A Response from the MRC Human Nutrition Research Unit to the House of Lords Science and Technology Select Committee Call for Evidence on Nanotechnologies and Food

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MRC Collaborative Centre for Human Nutrition Research (hereafter HNR) was established in 1998 to advance knowledge of the relationships between human nutrition and health by providing a national centre of excellence for the measurement and interpretation of biochemical, functional and dietary indicators of nutritional status and health. HNR conducts basic research in relevant areas, focusing on optimal nutritional status and nutritional vulnerability in relation to health, including the development of innovative methodologies. HNR responds to the strategic priorities of the wider scientific community by conducting research projects, within the scope of HNR's activities, in collaboration with, and on behalf of: other MRC establishments and groups, Government departments, industry, national and international agencies, universities, research foundations and charitable organisations. HNR also acts as an independent, authoritative source of scientific advice and information on nutrition and health in order to foster evidence-based nutrition policy and practice. In light of the work carried out at HNR and the expertise of our staff, our comments are confined primarily to the role of nutrition in securing good health for the whole population.

The Micronutrient Status Research section at MRC Human Nutrition Research, Cambridge, led by Dr Jonathan Powell, has a long history of research interests in mineral based nano- and micro-particles in the gastrointestinal tract in terms of exposure, uptake and potential cellular effects. We study both endogenously-formed mineral particles (mineralised calcium) and exogenous mineral particles (e.g. dietary ferritin or food additives such as silicates and titanium dioxide) and we use a range of approaches from synthetic chemistry and basic cellular thought to whole-animal studies (human and murine).

Introductory concepts

We consider a nanoparticle to be a non-living nano-scaled entity. Traditionally such particles would be considered ultra-fine, fine or coarse, depending upon size, and there is an increasing consensus that the ultra-fine fraction is equivalent in meaning to nanoparticulate, which would be of < 100 nm diameter. Biologically this makes sense because, as a rule of thumb, particles below 100 nm diameter tend not to trigger active uptake mechanisms (i.e. macro-pinocytosis and phagocytosis) but instead tend to be taken up through more constitutive endocytic mechanisms. Nonetheless we wish to point out that the gut is heavily exposed to fine particles (i.e. particles > 100 nm diameter) and that these should be considered in the overall picture. Additionally, the different mechanisms of uptake, determined by particle size, will affect intracellular exposure and outcomes.

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The gastrointestinal tract is a unique environment. Unlike any other tissue the gut has specific mechanisms for the purposeful uptake of nanoparticles as well as the inevitable inadvertent pathways that nanoparticles are able to access. The major pathways are as follows:

1. Epithelial cell endocytosis. This is for true ultra-fine particles and, for example, is the route of uptake of dietary ferritin.
2. Paracellular uptake of small ultra-fines, which may be enhanced through disease processes or drugs, or dietary agents that enhance this pathway.
3. Persorption, which will allow the uptake of fine and ultra-fine particles. This is a mechanism of inadvertent permeation where an enterocyte leaving the villous tip leaves a hole through which particles can permeate.
4. M-cell uptake overlying intestinal lymphoid aggregates. This is the classical route for the uptake of fine particles and is efficient but it is likely that ultra-fines also access this route.

A further aspect of the unique gut environment is that it contains many luminal toxins and antigens and, due to entropic forces, particles will bind these in the lumen with relatively high affinity. This will change the overall properties of the particle surface and the cellular effects of the antigen or toxin. It should be noted that there are recent data showing that prion infectivity is greatly increased when prions are ingested with particulates.

Immune cells from the gut will migrate to other organs and, therefore, there is a systemic route for distribution of particles from the gut as well as the obvious routing through venous and lymphatic channels.

Gut diseases may potentially increase permeability of nanoparticle uptake.

State of the science and its current use in the food sector

- *What are the main potential applications and benefits of nanotechnologies and nanomaterials in the food sector, either in products or in the food production process?*
- *What is the current state of the market for, and the use of, food products and food production processes involving nanotechnologies or nanomaterials, either abroad or in the UK?*
- *What might the 'next-generation' of nanotechnologies and nanomaterials look like? How might they be applied in the food sector, and when might they enter the market?*
- *What is the current state of research and development in the UK regarding nanotechnologies and nanomaterials which have or may have an application within the food sector? How does it compare to research and development in other countries?*
- *What are the barriers to the development of new nano-products or processes in the food sector?*

We wish to make clear to the Committee that nanoparticles are not a new phenomenon, they occur naturally and that the gut has been exposed to them presumably throughout evolution. However, due to marked technological advances over the last five to ten years, we are able to characterise nanoparticles so much better than before, which is at least one reason for their recent appearance on the scientific horizon. The main areas pertinent to the G.I tract are as follows:

