, it is not unreasonable to anticipate that more nanofood products will appear on the EU markets within the next few years.

**Current and projected applications of nanotechnology for the food sector**

Although nanotechnology applications for the food sector are relatively recent, there have been rapid developments in this area in recent years. The main developments so far been aimed at altering the texture of food components, encapsulating food components or additives, developing new tastes and sensations, controlling the release of flavours, and/or increasing the bioavailability of nutritional components. For food packaging applications, such developments have led to new materials with improved mechanical, barrier, and



antimicrobial properties. Broadly, the currently known and projected applications of nanotechnology for the food sector fall into the following main categories:

- Where food ingredients have been processed or formulated to form nanostructures;
- Where nano-sized, nano-encapsulated, or engineered nanoparticle additives have been used in food;
- Where nanomaterials have been incorporated to develop improved, 'active', or 'intelligent' materials for food packaging;
- Where nanotechnology-based devices and materials have been used; e.g. for nanofiltration, water treatment, nanosensors for food safety and traceability.

This study has indicated that virtually all known applications of nanotechnology in food and food packaging are currently outside the UK, mainly in the USA, Australia, New Zealand, South Korea, Taiwan, China and Israel. The information gathered as part of this study has not identified any UK or EU food company that has declared, or is currently known to be, using nanofood ingredients or additives in their products. The only exceptions are the synthetic form of the tomato carotenoid lycopene (from BASF Germany [Internet]) for addition to soft drinks and other food products, and the nano-micelle based carrier system NovaSOL® from Aquanova® Germany [Internet] for introduction of antioxidants and supplements in food and beverage products. The NovaSOL® technology, which is based on "product micelles" with a diameter of around 30 nm, has been applied to develop a range of solubilisates. Example applications include food additives such as benzoic acid, citric acid, and ascorbic acid, dietary supplements and functional food ingredients such as vitamins A and E,  $\alpha$ -lipoic acid, soybean isoflavones,  $\beta$ -carotene, lutein, omega-3 fatty acids, and coenzyme Q10. Despite the fact that currently there are only a handful of food and nutrition products containing nano- ingredients or additives that are available commercially, more than 150 products are reported to be under development (Cientifica 2006 [Internet]).

#### *Nanotechnology applications for food ingredients and additives*

A major focus of current nanotechnology applications in food is the development of nanostructured (or nanotextured) food ingredients and delivery systems for nutrients and supplements. For this, a variety of processes are being utilised, including nano-emulsions, surfactant micelles, emulsion bilayers, and reverse micelles (Weiss et al. 2006). The nanostructured food ingredients are being developed with the claims that they offer improved taste, texture, and consistency (Cientifica 2006 [Internet]). For example, low-fat



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nanostructured mayonnaise, spreads and ice creams claim to be as ‘creamy’ as their full fat alternatives and hence offer a healthier option to the consumer.

A number of nano-micelle based carriers for nutraceuticals and nutritional supplements are currently available (The Woodrow Wilson Nanotechnology Consumer Products Inventory [Internet]). In addition to Novasol® from Aquanova® Germany [Internet], these include Nano-structured supplements based on “Nano-Sized Self-assembled Liquid Structures (NSSL)” from NutraLease Ltd. Israel [Internet], and NanoCluster™ delivery system for food products from RBC Life Sciences® Inc. USA [Internet].

BioDelivery Sciences International [Internet] have introduced their Bioral™ nanocochleate nutrient delivery system for micronutrients and antioxidants. The nanocochleates (~50 nm in size) are based on phosphatidylserine carrier derived from soya bean, generally regarded as safe (GRAS). The “cochleates,” after the Greek name for a snail with a spiral shell, are obtained by the addition of calcium ions to small phosphatidylserine vesicles, which induces formation of discs that are fused into large sheets of lipid, and rolled up into nanocrystalline structures. The nanocochleate system is claimed to protect micronutrients and antioxidants from degradation during manufacture and storage.

Recently, self-assembled nanotubes have been developed from hydrolysed milk protein  $\alpha$ -lactalbumin, which can offer a new naturally-derived carrier for nanoencapsulation of nutrients, supplements and pharmaceuticals (Graveland-Bikker and de Kruif 2006).

Another major area of current nanotechnology applications is nanoencapsulation of food ingredients and additives. The use of microencapsulated food additives is already well established. For example, microencapsulation has been used to mask the taste and odour of tuna fish oil added to bread for health benefits (e.g. “Tip Top-up” brand bread from George Weston Foods, Australia [Internet]). A variety of other microencapsulated food ingredients and additives are available for use in a range of food products, and a recent trend in the healthfood area is microencapsulation of live probiotic microbes to promote healthy gut function. In this context, the nano-encapsulation of food ingredients and additives appears a logical extension of the technology into an already existing application area to provide protective barriers, flavour and taste masking, controlled release, and better dispersability for water-insoluble food ingredients and additives.

Nanoencapsulated substances are also being developed as part of interactive foods, which will allow consumers to modify the food depending on their own nutritional needs or tastes. One projected example is a colourless and tasteless beverage that would contain nanoencapsulated ingredients or additives that could be activated by a consumer at a particular microwave frequency. This would lead to activation of selected nanocapsules,

whilst the others would remain latent, releasing only the preferred flavour, colour or nutrients (Cientifica 2006 [Internet]).

A number of nutraceuticals and nutritional supplements containing nano ingredients and additives (e.g. vitamins, antimicrobials, antioxidants etc) are currently available. Virtually all of these products claim enhanced absorption and bioavailability of nano-sized ingredients in the body. Examples of these include different Nanoceuticals™ from RBC Life Sciences® Inc. USA [Internet]), and Nano Calcium/Magnesium from Mag-I-Cal.com USA [Internet]). The nano-selenium enriched Nanotea from Shenzhen Become Industry & Trade Co., Ltd. China [Internet] is another example. In some parts of China, selenium deficiency is the main cause of a number of ailments, and enhanced uptake and bioavailability of selenium through Nanotea is claimed to provide a variety of health benefits. A health supplement Nutri-Nano™ CoQ-10 from Solgar, USA [Internet], based on Aquanova's technology, and claimed for increased absorption of the fat soluble CoQ-10, is currently being marketed in the UK.

Among the few examples of currently available food additives is the synthetic form of the tomato carotenoid Lycopene, which has a particle size in the range of 100 nm (BASF's US Patent US5968251). The main food applications of Lycopene include soft drinks, baking mixtures and blancmanges. The addition of water-dispersible Lycopene to drinks not only provides colour, but is also claimed for certain health benefits. For example, synthetic Lycopene in combination with vitamin E has been reported to inhibit the growth of prostate cancer in mice (Limpens et al. 2006). The use of certain inorganic nanomaterials as food additives has also been the subject of patent applications. One example is a coating intended to provide moisture or oxygen barrier, and thereby improve shelf life and/or the flavour impact of confectionery products (Mars Inc.'s US Patent US5741505). The materials used for the coatings include the permitted food additives silicon dioxide (SiO<sub>2</sub>, E551), magnesium oxide (MgO, E530) and titanium dioxide (TiO<sub>2</sub> E171), which are preferably insoluble. The coating is applied using a continuous process as a thin amorphous film of 50 nm or less to prevent cracking of the barrier if the product is flexed. The flexibility of the coatings may be increased by the addition of other additives during production. Another example is nanosilver, which is being increasingly marketed as a health supplement. Aqueous dispersions of colloidal silver are available from a number of sources. Although no food products containing nanosilver is currently available, its use as an additive to prepare antibacterial wheat flour has been the subject of a recent patent application (WPI ACC NO: 2006-489267/200650, "Preparation method antibacterial wheat flour by using silver nanoparticles" by Park KH, Korea).

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*Nanotechnology applications for food packaging*

Nanotechnology derived food packaging materials are the largest category of current nanotechnology applications for the food sector. This review has identified the following main applications for food contact materials (FCMs):

- FCMs incorporating nanomaterials to improve packaging properties (flexibility, gas barrier properties, temperature/ moisture stability)
- ‘Active’ FCMs that incorporate nanoparticles with antimicrobial or oxygen scavenging properties
- ‘Intelligent’ food packaging incorporating nanosensors to monitor and report the condition of the food
- Biodegradable polymer-nanomaterial composites

Due to very large aspect ratios, a relatively low level of nanoparticle is sufficient to change the properties of packaging materials without significant changes in density, transparency, and processing characteristics (Lei et al. 2006). The addition of certain nanoparticles into shaped objects and films has been shown to render them light, fire resistant, and stronger in terms of mechanical and thermal performance, as well as make them less permeable to gases. For example, nanocomposites have been reported to have improved properties with regard to durability (Wang et al. 2003); temperature resistance (Alexandra and Dubois 2000, Kotsilkova et al. 2001); flame resistance (Ray et al. 2002); barrier properties (Alexandra and Dubois 2000, Xu et al. 2006); optical properties (Wan et al. 2003); processability due to lower viscosity (Schartel et al. 2005); and recycling properties (McGlashan and Halley 2003, Park et al. 2002, Park et al. 2003). This has led to the development of a variety of nanoparticle-reinforced polymers, also termed as ‘nanocomposites’, which typically contain up to 5% w/w nanoparticles.

