

Regulation of Nanotechnologies in Food in Australia and New Zealand

Nick Fletcher¹ and Andrew Bartholomaeus²

^{1,2} Food Standards Australia New Zealand

* Corresponding author: Nick.Fletcher@foodstandards.gov.au

Received 25 October 2011; final version received 24 November 2011

© 2011 Fletcher and Bartholomaeus; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract Nanotechnologies have the potential to offer many opportunities for innovation in the food sector with applications in agriculture, water treatment, food production, processing, preservation and packaging. Whilst nanotechnologies may offer benefits in food and food packaging, the use of nanoscale materials may also present regulatory challenges similar to those for other emerging technologies, with the main issues related to potential impacts on human health. As part of an integrated whole of government approach, Food Standards Australia New Zealand (FSANZ) has assessed the capacity of the food regulatory framework in Australia and New Zealand to manage any human health risks posed by nanotechnologies under the existing legislation, the Australia New Zealand Food Standards Code, and risk assessment framework. This review sets out the current regulatory requirements for the use of nanotechnologies in food in Australia and New Zealand, amendments to data requirements for risk assessment of nanoscale and microscale particulates in the FSANZ application handbook, and ongoing monitoring of the risks associated with the use of nanotechnologies in the food sector.

Keywords nanotechnologies, food, regulation, risk assessment, nanomaterial

1. Defining a 'regulatory target' for nanotechnologies in food

Nanotechnologies are comprised of a range of technologies, sciences, processes, materials, and applications that involve manipulation of substances at sizes in the nanoscale range. A number of definitions of nanomaterials and nanoparticles have been proposed by different committees and authorities, including International Organisation for Standardisation (ISO), with the commonality that these materials have at least one dimension of approximately 1-100 nm. However, to date there is no internationally agreed definition of nanotechnology or nanomaterials suitable for regulatory purposes.

The major issue is that definitions which rely solely upon linear dimension as their basis do not provide a sound foundation for regulatory responses because they do not capture any concept of novelty or hazard. Much of what is currently presented as nanotechnologies utilizes long standing principles, technologies and materials. Advances in sophistication, however, allow the achievement of higher levels of precision and uniformity in the size and other characteristics of previously available nano-dimensioned materials. For example,

emulsions with nanoscale micelle size have been produced and studied for many years and a significant body of literature exists which deals with their preparation and characterisation [1].

In addition, in the broadest sense, all materials have structure at the nanometre scale. Polymers, gels, emulsions, clays, colloids and larger organic molecules are nanoscale materials, many of them engineered, and our environment contains a wide range of natural and anthropogenic nanoscale particulates. Foods are also naturally composed of nanoscale materials composed of sugars, amino acids, peptides and proteins, many of which form organised, functional nanostructures. Humans have consumed these materials in foods throughout evolution without significant evidence of adverse effects related to the particulate nature of the materials.

The effective regulation of nanotechnologies in the food sector requires a clear regulatory target. Therefore, in responding to the increased sophistication of the nanotechnologies, the primary focus for FSANZ is not on size of the material *per se*, but on materials likely to exhibit physicochemical and/or biological novelty. Nanoscale materials that undergo dissolution in water or oil in the final food, or in the gastrointestinal tract, cease to be nanomaterials for the purposes of food regulation in Australia and New Zealand. Conversely, nanoscale or microscale materials that are insoluble in water and oil and non-biodegradable, particularly those that may not be readily excreted, may require additional regulatory scrutiny due to their particulate nature.

2. Application of nanotechnologies to food

A number of publications have dealt with the potential applications of nanotechnologies to food [1, 2, 3, 4], however the lack of agreed definitions has led to some confusion around the actual uptake of these technologies in the food sector. For example, the *FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications* report [5], and references reviewed therein, projected that the applications of nanotechnologies to the food sector will occur in three main areas:

- by developing nanostructured food products including emulsions, surfactant micelles and emulsion bilayers using generally existing technologies;
- through the use of nanosized or nanoencapsulated food additives such as colours, preservatives, flavourings and supplements; and
- food packaging with improved mechanical, barrier and antimicrobial properties.