1. Enhanced delivery of nutrients: nano-encapsulation or micellar protection of micronutrients and antioxidants to prevent them from degradation during manufacture and storage or under gastrointestinal conditions. These products are already in the marketplace, for example, Novasol is a product range of supplements from Aquasol which consists of pH-resistant micelles that deliver vitamins and antioxidants. Another example is Canola Active oil, produced by Shemen Industries, that delivers phytosterols to inhibit the transportation of cholesterol from the digestive system into the bloodstream.
2. Safety: nanosensors for pathogen and contaminant detection. Raflatac have recently released, commercially, a hydrogen sulphide indicator label for fresh poultry products, where the generation of hydrogen sulphide indicates spoilage. This label contains a nano-layer of silver that changes colour once it reacts with hydrogen sulphide
3. Smart packaging: Packaging that reacts to stimuli such as materials with self-healing properties when perforated or an intelligent ripeness indicator that responds to aroma as fruit ripens.
4. Reducing spoilage: nanoclays in food packaging prevent the permeation of oxygen to slow the ageing process of food or slow the ripening of fruits and vegetables. Honeywell are marketing an oxygen barrier based on nanoclays and a nylon resin that scavenges oxygen to extend the shelf-life of beer (Aegis® OX barrier).
5. Interactive food: foods and beverage products that can be personalized to fit the tastes, nutritional needs, or allergies of individual consumers. Kraft are one of the leaders in this field of research.
6. Taste or texture improvement: reduce consumption of fat, sugar and salt through the enhancement of taste characteristics. Slim Shake Chocolate is a product already in the market, which the manufacturer (RBC), claims to contain 4–6 nm silica nanoparticles that are coated with cocoa components ("cocoa clusters") and due to their high surface area provide a satisfactory sensory experience in a low fat and low sugar product. Another example comes from Unilever which aims to reduce the fat content in ice-cream from 16% to about 1% by decreasing the size of emulsion particles that give ice-cream its texture.
7. Equipment coating: application of nano-coating in food processing equipment to prevent the growth of biofilms that can lead to food spoilage and contamination. Many commercially available food containers are already coated with nano-silver, or anti-sticking nano-composites, and some refrigerators are coated with nano-silver. Zinc oxide is also being studied as a cheaper anti-microbial agent to replace nano-silver, and applications are expected in the near future.
8. Removal of unwanted chemicals or pathogens from food.
9. Food processing: nanosensors that can withstand extreme conditions (E.g. temperature, pressure, viscosity) and provide real-time data on processing conditions

Further examples can be found in the presentation given by Dr Dora Pereira of the MSR section at MRC-HNR (Appendix, page 3) to an audience of the Cambridge Science festival on the 13th of March. We would like to add that although the range of nanotechnologies that can be applied to food, or food production, is vast, and many different strategies are being developed or are already in the market, the perception of safety will determine public acceptance and may limit the growth in several areas.

Health and safety

- *What is the current state of scientific knowledge about the risks posed to consumers by the use of nanotechnologies and nanomaterials in the food sector? In which areas does our understanding need to be developed?*
- *Is research funding into the health and safety implications of nanotechnologies and nanomaterials in the food sector sufficient? Are current funding mechanisms fit for purpose?*
- *Can current risk assessment frameworks within the food sector adequately assess the risks of exposure to nanotechnologies and nanomaterials for consumers? If not, what amendments are necessary?*
- *Are the risks associated with the presence of naturally occurring nanomaterials in food products any different to those relating to manufactured nanomaterials? Should both types of nanomaterials be treated the same for regulatory purposes?*

Gastrointestinal exposure to nanoparticles may be natural, due to inadvertent environmental exposure or due to purposeful environmental exposure. Examples of naturally occurring nanoparticles are dietary ferritin, which is about 13 nm in diameter but when digested releases iron oxide particles of around 2 to 3 nm and the endogenous calcium phosphate particles that are formed within the gut lumen and appear to have diameters of 20 to 200 nm. It is likely the majority of natural nanoparticles to which the gut is exposed are mineral based. Inadvertent environmental exposure comes through soil, dust, exhaust fumes etc. In contrast, purposeful, man-made exposure is mainly through food additives and excipients or congeners that are used in supplements and medicines etc.

We believe that traditional toxicology models are not likely to capture much information when it comes to nanoparticle adverse effects. This is because any effects are likely to be mediated immunologically and, therefore, identified through chronic exposure and by interaction with individual genotypes. It may first be useful to categorise particles as fine or ultra-fine to identify their likely route of cellular uptake and thereafter to establish their chemical stability to predict cellular processing. It may thus become be possible to develop assays that will predict nanoparticle toxicity.