The polymer composites incorporating clay nanoparticles are among the first nanocomposites to emerge on the market as improved materials for food packaging. The nanoclay mineral used in these nanocomposites is montmorillonite (also termed as bentonite), which is a relatively cheap and widely available natural clay derived from volcanic ash/ rocks. Nanoclay has a natural nano- layer structure that limits the permeation of gases, and provides substantial improvements in gas barrier properties of nanocomposites (Ke and Yongping 2005, Akbari et al. 2006). Such improvements have led to the development of nanoclay-polymer composites for potential use in a variety of food packaging applications, such as processed meats, cheese, confectionery, cereals, boil-in-the-bag foods, as well as

in extrusion-coating applications for fruit juices and dairy products, or co-extrusion processes for the manufacture of bottles for beer and carbonated drinks (Akbari et al. 2006). The polymers used for clay-polymer nanocomposites are PA (polyamides), nylons, polyolefins, PS (polystyrene), EVA (ethylene-vinylacetate) copolymer, epoxy resins, polyurethane, polyimides and PET (polyethylene terephthalate). Example of available nanoclay composites include:

- Imperm® (from Nanocor® Inc. [Internet]) is used in multi-layer PET bottles and sheets for food and beverage packaging, to minimise the loss of CO<sub>2</sub> from the drink, and the ingress of O<sub>2</sub> into the bottle, and thus keep beverages fresher and extend shelf-life.
- Aegis® OX (Honeywell [Internet]) polymerized nanocomposite film is an oxygen-scavenging barrier resin formulated for use in co-injection PET bottle applications e.g. beer, fruit juice and soft drinks. The resins are a blend of active and passive nylon using O<sub>2</sub> scavengers and passive nanocomposite clay particles to enhance the barrier properties for retaining CO<sub>2</sub> and keeping O<sub>2</sub> out.
- Durethan® KU2-2601 (Bayer AG) is a new hybrid plastic, which comprises polyamide (PA) and layered silicate barriers. The plastic incorporates Nanocor's clay to produce a film with increased barrier properties, enhanced gloss and stiffness. It is intended for use in applications where conventional PA is too permeable and EVOH coatings too expensive e.g. paperboard juice containers (Joseph and Morrison 2006).

The known industrial applications of nanoclay in multilayer film packaging include beer bottles, carbonated drinks, and thermoformed containers (Plastic Technology [Internet]). Miller Brewing Co. (USA) and Hite Brewery Co. (South Korea) are reported to be using the technology in their beer bottles (Plastic Technology [Internet], Big Idea Investor [Internet]).

Polymer nanocomposites incorporating metal or metal oxide nanoparticles have been developed for antimicrobial 'active' packaging, abrasion resistance, UV absorption, and/ or strength. The nanomaterials used as UV absorbers (e.g. titanium dioxide) can prevent UV-degradation in plastics such as PS, PE (polyethylene), and PVC (polyvinylchloride). The metal and metal oxide nanomaterials commonly used are silver (Ag), gold (Au), zinc oxide (ZnO), silica (SiO<sub>2</sub>), titanium dioxide (TiO<sub>2</sub>), alumina (Al<sub>2</sub>O<sub>3</sub>) and iron oxides (Fe<sub>3</sub>O<sub>4</sub>, Fe<sub>2</sub>O<sub>3</sub>). Other semi-conductor nanoparticles (e.g. cadmium telluride/ gallium arsenide) have also been used in development of nanocomposites (Garland 2004, Breaking News on Food Processing & Packaging- Europe 2005 [Internet]).

Based on the antimicrobial action of nanosilver, a number of 'active' FCMs have been developed that are claimed to preserve the food materials within longer by inhibiting the

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growth of microorganisms. Examples include “FresherLonger™ Miracle Food Storage Containers” and “FresherLonger™ Plastic Storage Bags” from Sharper Image® USA [Internet], “Nano Silver Food Containers” from A-DO Korea [Internet], and “Nano Silver Baby Milk Bottle” from Baby Dream® Co. Ltd. (Korea) [Internet]. Nanosilver has also been incorporated into the inner surface of domestic refrigerators (LG, Samsung and Daewoo) to prevent microbial growth and maintain a clean and hygienic environment in the fridge. Nanoparticulate forms of certain metals, especially silver, have also been used in the development of antimicrobial ‘active’ coatings; such as antibacterial kitchenware, tableware and pet products from Nano Care Technology, Ltd. China [Internet], and nanosilver coated cutting board from A-DO Korea [Internet]. The antimicrobial properties of nano- zinc oxide and magnesium oxide, have recently been discovered at University of Leeds (Food Production Daily [Internet]) Compared to nanosilver, the nanoparticles of zinc oxide and magnesium oxide are expected to provide a more affordable and safe food packaging solutions in the future. SongSing Nano Technology Co., Ltd. Taiwan [Internet] have recently introduced their Nano Plastic Wrap that contains nano zinc oxide based light catalyst, claimed to sterilize in indoor lighting.

The main risk of consumer exposure to nanoparticles from food packaging is likely to be through potential migration of nanoparticles into food and drinks. However, such migration data are currently not available, despite the fact that a number of FCMs containing nanomaterials are already available and in commercial use in some countries. To date, there is only one published study that has determined the migration of minerals (Fe, Mg, Si) from biodegradable starch/ nanoclay nanocomposite films (Avella et al. 2005). The results of this study showed an insignificant trend in the levels of Fe and Mg in packaged vegetables, but a consistent increase in the amount of Si (the main component of nano-clay). This study, however, provides only a small piece of information for a biodegradable material, and not for the plastic nanocomposites more likely to be used in food and drink containers, such as PET, PE, and PP.

*Developments at R&D stage*

It has been estimated that over 200 companies worldwide are conducting R&D into the use of nanotechnology in engineering, processing, packaging or delivering food and nutritional supplements (IFST Nanotechnology Information Statement, 2006 [Internet]). It is also understood that a number of nanotechnology products and applications is currently at different stage of development. A search of patent databases carried out as part of this review found more than 450 patent entries with regard to applications of nanotechnology in



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3 food or FCMs. A large majority of these are, however, aimed at analytical, therapeutic and  
4 health supplement applications, and only 79 were found to be relevant to direct applications  
5 for food or FCMs.  
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9 The main focus of current R&D appears to be at optimising or altering the appearance of  
10 food, such as colour, flavour, texture, consistency; controlling the release of flavours and  
11 nutrients; enhancing the absorption of nutrients or nutraceuticals; extending the shelf-life of  
12 foods and improving stability; removing undesirable molecules from foods (e.g. through  
13 nanofiltration); using nanosensors to enhance traceability and safety of food products;  
14 developing interactive or functional foods, and enabling consumers to modify food  
15 depending on their own nutritional needs or tastes. A major thrust of current research is  
16 directed towards developing new and improved food packaging materials. In this regard,  
17 polymer nanocomposite films incorporating nanoparticles, nanosensors, or antigen detecting  
18 biosensors are being developed for use in 'smart' packaging. When available, the embedded  
19 sensors in a packaging film will be able to detect food spoilage organisms and trigger a  
20 colour change to alert the consumer that the shelf life is ending/ended. Examples include  
21 Nano Bioswitch / 'Release-on-Command' (Food Packaging using Nanotechnology Methods,  
22 2004 [Internet]) that will provide a basis for intelligent preservative packaging technology that  
23 will release a preservative if food begins to spoil. Nanoscale-sensing devices are also under  
24 development that, when attached to food products and packaging, will enable the food or  
25 food ingredients to be traced back to the source of origin. Further developments in this field  
26 include the so called 'Electronic Tongue' technology that is made up of sensor arrays to  
27 signal condition of the food (Garland, 2004; Food Packaging using Nanotechnology  
28 Methods, 2004 [Internet]). DNA based biochips are also under development (Garland, 2004),  
29 which will be able to detect the presence of harmful bacteria in meat or fish, or fungi affecting  
30 fruit. Other advances in this field include BioSilicon™ from pSivida Australia [Internet], which  
31 is nanostructured silicon with nano-pores for potential applications in food packaging.  
32 pSiNutria products are also being developed with the aim to enable detection of pathogens  
33 in food, and variations of temperature during food storage.  
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50 Among the near-market developments are nanomaterial based next-generation packaging  
51 displays that include Radio Frequency Identification Display (RFID). These displays involve  
52 utilisation of smart labels that will assist quick and accurate distribution of a wide variety of  
53 goods with limited shelf-life. Also under development are RFID incorporating polymeric  
54 transistors that use nanoscale organic thin-film technology. The RFID systems will be  
55 designed to operate automatically, and will provide exception reports for anomalies like  
56 temperature, short-life span products, etc (Garland, 2004).  
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Other innovations at R&D stage include the development of nanoscale dirt-repellent coatings with a ‘Lotus Effect’ (the term refers to water droplets forming beads on the surface of lotus leaves due to nanoscale wax pyramids) for self-cleaning surfaces with potential applications in abattoirs and meat processing plants (Garland, 2004). Some nanocomposites under development, incorporating carbon nanotubes and nanofibres for enormous strength, may also find applications as FCMs. Other nanocomposites incorporating nanoencapsulated substances are being developed for applications such as anti-bacterial and scented packaging (Garland, 2004).