However, despite the wide ranging projected applications of nanotechnologies in food, there appears to be little publically available evidence of cases where approvals for new or novel nanoscale materials have been issued by regulatory authorities. In November 2008, the European Food Safety Authority (EFSA) evaluated titanium nitride particles intended to be used as an additive in polyethylene terephthalate (PET) bottles at up to 20 mg/kg. Titanium nitride is chemically inert and completely insoluble in all food simulants tested. It was concluded that as no titanium migrates from the packaging there is no exposure via food and as such no toxicological concern [6]. In November 2008, the EFSA Scientific Panel on Food Additives and Nutrient Sources published its opinion on a petition to approve a nanoscale particulate form of silver called silver hydrosol. This aqueous colloidal suspension of particles of silver had an average particle size of 0.8 nm at a concentration of 10 mg/kg or 23 mg/kg in purified water. The Panel concluded that due to the lack of an appropriate dossier supporting the use of silver hydrosol, the safety of silver hydrosol and the bioavailability of silver from it could not be assessed [7].

3. Governance Framework in Australia and New Zealand

Food Standards Australia New Zealand (FSANZ), established pursuant to s12 of the Food Standards Australia New Zealand Act 1991 (the Act), is responsible for maintaining the Australia New Zealand Food Standards Code (the Code). The Code sets out standards related to the composition, labelling, safe handling and primary production of foods sold in Australia and New Zealand. Food standards have the force of law. It is an offence in New Zealand, and a criminal offence in Australia to supply food that does not comply with relevant food standards. FSANZ is required by the Act to observe certain processes in the course of developing or reviewing food regulatory measures. However the Authority must have regard to the following overarching objectives, in priority order:

1. the protection of public health and safety; and
2. the provision of adequate information relating to food to enable consumers to make informed choices; and
3. the prevention of misleading or deceptive conduct.

The Authority must also have regard to the following:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food;

- any written policy guidelines formulated by the Council for the purposes of this paragraph and notified to the Authority.

4. Applicability of existing standards in the Code to foods manufactured using nanotechnologies or containing novel nanoscale materials

The Code includes food standards for food additives, vitamins and minerals, processing aids, contaminants and natural toxicants, articles and materials in contact with food, and novel foods

(<http://www.foodstandards.gov.au/foodstandards/foodstandardscode.cfm>). These regulatory measures require pre-market assessment for food additives, processing aids, nutritive substances and novel foods added to foods or used in food production where there is no presumption or demonstration of safety. Existing standards contain no limitations around particle size and there is currently no specific standard relevant to nanotechnologies in the Code.

Applications for new food substances manufactured using nanotechnologies, or incorporating novel nanoscale materials will be evaluated under existing standards. In December 2008, FSANZ strengthened requirements around particle size in its Application Handbook to ensure that an applicant provides appropriate information for FSANZ to conduct a risk assessment on a product manufactured using nanotechnologies. The FSANZ Application Handbook now requires that in cases where particle size is important to achieving the technological function or may relate to a difference in toxicity, the applicant must provide information on particle size, size distribution, and morphology, as well as any size-dependent properties

(http://www.foodstandards.gov.au/_srcfiles/Application%20Handbook%20as%20at%201%20August%202011.pdf).

The lack of an agreed definition of nanotechnology or nanoscale materials does not alter these data requirements because applicants must provide this information for all particulate material whether it be of nanoscale or microscale dimension. This obviates concerns around whether a size range of 1-100 nm is sufficient to capture any human health and safety risks posed by particulate material in the sub-micron size range. Thus, it avoids the concept of a 'one size fits all definition' which may fail to capture the necessary information for assessing risk associated with nanoscale materials [8].

The regulatory pathway for materials with a history of use that are already approved under existing Standards, and which could be marketed with particle sizes in the nanoscale, is less certain than for new or novel nanoscale materials. Nevertheless, the general requirements of State

and Territory legislation apply, meaning that all food must comply with the Code and be safe for human consumption. FSANZ also has the capacity to establish relevant restrictions in the Code should it become aware of a risk posed by a nanoscale material of an existing substance approved under existing Standards.