Several companies are developing nano-delivery systems that enhance the absorption of antioxidants known to provide health benefits. However, many of these antioxidants are normally poorly absorbed and may not be well tolerated at higher levels, which may result in “too much of a good thing” scenarios. Therefore, prior knowledge based on normal delivery of nutrients should be ignored and these nano-delivered nutrients should be treated as novel chemical entities. However, the use of naturally occurring nanomaterials (e.g. ferritin) may be fast-tracked in future regulatory processes providing that there is evidence of their consumption over periods of time long enough to guarantee their safety, and that their administration is not substantially above what would be found in an average diet. MRC-HNR is working on the synthesis and commercialisation of ferritin-core mimetics as novel iron supplements.

Regulatory framework

- *Is the regulatory framework for nanotechnologies and nanomaterials fit for purpose? How well are imported food products containing nanotechnologies and nanomaterials regulated?*

- *How effective is voluntary self-regulation either in the UK or EU or at an international level? What is the take up by companies working in the food sector?*
- *Will current regulations be able adequately to control the next generation of nanotechnologies and nanomaterials?*
- *Is there any inter-governmental co-operation on regulations and standards? What lessons can be learned from regulatory systems in other countries?*

Currently, legislation does not account for the nano-scaling of current approved excipients and additives. An example of this is noted above, namely that amorphous silica is an approved particulate which recently has been nano-sized by RBC in their Slim Shake Chocolate product and thus has 'inherent' FDA approval although the original toxicity testing is likely to have been carried out on particles of tens of micrometres in diameter. We, therefore, believe that the regulatory process should be based on a case-by-case approach.

Public engagement and consumer information

What is the current level of public awareness of nanotechnologies, and the issues surrounding the use of nanotechnologies and nanomaterials in the food sector? What is the public perception of the use of such technologies and materials?

We have not carried out any surveys to consider the level of public awareness or perception of nanotechnologies in the food sector.

How effective have the Government, industry and other stakeholders been in engaging and informing the public on these issues? How can the public best be engaged in future?

Efforts to inform the public have not kept pace with the growth of this new technology area. This increases the risk that a false alarm over safety or health consequences could undermine public confidence, engender consumer mistrust, and, as a result, damage the future of nanotechnology, before the most exciting applications are realised.

In the latest national MORI Survey for the Office of Science and Technology (2005) a large proportion of those surveyed said that they wanted to hear about new developments in science and technology before they happen, not afterwards; and 49% said that they receive too little information about science (more than twice the proportion than in 1999/2000). The Wellcome Trust document "Engaging Science: Thoughts, deeds, analysis and action report" (2006) recognises the value of a well informed public debate "to enable a wide range of opinions to feed into policy-making discussions."

If the public is to trust, debate and value scientific progress, we need a society engaged with contemporary science. Scientists themselves need to be encouraged, trained and supported in communicating their work. Stimulating public interest in science, its potential applications, misapplications and impacts, as well as the nature of science itself can be achieved through the development of a clear public engagement strategy with specific audiences identified, measurable objectives and outputs.

What lessons can be learned from public engagement activities that have taken place during the development of other new technologies?

The value of public engagement within the fields of science and nutrition is increasingly recognised but, to date, under-utilised. A report prepared for the Research Councils UK and the Department for Innovation, Universities and Skills highlights that "direct dialogue with the public should move from being an optional add-on to science-based policy making and to the activities of research organisations and learned institutions, and should become a normal and integral part of the process" (People Science and Policy Ltd/TNS 2008). Moreover it notes that the public increasing want more information; 8 out of 10 people agreed that "science is such a big part of our lives we should all take an interest."

The Nutrition and Health Communications team at MRC HNR has a strong track record in engaging with a variety of different audiences to drive improvements in public health. Our aim is to build bridges between our scientists and people of all ages and from all walks of life to consider, question and debate the key issues in relation to diet and health and to stimulate their awareness and enthusiasm for science in society.

Public engagement has many different levels and mechanics and is a key part of the MRC Corporate Communications Strategy. At HNR our activities tend to focus on issues directly relevant to our own research or broad nutrition and health messages about a healthier diet. Our key learnings are:

- Develop a communications plan with agreed key messages appropriate to the audiences
- Provide an in depth briefing to journalists at an early stage and keep them regularly informed
- Encourage and train scientists to engage with the public
- Make scientists accessible to the media throughout the communication process
- Engage leading medical research and scientific bodies to make a positive and proactive contribution to the debate, not just defensive responses

Given our particular research interest in the area of nanoparticles we are at the start of a scoping exercise to identify how we might contribute to the debate across a variety of audiences, including the public. We shall observe the progress of this Inquiry in some detail and would welcome the opportunity to discuss public engagement opportunities in more detail.

Should consumers be provided with information on the use of nanotechnologies and nanomaterials in food products?

Public attitudes towards new technologies play an increasingly crucial role in supporting their development and application. The public should be provided with information on the use of nanotechnologies and nanomaterials in food productions because public opinion has the potential to influence the public policy and regulatory environment in either positive or negative directions, with recent examples including biotechnology and genetically modified crops. It also impacts on the investment environment, with investors influenced by actual and potential community and shareholder concerns.