*Potential indirect sources of food contamination by nanoparticles*

The growing use of materials, products and applications of nanotechnology may pose new indirect sources of food contamination with nanoparticles in the future. Such risk of exposure may arise from the use of nano-sized pesticides and veterinary medicines, contact of food with nanoparticulate-based coatings during preparation or processing, or potential migration of nanoparticles from food packaging. There are already known examples of pesticide formulations that are based on microemulsion (such as Syngenta’s herbicide Flex, and Isagro’s fungicide Eminent) or microencapsulation technology (such as Syngenta’s insecticide Karate Zeon, and Dow Agroscience’s insecticide Empire). It has been reported that some of the pesticide microemulsions have droplets in the nanoscale range (50-100 nm) (Evans 2006). It has also been reported that some agrochemical companies may be carrying out R&D into the development of nano-forms of pesticides, veterinary medicines and other agrochemicals. These (promised) nanotechnology-based pesticide formulations have been hailed for safety in handling, controlled delivery, better dispersions in water, and potential reduction in the use of active ingredients due to better administration into pests, plants and animals (Evans 2006). However, this review, and the recent report by Evans (2006), did not find any ‘intentionally developed’ nano-pesticide or veterinary product that is currently available commercially.

Also, as the environmental behaviour, distribution and fate of nanoparticles is currently not fully understood, it is difficult to assess whether nanoparticles in the environment will bioaccumulate/ bioconcentrate in the food chain.

**Potential consumer safety issues**

The main likely route of entry of micro- or nano-sized particles to the gut is through consumption of food and drinks. The consumer safety implications from nanotechnology



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3 applications in food are also intrinsically linked to the physicochemical nature of the  
4 nanoparticles, and the likelihood and extent of exposure through consumption of nanofoods.  
5 It is known that nanoparticles have much larger surface areas, and that they may exhibit  
6 substantially different physicochemical and biological properties compared their conventional  
7 forms. Very few studies have been carried out so far into the toxicology of nanomaterials,  
8 and much of the published research relates to inhalation exposure to engineered  
9 nanoparticles. The potential effects of nanoparticles through the gastrointestinal (GI) route  
10 are largely unknown. The application of nanotechnology in food has therefore led to  
11 concerns that ingestion of nano-sized ingredients and additives through food and drinks may  
12 pose certain hazards to consumer health. Such concerns have arisen from a growing body  
13 of scientific evidence which indicates that free engineered nanoparticles can cross cellular  
14 barriers, and that exposure to some forms can lead to increased production of oxyradicals  
15 and consequently oxidative damage to the cell (Li et al. 2003, Donaldson et al. 2004,  
16 Oberdörster 2004, Geiser et al. 2005). In an *in vitro* study on human epithelial cell cultures  
17 using fluorescence labelled SiO<sub>2</sub> nanoparticles, Chen and Mikecz (2005) have shown that  
18 particles smaller than 70 nm could enter cell nuclei. The study also found protein  
19 accumulation in the nuclei, and indication for impairment of DNA replication and  
20 transcription. Although SiO<sub>2</sub> is used as an additive to food and food packaging, it is not  
21 known whether its intake through the GI route, along with other food substances, will lead to  
22 comparable effects *in vivo*.

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24 A healthy digestive system only allows absorption of nutrients from the gut after digestion of  
25 foods. The gut wall is designed to ensure the passage of dietary nutrients, and prevent the  
26 passage of larger or foreign material. In relation to nanostructured food ingredients, it is  
27 known that certain food substances exist naturally, or are metabolised in the body, at a  
28 nano-scale. Many food proteins are globular structures, reported to be between 10's to 100s  
29 nm in size, and most polysaccharides and lipids are linear polymers less than 2 nm in  
30 thickness (IFST, 2006 [Internet]). The main concern in this regard is that processing of food  
31 ingredients to make them nano-sized may make them different from those that exist  
32 naturally. As nano-sized food ingredients and additives are likely to have a greater ability to  
33 cross the gut wall, their enhanced absorption and bioavailability would give rise to higher  
34 internal exposure, with higher plasma concentrations (from higher absorption rate), or higher  
35 area-under-the-curve exposure (from higher uptake efficiency). A number of possible  
36 consumer health implications may thus be envisaged to emerge from the consumption of  
37 food and drinks containing nano-sized ingredients and additives. For example, a greater  
38 absorption of certain nano-ingredients may change nutrient profile in the body, or a greater  
39 absorption of nano-additives may lead to increased health consequences. It is also of

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concern that the introduction into foods of nanoparticles designed to carry dietary supplements could lead to introduction of foreign substances into the blood.

Some engineered nanoparticles, such as nanosilver, are known to have strong antimicrobial activity, but at present there is no published research on their potential effects on the gut natural microflora. The behaviour, interaction, and fate of nanoparticles in the GI tract is not known, and it is possible that they will not remain in a free form (and hence not available for translocation) due to certain transformations in the gut, e.g. agglomeration, aggregation, adsorption or binding with other food components, reaction with acid and digestive enzymes etc. Such knowledge gaps make it difficult to estimate the likelihood and extent of exposure to free nanoparticles, and to assess the overall risk to an average consumer from consumption of nanofood and drinks.

*Nanosized ingredients and additives in relation to digestion of food*

The three main constituents of food; proteins, carbohydrates and lipids are each digested in a different manner. However, a common factor between the three is that digestion of their constituents occurs at the nanoscale. Based on this, it could be argued that the processing of foods at the nanoscale would simply improve the speed or efficiency of their digestion, uptake, bioavailability and metabolism in the body. Indeed, within the nutrition market there are already supplements that claim to contain di- and tri- peptides, and are thus more readily digestible (Crisalle 2007 [Internet]). In contrast, it could be argued that since the processing of substances to this scale often alters their properties, then nano-scale processing of foods may alter how the food ingredients 'behave' upon breakdown within the gut, and as a consequence how they are treated in the GI tract. This is an important aspect that needs further research, as it will also provide answer to an important regulatory question, i.e. are changes in composition and properties of a nano-processed food significant enough to be considered automatically a novel food?

The intestinal wall is folded into villi to maximise the surface area for digestion. The villi surface is composed of two main cell types: enterocytes (the majority) and goblet cells. Translocation of particles through the intestine depends on 4 main factors: 1. diffusion and accessibility through mucus lining the gut wall, 2. initial contact with enterocytes or M-Cells, 3. cellular transport, 4. post-translocation events (Hoet et al. 2004).

### *Translocation of particulates through intestinal mucus*

The epithelial cells of the gut wall are lined by a mucus layer, which is secreted by goblet cells. Mucus is principally composed of proteins (called mucins) within an electrolyte suspension (des Rieux *et al*, 2006), and helps to trap pathogens and remove foreign materials before they come into contact with the gut epithelium. Passage of particulates through the intestinal mucus is dependant on multiple factors, two of these being particle size and charge.

The mucus lining the GI epithelia forms a mesh-like barrier through which it was originally thought that passage of molecules over ~55 nm in diameter was prevented. It has also been demonstrated that smaller particles are able to diffuse through the mucus layer faster than larger particles (Szentkuti 1997). The passage of particles through intestinal mucus is also dependant on surface charge. Szentkuti (1997) showed that particles of various sizes and charges diffused through intestinal mucus at differing rates. Cationic nanoparticles were found to become entrapped within the negatively charged mucus, whereas carboxylated (anionic) microparticles were able to diffuse successfully through to the epithelial surface.

It has recently been discovered that pores within the mucus layer are much larger than originally anticipated. Researchers at the John Hopkins University, Maryland have recently published evidence to suggest that particles as big as 200 nm can pass through mucus pores when coated with polyethylene glycol (a substance used commonly to coat drug particles to prevent uptake by phagocytic immune cells) (Samuel *et al*. 2007).

### *Contact with enterocytes and M cells*

Absorption of food occurs mainly through enterocytes situated on the villi of the gut wall epithelium. Enterocytes serve two main functions - to control passage of macromolecules and pathogens, and to allow absorption of dietary constituents. Contained within both intestinal mucus and gut wall epithelium are aggregates of lymphoid nodules, commonly referred to as Peyer's Patches, and within the epithelium of Peyer's Patches are M Cells. These take in samples of foreign material and deliver them to underlying lymphocytes to elicit immune responses and thus control disease (Berne and Levy 2000). It is here that foreign objects that have passed through intestinal mucus are usually accumulated. Under normal circumstances, passage of particles through enterocytes takes place after foodstuffs have been digested into their constituents, and this process may be passive, facilitated, or active depending on the characteristics of the breakdown product.

*Cellular translocation*

Once food constituents have been broken down by enzymes, diffused through the gut mucosa, and absorbed through the enterocytes of the epithelia, they are translocated across the cells and pass into the hepatic circulation. There are several mechanisms by which particles may pass through the epithelia. These are - transcytosis by enterocytes (as with normal digestion), transcytosis by M Cells (although this is more likely to lead to accumulation within M Cells, and a consequent immune reaction), passive diffusion across the epithelia or paracellular transport.

The time between the initial contact of particulates with the epithelial wall, to their absorption and translocation across cells is relatively slow. Szentkuti (1997) reported that accumulation of particles within the cell layer under the intestinal epithelium was still relatively low after several days of oral gavage of particles within rats.

Translocation through intestinal epithelia occurs by transcytosis through enterocytes. This is the basis of normal absorption (e.g. selective uptake of peptides or amino acids through transporters within the brush border). It is well documented that GI uptake of exogenous nanoparticles is greater than microparticles. Desai et al. (1996) showed that translocation of nanoparticles, 100 nm in diameter, is 15-250 times greater than that of micromolecules, which are more likely to become lodged within Peyer's patches (des Rieux et al. 2006). The GI uptake of nanoparticles has been shown to be 2-200 times greater on Peyer's Patches, despite the fact that these only represent ~1% of the total intestinal surface (des Rieux et al. 2006).

Translocation of manufactured nanoparticles through the epithelium is likely to be dependant on the physiochemical properties of the nanoparticle e.g. zeta potential, hydrophobicity, size, presence/ absence of a ligand, and physiology of the intestinal tract e.g. healthy vs diseased state (where translocation may be increased or decreased depending on the illness) (des Rieux et al. 2006).

In relation to nanoscale processed foodstuffs, the issue of altered translocation arises only if the properties of the food's constituents are altered by processing. In addition, if engineered nanoscale additives or ingredients have been purposely introduced into the foods, or have migrated from packaging, their properties and potential effect on digestion must also be considered. In these cases, the 'novel' properties of each food would have to be determined in order to predict whether translocation would differ from the normal.

Under normal physiological conditions, paracellular transport of nanoparticles would be extremely limited, as pore size at tight junctions is between 3 and 10Å (0.3-1.0 nm) (des Rieux et al 2006). However, research into improving paracellular transport through gut

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3 epithelia is being carried out alongside medical research into targeted drug delivery. For  
4 example, research into using positively charged poly(acrylic) acids to aid nanoparticle  
5 passage via interaction with the negatively charged surface of the epithelium, or complexing  
6  $\text{Ca}^{2+}$  involved in the structure of tight junctions (des Rieux et al. 2006).  
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### 10 11 12 *The influence of particles in disease* 13

14 Investigation of the possible link between micro and nanoparticles and exacerbated  
15 symptoms in individuals with compromised GI functionality (Irritable Bowel Disease (IBD) or  
16 Crohn's Disease) has led to the questions about whether the presence of dietary micro- and  
17 nano-particles may also elicit inflammatory responses in unaffected humans. The modern  
18 Western diet means that the gut mucosa is continuously exposed to inorganic micro- and  
19 nano-particles. These dietary micro- and nano-particles may generally be grouped into three  
20 forms: natural contaminants (e.g. soil and dust), food additives, and those formed *de novo*  
21 from the environment or from the gut lumen (e.g. calcium phosphate) (Lomer et al. 2001).  
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28 The micro- and nano-particles commonly found in food are typically oxides of silicon,  
29 aluminium and titanium (Powell et al. 2000). For example, microparticulates such as titanium  
30 dioxide and aluminosilicates are used as food additives: titanium dioxide is present in  
31 anatase (E171), and aluminosilicates are commonly added to granular and powdered foods  
32 as anti caking agents (Lomer et al. 2001). These particles are highly stable, and are not  
33 degraded in the intestine. They are therefore typically taken up by M Cells of Peyer's  
34 Patches and passed to underlying macrophages. As macrophages are also unable to digest  
35 the particles, it is common to see pigmentation in cells at the base of human intestinal  
36 lymphoid aggregates due to particle accumulation (Powell et al. 2000). Concomitantly, both  
37 titanium dioxide (anatase) and aluminosilicate (as kaolinite) are commonly seen in these  
38 lymphoid aggregates (Powell et al. 1996).  
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46 Studies so far have focussed heavily on microparticulates, and initial findings indicate that  
47 they appear not to be indicated as stimulants for Crohn's disease or IBD when presented  
48 alone. As the particles pass through the intestinal tract, they come into contact with, and  
49 adsorb luminal constituents, such as calcium ions and lipopolysaccharide. It has been shown  
50 that microparticle-calcium-lipopolysaccharide conjugate activates both peripheral blood  
51 mononuclear cells (Powell et al. 2000), and intestinal phagocytes, which are usually resistant  
52 to stimulation (Ashwood et al. 1999). This indicates that microparticles may be adjuvant  
53 triggers for exacerbation of disease within sufferers of Crohn's disease and IBD (Lomer et al.  
54 2002). However, little is known about whether micro- or nano-particles are linked to the  
55 initiation of the diseases (Lomer et. al 2005).  
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Trials carried out so far to test whether reduction of microparticles in the diet can reduce the symptoms and Crohn's and IBD, have produced contradicting results. In a double blind randomised study, Lomer et al. (2002) demonstrated that a particle-low diet alleviated the symptoms of Crohn's Disease. However, recent clinical findings have suggested that reducing microparticle intake in Crohn's sufferers has no effect on the disease (Lomer 2005). It is therefore evident that despite initial attempts to establish the presence or absence of a link between compromised functionality of the GI-tract and initiation or exacerbation of disease, there is a requirement for considerable further research.

**Adequacy of current regulatory frameworks**

Two regulatory gap analysis studies have so far been carried out with regard to the EU food laws and the use of food nanotechnology. The UK Food Standards Agency (FSA) published a (draft) review that considered the regulatory implications and risk assessment in relation to applications of nanotechnologies in food (Draft report of FSA regulatory review, 2006). The second regulatory gap analysis by Chaudhry et al. (2006) assessed existing regulatory frameworks relevant to food and food packaging, among a number of other current and projected products and applications of nanotechnology. Both of the assessments concluded that food / food packaging applications of nanotechnology will be subject to some form of approval process before being permitted for use. However, they have also highlighted the general lack of knowledge in relation to the potential consumer health risks

*Regulatory aspects relating to nanoscale food additives*

The use of food additives in the EU is controlled by European Parliament and Council legislation and is based on the principle that only additives that are explicitly authorised may be used in food. In addition, the quantities permitted are often limited and their use in some cases is restricted to specific foodstuffs. Under the law, food additives are defined as substances that are not normally consumed as food itself, but are intentionally added to food for a technological purpose, such as food preservation. Substances that are used for the purpose of imparting flavour and/or taste are not considered food additives *per se* (separate legislation generally applies to these substances), and neither are substances that may be used for a technological function, but are considered as food ingredients, such as sodium chloride or saffron. Prior to their authorisation by the Commission, food additives are evaluated for their safety by the European Food Safety Authority (EFSA). This role was previously the responsibility of the independent scientific committees, such as the Scientific Committee on Food.



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Legislation most relevant to nanoscale food additives is provided under Framework Directive 89/107 and the subordinate legislation. Nano food additives are assessed either as novel additives or, where a macro-equivalent is already approved, through potential amendments of the appropriate specifications including purity criteria under the Directive 96/77/EC.

In July 2006, the European Commission published a set of four proposed Regulations which are set to replace the current system and provide a common basis for controls on food additives (COM/2006/0428 final), food flavourings (COM/2006/0427 final) and food enzymes (COM/2006/0425 final), and a common authorisation procedure (COM/2006/0423 final). These proposals bring together all of the existing food additive regulations and propose to introduce comitology for additive approvals in place of the cumbersome co-decision procedure. Moreover, in line with the decision to separate risk assessment and risk management, all applications for the approval of new food additives will be directed to EFSA, which will carry out safety evaluations and risk assessment. At present this task would fall to the EFSA AFC Panel (Additives Flavours and Food Contact Materials). The inclusion of a food additive in the Community positive list will be considered by the Commission on the basis of the opinion from EFSA. In addition to the safety of the substance, the other general criteria (technological need, consumer aspects) have to be examined before a food additive may be included in the Community positive list. This will be done by the Standing Committee on the Food Chain and Animal Health (SCFCAH).

For every authorised food additive included in the positive list, a specification must be laid down that contains the criteria on the purity and defines the origin of the food additive, and the verification of such criteria. The most relevant aspect in relation to the use of nano-scale food additives is perhaps in the re-evaluation of safety assessment. To ensure that food additives, once permitted, are kept under continuous observation and re-evaluation wherever necessary, producers or users of food additives will be obliged to inform the Commission of any new information which may affect the safety assessment of a food additive. These must include any significant change in the manufacturing process or in specifications, changing conditions of use, and any new scientific information. Whether or not developments in nanotechnology constitute new scientific information may be for EFSA to assess in the first instance.

Food processing aids, interestingly, are not included within the scope of the proposed Regulation, which may have implication on the use of certain nanotechnologies. For example, carrier systems used to protect additives during processing only appear under the auspices of novel foods. It is clear that food additives must at all times comply with the approved specifications. The definitions laid down in Article 3 of the proposed Regulation list certain substances that are not to be considered as food additives. Among these are



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substances that are mentioned in the examples given in section 2.1, which could lead to a greying of the distinctions e.g. certain types of dextrin and modified starches, gelatine, and products containing pectin.

The specification should include information to describe *adequately* the food additive i.e. to ensure that in all relevant aspects it corresponds to the additive that has been assessed for safety. While existing food additive specifications are to be maintained until the corresponding additives are entered into the Annexes of the new Regulation, there are as yet no criteria within the specifications that cover the use of nanoparticles *per se*. For example, in the case of a coating intended to provide moisture or oxygen barrier to confectionery products (Mars Inc.'s US patent US5741505), the purity specification for silicon dioxide (E551) describes only the process by which SiO<sub>2</sub> may be produced for food additive use (i.e. no definitions for source materials are prescribed). However, the source compounds for SiO<sub>2</sub> used in the production of the nanoscale SiO<sub>2</sub> coatings includes organosilicates, silanes, chlorosilanes and tetraethylorthosilane. In addition, the current EU purity specification for TiO<sub>2</sub> (E171) does not prescribe criteria related to particle size, which clearly is a principal issue in terms of the use of nanotechnology. This additive was last evaluated in 1977.

*Regulatory aspects relating to nanoscale food ingredients*

The European Legislation of particular relevance to nanoscale food ingredients is Regulation (EC) 258/97 concerning Novel Foods and Novel Food Ingredients, which establishes a mandatory pre-market approval system for all novel foods.

A 'novel' food is defined as a food or food ingredient not having a significant history of human consumption within the Community prior to May 1997, and which falls within one of several defined categories. The categories that may have relevance to nanotechnology include "foods and food ingredients with a new or intentionally modified primary molecular structure"; and "foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances".

Considering the current and projected applications of nanotechnologies in food, it is unlikely that most nano-structured food products (at least in the foreseeable future) would fall under the first category, i.e. they would not necessarily have a different molecular structure compared to normal processed food. There is, however, a strong likelihood that they would fall under the second category *providing that* the attached caveat is fulfilled. The onus for

recognising that a food substance falls under the latter category, and alerting the competent food assessment body, lies with the person responsible for placing the product on the market. However, in the case of nano-structured foods, Regulation (EC) 258/97 would only appear to be applicable if a substance was regarded both as 'novel' *and* its nutritional value, metabolism or level of undesirable substances was substantially altered compared to its macro-scale counterpart. If a company responsible for placing a nanofood product on the market did not recognise it to be novel (e.g. because the ingredients already have a history of use at the macro-scale), and/or did not consider the properties of the nanofood to be substantially different from its macro-scale counterpart (e.g. because of a lack of information to the contrary, or the lack of a precise definition of the term 'substantially altered'), then it is possible that a safety evaluation under (EC) 258/97 will not be carried out. Thus, the caveat attached to the definition of this category of novel foods lead to an uncertainty over whether a nano-structured food product would fall under this category, or would be required to test to show that their nutritional value, metabolism or level of undesirable substances have not been affected. It is also not clear whether this regulatory framework would apply to food ingredients that *have* a significant history of use, but may already be marketed (by chance not by design) in forms that contain particle sizes of 100 nm or less. This is where clarity is needed in the wording of the definition for this category of novel foods in relation to nano-structured foods.

#### *Regulatory aspects relating to nanotechnology-derived FCMs*

The main European regulatory controls governing the composition, properties and use of FCMs or articles in the EU stem from Regulation (EC) 1935/2004. The principle underlying this Framework Regulation is that any material or article intended to come into contact directly or indirectly with food must be sufficiently inert to preclude substances from being transferred to the food in quantities large enough to endanger human health, or to bring about an unacceptable change in the composition of the food or a deterioration in its organoleptic properties.

The Framework Regulation applies to all materials, including plastics, paper, metals, glass, ceramics, rubber, etc. The main focus is on food packaging materials but other food contact uses are included too, such as cooking utensils, domestic appliances, food processing and transport equipment, hoses, conveyor belts, etc.

The regulation is inclusive in that it deals with any FCM that may transfer its constituents into food with deleterious results, rather than dealing with specific components or types of component. As such it is broad enough to encompass the migration of 'nanocomponents'

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into food from FCMs. However, it only precludes the use of substances if they are transferred in quantities large enough to endanger human health. This implies, therefore, that the transfer rate and the properties of the substance are known. In the case of nanocomponents this may not always be the case. Thus in order for Regulation (EC) 1935/2004 to be effective in terms of any potential risk from nanocomponents, pro-active testing of such components would need to be carried out in order to identify their potential hazard and determine any dose response.

The Regulation also applies, *inter alia*, to the use of:

- ‘active FCMs and articles’, where this refers to materials and articles that are intended to extend the shelf-life or to maintain or improve the condition of packaged food. Such materials are designed to release or absorb substances into or from the packaged food or the environment surrounding the food; and
- ‘intelligent FCMs and articles’, where this refers to materials and articles which monitor the condition of packaged food or the environment surrounding the food.

The Regulation recognizes that active and intelligent FCMs are not inert by design, unlike traditional FCMs, and therefore addresses the main requirements for their use. The Regulation distinguishes new active FCMs from those that have been traditionally used to release their natural ingredients into specific types of food during the process of their manufacture, such as wooden barrels used for sherry wine or whisky spirit. Active FCMs may change the composition or the organoleptic properties of the food only if the changes comply with the Community provisions applicable to food, such as the provisions of Directive 89/107/EEC on food additives. So if an active packaging material is intended to release say an antioxidant or a preservative intended to have a technical effect on the food, then that substance must first be/ become an approved food additive. Thus any nano-sized ingredient intended to be released would have to first be evaluated as a direct food additive.

In addition to the general provisions of the framework regulation, applicable to all FCMs, more detailed EU regulations have been adopted for plastics, ceramics and regenerated cellulose. Other materials including paper, paperboard, rubber, coatings, inks and adhesives have National Laws that are not harmonised at EU level. The general approach for all materials, is that the substances needed to make the material, such as monomers (starting substances), additives, and potential contaminants thereof, are included in positive lists of permitted ingredients that can be used to the exclusion of all other substances. For plastics monomers the EU list is a strict positive list. For plastic additives, as a transitional measure some additives not yet evaluated at EU level are permitted to be used under existing National rules. Restrictions on these substances take the form of limits on their migration into

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3 foodstuffs or as limits on the composition of the materials. In principle these are applicable  
4 also to nanomaterials. However such safe maximum migration limits have been determined  
5 for macro-components and may not apply in the case of their nano-equivalent substance,  
6 due to possible differences in their physicochemical or biological properties. Similarly, limits  
7 on the composition of materials are based on a basic consideration of their migration  
8 properties – this means that composition limits are an indirect way to limit migration into  
9 foods. But again for nanomaterials the composition-migration relationship may be different  
10 and different compositional limits (higher or lower) may be needed to afford the safe level of  
11 protection against excessive chemical migration.  
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15 As well as establishing limits for migratable or extractable substances, there are also test  
16 procedures described in regulations that instruct how to test materials for compliance. For  
17 example, Directive 82/711/EEC gives the basic rules necessary for testing migration from  
18 plastics and Directive 85/572/EEC describes the simulants (simple test liquids intended to  
19 mimic foods) to be used for testing migration from plastics. These test procedures were  
20 conceived for conventional FCMs. Chemical migration is described as a molecular diffusion  
21 process with migration levels depending on diffusion coefficients and partition coefficients of  
22 the chemicals, in the packaging material and into the food. Clearly the soluble components  
23 of any nano-particulates should follow the same physicochemical rules, but it is not clear if  
24 transfer of the nanoparticles themselves can be thus described. Particularly in the case of  
25 nano-surface coatings, different transfer mechanisms may occur. It needs to be determined  
26 whether or not the current test procedures using extraction solvents or food simulants are  
27 suitable mimics of foodstuffs with respect to the possible transfer of nanoparticles from  
28 FCMs into foods.  
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32 Until specific testing is carried out, or deleterious effects are noted and there is persuasive  
33 evidence for thinking otherwise, nano-materials and articles will be managed by the  
34 Regulation in the same way as their macro counterparts. The legislation clearly places the  
35 onus squarely on the shoulders of manufacturers to ensure the safety of their products. Thus  
36 the gap is not necessarily a regulatory one, but potentially one of compliance by  
37 manufacturers if they have not carried out an adequate risk assessment based on data for  
38 migration, toxicity and intake. Given this, it may not be necessary to create additional /  
39 separate regulations for nanosubstances.  
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#### 42 *Regulatory aspects relating to general food safety and consumer health protection*

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44 EC Food Law Regulation 178/2002, laying down the general principles and requirements of  
45 food law, establishing the European Food Safety Authority, and laying down procedures in  
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matters of food safety, provides the basis for the assurance of a high level of protection of human health and consumers' interest in relation to food. EU Food Law Regulation 178/2002 requires that food placed on the market is not unsafe. The traceability of nanomaterials used as food ingredients or additives is also covered under the existing requirements of Regulation 178/2002. Due to the inclusive nature of EU Food Law Regulation 178/2002, the general safety articles embodied therein will, by implication, encompass nanofood and FCMs containing nanomaterials. Specifically, food would not be eligible for marketing if it contained substances harmful to health. The ultimate responsible for ensuring that the final food is safe rests with the seller who offers the food or packaged food for sale, or who offers unfilled materials or articles for sale to consumers for home-use.

Commission Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs, is intended to provide consumers with an increased measure of protection by setting maximum levels for a number of specified contaminants in relation to certain specified categories of food. Substances that are restricted include heavy metals (lead, cadmium and mercury) environmental chemical contaminants (dioxins, nitrate) and mycotoxins (aflatoxins and patulin). It is, however, unlikely that nanomaterials used in the production of food or FCMs will be made using these toxic substances nor should they contain significant impurities of them.

#### *Summary of regulatory inadequacies and gaps, and potential applicability of precautionary principle*

It is clear from the assessment of relevant EU legislation that most applications of nanotechnology in food and FCMs will be subject to some form of approval process before being permitted for use. However, it is also clear that:

- current legislation pertaining to food ingredients, food additives, and FCMs does not differentiate between substances produced routinely by 'standard' manufacturing methods and those developed by nanotechnology. For example, current legislation does not differentiate between 'conventional' and 'nano' forms of food additives already approved for use in food. There is currently no size limitation on particle size for food additives. Particle size is only specified for E460 cellulose (microcrystalline), where smallest particle size should not get below 5 micrometer ( $\mu\text{m}$ );
- there is a lack of clarity in the definition of novel foods under relevant regulations that may lead to uncertainty as to whether (and when) a food processed at nano-scale should be considered a novel food;

- there is a lack of information on the extent of migration of nano (and non-nano) components from nanotechnology derived FCMs
- there is a lack of knowledge of the possible health effects of nanosized food ingredients and additives to enable adequate risk assessment

Currently there is no provision in the European food laws for the development of specific measures to deal with 'nanocomponents' as a separate class of materials. In a joint statement on nanomaterial toxicology issues, the independent UK Committees on Toxicity, on Mutagenicity, and on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COT, COM, COC) stated that there is no need to develop a new approach to risk assessment of nanomaterials, but there is a clear need to provide hazard identification data on the widest possible range of nanomaterials. In the absence of such data the Committees stated that it was not possible to derive conclusions about the spectrum of toxicological effects that might be associated with nanomaterials.

A working document is currently being discussed by the European Commission and Member States that may become a proposal for rules on substances and materials that are problematic and not dealt with elsewhere in the legislation. If and until such legislation is completed and adopted the products of nanotechnology will continue to be dealt with by a combination of general EU food law and more specific controls on particular materials and articles. Specific legislation dealing with nanocomponents in food and FCMs is only likely to be made if there is sound scientific evidence to show that such materials present a higher risk than macro equivalents.

In the absence of detailed toxicological data, but in view of the potential of some nanoparticles to cause harm, it may also be appropriate to consider application of precautionary principle (PP) for certain applications of nanotechnology in the food sector. The PP is a well-accepted tenet of international law, and is an attempt to legally codify the maxim "better safe than sorry". Originally applied in the EU in terms of environmental protection, it has since been accepted that its scope is much wider, and can be applied to the protection of human health. In 2000, the EC adopted a Communication on the use of the PP (Communication from the Commission on the precautionary principle', 2000), which provides a reasoned and structured framework for action in the face of scientific uncertainty or absence of scientific consensus. The Communication gives grounds for assigning responsibility for producing the scientific evidence necessary for a comprehensive risk assessment. Recourse to the PP presupposes that potentially harmful effects deriving from a product or process have been identified, and that existing scientific evaluation does not allow the risk to be determined with sufficient certainty.



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The PP is also incorporated into EU food law in Article 7 of Regulation 178/2002, which states that where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment. However, although there is emerging evidence to suggest that certain engineered nanoparticles have the potential to cause harm to human health, it is unclear at present whether there is enough scientific basis to invoke the PP in all applications of nanotechnology for food contact materials. A recent IFST report has recommended that nanoparticles be treated as new, potentially harmful materials, until testing proves their safety (IFST response to FSA nanotechnology review [Internet]). More research is needed to provide a better understanding of the level of risk, but it would be prudent to consider application of the PP in certain high-risk applications; for example, where free engineered nanoparticles have been introduced into food/ drinks, and where such food/ drinks are likely to be consumed in large quantities and/or by a large proportion of the population. It may also be an opportune time to consider the merits of including the PP in the Novel Foods Regulations, given the current review of those regulations.

**Conclusions**

The findings of this review are in agreement with a recent report by Cientifica (2006) in that nanotechnology applications in the EU's food industry are currently at an elementary stage. As with any new technology, most current and near-future applications of nanotechnology for food are likely to be for high-value products, in particular food packaging and nano-carrier systems for nutritional supplements and nutraceuticals. This review has shown that a number of nanotechnology based supplements, nutraceuticals, additives, and FCMs are already available in some countries. It is also widely anticipated that such applications will emerge on the UK/ EU market in the next few years. The available information is, however, very sparse in terms of potential health risks that may arise from the consumption of nano-food and drinks. Much of the available information is in relation to inhalation toxicology and in relation to engineered nanoparticles, and there are major gaps in knowledge with regard to the behaviour, fate and effects of nano-sized food ingredients and additives via the GI route. Such uncertainties and lack of knowledge make it likely that applications of nanotechnologies in the food sector will attract a lot of public concern in the coming years. This is because such applications, at least in theory, have the potential to lead to exposure of a large number of consumers to nanoparticles. There is, therefore, an urgent need for considerable amount of research into the behaviour of foodstuffs both manipulated or



processed at the nanoscale, and the properties of manufactured nanoparticles that may be introduced into foods either deliberately, or as a result of contamination. In view of the gaps in knowledge identified in this report, a few potential researchable issues have been highlighted below. At present, many of these remain conceptual, but the development of foodstuffs containing manufactured nanoparticles or nanostructures must take into account such possible outcomes. For example, research is needed to establish:

- physicochemical properties of manufactured nanoparticles that may be used as food additives, and whether nanosized additives bind to other food components, agglomerate, or remain as free particles in the GI tract;
- potential effects of nanosized food additives on the function of the GI tract, gut epithelium and other cells, and on the gut natural microflora;
- the extent of changes in the absorption and bioavailability of nanosized additives, compared to macro-scale equivalents, and the toxicological significance of such changes;
- whether the introduction of a nano food ingredient or additive has a significant effect on the normal nutrient/ metabolite transport, and does this alter the overall nutrient profile in the body;
- whether changes in the composition of a food processed at nano-scale makes it significantly different to warrant (automatic) consideration as a novel food;
- whether there are any changes to the way in which food constituents are digested as a consequence of their nanoscale processing; for example, can the introduction into foods of engineered nanoparticulates (e.g. designed to carry dietary supplements) lead to introduction of foreign substances into the blood?
- whether there is a significant risk of indirect contamination of food through migration of nanoparticles from food packaging or active surfaces used in food processing.

Interdisciplinary research is vital to address the current uncertainties, and much can be learnt from parallel areas of medical research looking into the passage of nanoparticles through the gut as a vehicle for targeted drug delivery. The brief regulatory assessment presented in this review indicates that despite a plethora of regulatory layers aimed at controlling the risks in the food area, most current frameworks are not designed to cope explicitly with the new challenges posed by the advent of nanotechnology. For a regulatory framework to be effective in controlling the potential risks from application of

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nanotechnology, the relevant legislation needs to provide a clear definition that encompasses the distinctive properties of nano ingredients and additives, a clearly defined responsibility/ liability for relevant products and applications, and appropriate permissible limits that relate to the (potential) effects of nano substances in food. Any adjustments to regulations will, however, need to be negotiated at the EU level, whilst taking into account other international frameworks in order to develop a harmonised strategy for the governance of nanotechnology risks. Although there is not enough scientific knowledge at present to warrant application of the precautionary principle to nanofood, it would be in the food industry's own benefit to develop appropriate initiatives to self-regulate and test those nanotechnology applications that may carry a relatively greater risks to consumers.

Like any other new technology, public confidence, trust, and acceptance are likely to be the key factors that will determine the success or failure of nanotechnology applications for the food sector. The food industry is already suspected by some quarters of secretly using nanotechnology in their products (Food Chemical News, 2007). It would, therefore, be prudent for the industry to adopt a proactive approach by forming appropriate stakeholder forums aimed at tackling the issues head-on by informing, engaging and consulting consumers at the outset. One of the contentious, but important, issues in this regard is that of the labelling of foodstuffs that are products of nanotechnology. It is a key issue that requires thorough consideration and consultation with stakeholders, but food industry could consider declaring the use of nano-additives voluntarily, especially where free engineered nanoparticles have been introduced into food/ drinks, and where such products are likely to be consumed in large quantities and/or by a large proportion of the population.

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**References**

A-DO. Available: [www.adox.info/?doc=shop/list.php&ca\\_id=110](http://www.adox.info/?doc=shop/list.php&ca_id=110). Accessed 11 April 2007.

Akbari Z, Ghomashchi T, Aroujalian A. 2006. Potential of nanotechnology for food packaging industry. a paper presented at "Nano Micro Technologies in the Food Health Food Industries" Conference organised by Institute of Nanotechnology, 25-26 October 2006 Amsterdam.

- Alexandra M, Dubois P. 2000. Polymer-layered silicate nanocomposites: preparation, properties and uses of a new class of materials. *Materials Science & Engineering R-Reports*. 28 (1-2): 1-63.
- Aquanova®: Available: [www.aquanova.de/](http://www.aquanova.de/), accessed 05 March 2007.
- Ashwood P, Evans AM, Berisha F, Walker-Nthenda L, Thompson RPH, Powell JJ. 1999. Lipopolysaccharide (LPS) adsorbed into inorganic dietary particles hyperstimulates intestinal mononuclear cells. *Gut* 44 (suppl 1): A92.
- Avella M, De Vlieger JJ, Errico ME, Fischer S, Vacca P, Volpe MG. 2005. Biodegradable starch/clay nanocomposite films for food packaging applications. *Food Chemistry* 93: 467-474.
- Baby Dream® Co. Ltd. Available: <http://babydream.en.ec21.com/>. Accessed 11 April 2007.
- BASF: FDA acknowledges GRAS notification for BASF synthetic lycopene: Nutritional supplement used in tablets or to fortify food and beverages, Available: [www.basf.com/corporate/news2003/newsinfo\\_gras\\_notification.html](http://www.basf.com/corporate/news2003/newsinfo_gras_notification.html). Accessed 30 July 2007.
- Berne RM, Levy MN. 2000, *Principles of Physiology*; Third Edition; Mosby Inc; Missouri.
- Big Idea Investor. Available: [www.bigideainvestor.com/index.cfm?D=603](http://www.bigideainvestor.com/index.cfm?D=603). Accessed 30 July 2007.
- BioDelivery Sciences International**: Available: [www.biodeliverysciences.com/](http://www.biodeliverysciences.com/). Accessed 30 July 2007.
- Breaking News on Food Processing & Packaging- Europe, Nanotech discovery promises safer food packaging. *Food Production Daily*. Available: [www.foodproductiondaily.com/news/printNewsBis.asp?id=59980](http://www.foodproductiondaily.com/news/printNewsBis.asp?id=59980). Accessed 30 July 2007.
- BSI: British Standard Institute's Publicly Available Specification (PAS 71:2005). Available: [www.bsi-global.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/PAS-71/](http://www.bsi-global.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/PAS-71/). Accessed 30 July 2007.
- Chaudhry Q, Blackburn J, Floyd P, George C, Nwaogu T, Boxall A, Aitken R. 2006. A scoping study to identify regulatory gaps for the products applications of nanotechnologies. Central Science Laboratory SHutton York. Available: [www.defra.gov.uk/science/Project\\_Data/DocumentLibrary/CB01075/CB01075\\_3373\\_FRP.doc](http://www.defra.gov.uk/science/Project_Data/DocumentLibrary/CB01075/CB01075_3373_FRP.doc). Accessed 16 January 2007.
- Chaudhry Q, Boxall A, Aitken R, Hull M. 2005. A scoping study into the manufacture use of nanomaterials in the UK. Central Science Laboratory York. Available: [www.defra.gov.uk/science/Project\\_Data/DocumentLibrary/CB01070/CB01070\\_3156\\_FRP.doc](http://www.defra.gov.uk/science/Project_Data/DocumentLibrary/CB01070/CB01070_3156_FRP.doc). Accessed 16 January 2007.
- Chen H, Weiss J, Shahidi F. 2006. Nanotechnology in nutraceuticals and functional foods. *Food Technology* 60(3):30-6.
- Chen MA, von Mikecz. 2005. Formation of nucleoplasmic protein aggregates impairs nuclear function in response to SiO<sub>2</sub> nanoparticles. *Experimental Cell Research* 305: 51-62.
- Cientifica Report. 2006. "Nanotechnologies in the Food Industry" published August 2006. Available: [www.cientifica.com/www/details.php?id=47](http://www.cientifica.com/www/details.php?id=47). Accessed 24 October 2006.
- Crisalle L. 2007. Types of Protein Differences in Quality. Available: [www.exerciseandnutritionworks.com/t-protowhey1.aspx](http://www.exerciseandnutritionworks.com/t-protowhey1.aspx). Accessed 30 July 2007.
- CSL Nanomaterials Database: Available (restricted access): <http://nanotech.csl.gov.uk/>. Accessed 17 November 2006.

- des Rieux A, Fievez V, Garinot M, Schneider Y-J, Préat V. 2006. Nanoparticles potential oral delivery systems of proteins vaccines: A mechanistic approach. *Journal of Controlled Release* 116: 1-27.
- Desai MP, Labhasetwar V, Amidon GL, Levy RJ. 1996. Gastrointestinal uptake of biodegradable microparticles: effect of particle size. *Pharmaceutical Research* 13: pp1838-1845.
- Donaldson K, Stone V, Tran CL, Kreyling W, Borm PJ. 2004. Nanotoxicology. *Occupational and Environmental Medicine* 619:727-8.
- Draft report of FSA regulatory review. 2006. A review of potential implications of nanotechnologies for regulations risk assessment in relation to food. Available: [www.food.gov.uk/multimedia/pdfs/nanotech.pdf](http://www.food.gov.uk/multimedia/pdfs/nanotech.pdf). Accessed 30 July 2007.
- ETC Group Report 2003. "Size Matters! ETC Group: New information provides more evidence for mandatory moratorium on synthetic nanoparticles". Available: [www.etcgroup.org/en/materials/publications.html?id=164](http://www.etcgroup.org/en/materials/publications.html?id=164). Accessed 30 July 2007.
- ETC Group Report. 2004. "Down on the farm: the impact of nano-scale technologies on food agriculture". [www.etcgroup.org/upload/publication/80/01/etc\\_dotfarm2004.pdf](http://www.etcgroup.org/upload/publication/80/01/etc_dotfarm2004.pdf). Accessed 16 February 2007.
- Evans SM, Ashwood P, Warley A, Berisha F, Thompson RP, Powell JJ. 2002. The role of dietary microparticles calcium in apoptosis interleukin-1beta release of intestinal macrophages. *Gastroenterology* 1235:1543-1553.
- Food Chemical News. 2007. Food industry accused of secretly using nanotechnology. 2 July 2007, 13-14.
- Food Packaging using Nanotechnology Methods. 2004. An Overview of 'Smart Packaging' 'Active Packaging' *Advance Magazine*. Food Marketing Institute, February 2004. Available: [www.azonano.com/details.asp](http://www.azonano.com/details.asp). Article ID- 1317. Accessed 14 February, 2007.
- Food Production Daily. Nanotech discovery promises safer food packaging. Available: [www.foodproductiondaily.com/news/ngasp?n=59980-nanotech-discovery-promises](http://www.foodproductiondaily.com/news/ngasp?n=59980-nanotech-discovery-promises). Accessed 29 July 2007.
- Garland A. (Ed). 2004. Nanotechnology in Plastics Packaging, *Commercial applications in nanotechnology*, Pira International Limited, UK, 2004. pp14 –63.
- Geiser M, Rothen-Rutishauser B, Kapp N, Schürch S, Kreyling W, Schulz Y, Semmler M, Im Hof V, Heyder V, Gehr P. 2005. Ultrafine Particles Cross Cellular Membranes by Nonphagocytic Mechanisms in Lungs and in Cultured Cells. *Environmental Health Perspectives* 113 (11): 1555-1560.
- George Weston Foods. Available: [www.gwf.com.au/brands/tiptop.htm](http://www.gwf.com.au/brands/tiptop.htm). Accessed 30 July 2007.
- Graveland-Bikker JF, de Kruif CG. 2006. Unique milk protein-based nanotubes: food and nanotechnology meet *Trends in Food Science and Technology* 175:196–203.
- Helmut Kaiser Consultancy. 2004. Study: nanotechnology in food and food processing industry worldwide, 2003–2006–2010–2015. Available: [www.hkc22.com/Nanofood.html](http://www.hkc22.com/Nanofood.html). Accessed: 30 July 2007.
- Hoet PHM, Brüske-Hohlfeld I, Salata OV. 2004. Nanparticles: Known and Unknown Health Risks. *Journal of Nanobiotechnology* 2(12):1-15.
- Honeywell: Available: [www.honeywell.com/sites/sm/aegis/aegis\\_ox.htm](http://www.honeywell.com/sites/sm/aegis/aegis_ox.htm). Accessed 30 July 2007.

- IFST Nanotechnology information statement: Institute of Food Science Technology Trust Fund. 2006. Available: [www.ifst.org/uploadedfiles/cms/store/attachments/nanotechnology.pdf](http://www.ifst.org/uploadedfiles/cms/store/attachments/nanotechnology.pdf). Accessed: 30 July 2007.
- IFST response to FSA nanotechnology review: Institute of Food Science Technology "FSA Draft Report on a Regulatory Review of the Use of Nanotechnologies in Relation to Food". Available: [www.ifst.org/uploadedfiles/cms/store/ATTACHMENTS/ResponseFSA\\_NanotechnologiesT405app.pdf](http://www.ifst.org/uploadedfiles/cms/store/ATTACHMENTS/ResponseFSA_NanotechnologiesT405app.pdf). Accessed 30 July 2007.
- Joseph T, Morrison M. 2006. Nanotechnology in Agriculture Food: A Nanoforum report published in April 2006. Available: [www.nanoforum.org](http://www.nanoforum.org). Accessed 03 June 2006.
- Ke Z, Yongping B. 2005. Improve the gas barrier property of PET film with montmorillonite by in situ interlayer polymerisation. *Materials Letters* 59: 3348-3351.
- Kotsilkova R, Petkova V, Pelovski Y. 2001. Thermal analysis of polymer-silicate nanocomposites *Journal of Thermal Analysis. Calorimetry* 64:591-598.
- Lei SG, Hoa SV, Ton-That M-T. 2006. Effect of clay types on the processing properties of polypropylene nanocomposites. *Composites Science and Technology* 66: 1274-1279.
- Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, Nel A. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environmental Health Perspectives*. 111(4): 455-460.
- Limpens J, Schröder FH, de Ridder CMA, Bolder CA, Wildhagen MF, Obermüller-Jevic UC, Krämer K, van Weerden WM. 2006. Combined lycopene vitamin e treatment suppresses the growth of PC-346C human prostate cancer cells in nude mice. *Journal of Nutrition* 136:1287-1293.
- Lomer MC, Grainger SL, Ede R, Catterall AP, Greenfield SM, Cowan RE, Vicary FR, Jenkins AP, Fidler H, Harvey RS, Ellis R, McNair A, Ainley CC, Thompson RP, Powell JJ. 2005. Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. *European Journal of Gastroenterology and Hepatology* 17: 377-384.
- Lomer MC, Harvey RS, Evans SM, Thompson RP, Powell JJ. 2001. Efficacy tolerability of a low microparticle diet in a double blind randomized pilot study in Crohn's disease. *European Journal of Gastroenterology and Hepatology* 132:101-106.
- Lomer MC, Thompson RP, Powell JJ. 2002. Fine and ultrafine particles of the diet: influence on the mucosal immune response association with Crohn's disease. *Proceedings of the Nutrition Society* 611:123-130.
- Mag-I-Cal.com. Available: [www.mag-i-cal.com/](http://www.mag-i-cal.com/). Accessed 30 July 2007.
- Maynard AD, Aitken RJ, Butz T, Colvin V, Donaldson K, Oberdorster G, Philbert MA, Ryan J, Seaton A, Stone V, Tinkle SS, Tran L, Walker NJ, Warheit DB. 2006. Safe handling of nanotechnology. *Nature* 444: 267-269.
- McGlashan SA, Halley PJ. 2003. Preparation characterization of biodegradable starch-based nanocomposite materials. *Polymer International* 52: 1767-1773.
- Nano Care Technology, Ltd. Available: [www.nanocaretech.com/En\\_ArticleShow.asp?ArticleID=13](http://www.nanocaretech.com/En_ArticleShow.asp?ArticleID=13). Accessed 30 July 2007.
- Nanocor®: Available [www.nanocor.com/Cases/case\\_imperm.asp](http://www.nanocor.com/Cases/case_imperm.asp). Accessed 30 July 2007.
- Nutralease: Available: [www.nutralease.com/index.asp](http://www.nutralease.com/index.asp). Accessed 10 October 2006.



- Oberdörster E. 2004. Manufactured Nanomaterials Fullerenes C<sub>60</sub> Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass. *Environmental Health Perspectives* 112(10): 1058-1062.
- Park HM, Lee WK, Park CY, Cho WJ, Ha CS. 2003, Environmentally friendly polymer hybrids Part 1 Mechanical thermal barrier properties of thermoplastic starch/clay nanocomposites. *Journal of Materials Science* 38: 909–915,
- Park HM, Li X, Jin CZ, Park CY, Cho WJ, Ha CS. 2002. Preparation properties of biodegradable thermoplastic starch/clay hybrids. *Macromolecular Materials Engineering* 287 553–558.
- Plastic Technology. Available: [www.ptonline.com/articles/kuw/12437.html](http://www.ptonline.com/articles/kuw/12437.html). Accessed 30 July 2007.
- Powell JJ, Harvey RS, Ashwood P, Wolstencroft R, Gershwin ME, Thompson RP. 2000 Immune potentiation of ultrafine dietary particles in normal subjects patients with inflammatory bowel disease. *Journal of Autoimmunity* 141:99-105
- Powell JJ, Harvey RS, Thompson RP. 1996. Microparticles in Crohn's disease--has the dust settled? *Gut* 392:340-341.
- pSivida: Available: [www.psivida.com/News/download/ASX/ASX%20Release-pSiNutria%20Dec%202005.pdf](http://www.psivida.com/News/download/ASX/ASX%20Release-pSiNutria%20Dec%202005.pdf). Accessed 30 July 2007.
- Ray SS, Maiti P, Okamoto M, Yamada K, Ueda K. 2002. New polylactide/ layered silicate nanocomposites, 1. Preparation characterization properties, *Macromolecules* 35: 3104-3110.
- | **RBC Life Sciences® Inc**: Available: [www.royal-health.com/products.htm](http://www.royal-health.com/products.htm). Accessed 10 May 2007.
- Roco MC, Bainbridge WS. (Eds). 2001. Societal Implications of Nanoscience Nanotechnology. Kluwer Academic Publishers Boston, pp 3-4.
- Royal Society and Royal Academy of Engineering. 2004. *Nanoscience Nanotechnologies: opportunities uncertainties*. Available: [www.nanotec.org.uk/finalReport.htm](http://www.nanotec.org.uk/finalReport.htm). Accessed 20 November 2005.
- Samuel K, Lai D, O'Hanlon E, Harrold S, Man ST, Wang, Y-Y, Cone R, Hanes J. 2007. Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus; *Proceedings of the National Academy of Sciences* 104: 1482-1487.
- Schartel B, Po'tschke P, Knoll U, Abdel-Goad M. 2005, Fire behaviour of polyamide 6/multiwall carbon nanotube nanocomposites. *European Polymer Journal* 415: 1061-1070.
- Sharper Image®. Available: [www.sharperimage.com/us/en/catalog/categoryview/catid\\_685320823](http://www.sharperimage.com/us/en/catalog/categoryview/catid_685320823). Accessed 16 January 2007.
- | **Shenzhen Become Industry & Trade Co., Ltd.** Available: [www.369.com.cn/En/nanotea.htm](http://www.369.com.cn/En/nanotea.htm). Accessed 30 July 2007.
- Slogar: Available: [www.revital.co.uk/Solgar\\_Nutri\\_Nano\\_CoQ\\_10](http://www.revital.co.uk/Solgar_Nutri_Nano_CoQ_10). Accessed 30 July 2007.
- SongSing Nano Technology Co., Ltd. Available: [www.nanotechproject.org/index.php?id=44&action=view&product\\_id=1342](http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1342). Accessed 06 July 2007.
- | **Szentkuti L.** 1997. Light microscopical observations on luminally administered dyes, dextrans, nanospheres and microspheres in the pre-epithelial mucus gel layer of the rat distal colon. *Journal of Controlled Release* 46: 233-242.

The Institute of Food Science Technology Report  
[www.ifst.org/uploadedfiles/cms/store/ATTACHMENTS/ResponseFSA\\_NanotechnologiesT405apppdf](http://www.ifst.org/uploadedfiles/cms/store/ATTACHMENTS/ResponseFSA_NanotechnologiesT405apppdf)

The Sunday Telegraph. 2006. "Quietly nanotechnology joins the food chain": 22 October 2006. p5.

The Woodrow Wilson Nanotechnology Consumer Products Inventory. Available: [www.nanotechproject.org/consumerproducts](http://www.nanotechproject.org/consumerproducts). Accessed 16 May 2007.

Wan C, Qiao X, Zhang Y, Zhang Y. 2003. Effect of different clay treatment on morphology mechanical properties of PVC-clay nanocomposites. *Polymer Testing* 22: 453-461.

Wang KK, Koo CM, Chung IJ. 2003. Physical properties of polyethylene/ silicate nanocomposite blown films. *Journal of Applied Polymer Science* 89: 2131-2136.

Weiss J, Takhistov P, McClements DJ. 2006. Functional Materials in Food Nanotechnology. *Journal of Food Science* 719: R107-R116.

Xu B, Zheng Q, Song Y, Shangguan Y. 2006. Calculating barrier properties of polymer/clay nanocomposites: Effects of clay layers. *Polymer* 47: 2904-2910.