The regulation in the Code which covers articles and materials in contact with food (Standard 1.4.3) does not specify details of materials to be added to or used to produce food packaging materials or articles in contact with food. For plastic materials, the standard makes voluntary reference to Australian Standard 2070 – 1999, which in turn references relevant United States and European Union legislation and any subsequent amendments and revisions. The responsibility rests with food manufacturers and retailers to ensure that their products are safe and that they comply with all relevant legislation. FSANZ is currently reviewing regulatory requirements for food packaging materials in Australia and New Zealand to determine whether there is a need for change to current requirements, including a consideration of the application of nanotechnologies in this area.

5. Comparison with current international requirements for nanoscale materials

A United States Food and Drug Administration Task Force was charged with determining regulatory approaches that would enable the continued development of FDA-regulated products that use nanoscale materials, and to identify and recommend ways to address any knowledge or policy gaps in order to evaluate safety aspects of products that contain nanoscale materials. The report was published on 25 July, 2007 (<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf>). The Task Force concluded that classes of products with nanoscale materials do not necessarily present greater safety concerns than classes of products without nanoscale materials and chose not to adopt a precise definition for "nanoscale materials," "nanotechnology," or related terms.

In June 2011, the FDA released draft guidance for manufacturers, suppliers, importers and other stakeholders. The guidance is applicable for all FDA-regulated areas and is intended to help industry consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise for products derived through nanotechnologies. The position of the FDA does not appear to have changed substantially from the 2007 Taskforce report. The guidance does not establish definitions and reiterates that the FDA does not consider products containing nanomaterials or manufactured through the use of nanotechnology as necessarily intrinsically benign or harmful

(<http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>).

However, the document does seek to provide guidance for considering whether an FDA-regulated product contains nanomaterials, or involves the use of a nanotechnology. In that respect, the FDA will ask whether an engineered product has at least one dimension in the size range of 1-100 nm, or whether the material exhibits properties or phenomena that are attributable to its size dimension, up to a dimension of about 1 μm . Therefore, this guidance recognises the need to consider potential novel chemical or biological properties for nanoscale materials, and also, that these effects could occur outside of the 1-100 nm size range.

In the European Union, a novel foods proposal that would have included a definition of engineered nanomaterials in the area of food recently failed to pass the conciliation procedure. Existing legislation relevant to nanotechnologies in foods includes Regulation EC/1333/2008 which sets out a common authorisation procedure for additives, enzymes and flavourings. Essentially the regulation requires that when a food additive is produced by a significantly different method, or from different starting materials than that which was evaluated by the Authority or the specifications laid down, then this should be submitted to the Authority for evaluation. This includes a change in particle size, including the use of nanotechnology. Article 12 of the regulation requires that the food additive prepared by those new methods or materials will require a new entry in Community lists or a change in specification before it can be available on the market.

Regulation 450/29 on active and intelligent packaging states that "new technologies that engineer substances in particle size that exhibit chemical and physical properties that significantly differ from those at a larger scale, for example, nanoparticles, should be assessed on a case-by-case basis as regards their risk until more information is known about such new technology."

6. Adequacy of risk assessment methodologies for novel nanoscale materials in foods

FSANZ considers that the current risk assessment framework and toxicological testing methodologies are generally sufficient for assessing new or novel nanoscale materials but accepts that modifications to current protocols may be warranted as the state of the science, and sophistication of the nanotechnologies, advance. This view is consistent with a body of international opinion including that of EFSA, and an FAO/WHO expert consultation on the application of nanotechnologies in food and agriculture [5, 9].

A key area critical to the safety assessment of nanoscale and microscale particulates is an understanding of the pharmacokinetics of these materials, as this is a key potential determinant of physiological novelty. Conceptually, in order to be absorbed intact from the gastrointestinal tract, a particulate food additive in the final food (nanoscale or microscale) must first resist dissolution and degradation in the stomach and intestine and be able to pass across the gastric mucosa to the apical surface of the epithelia where it can be taken up from the intestinal lumen. Dissolution can be defined as a dynamic process by which a particle which has some solubility in the local environment goes into a solution phase to form a homogenous mixture. The rate of dissolution is influenced by size, solute concentration, surface area, surface morphology, surface energy, dissolution layer properties and aggregation. Because both particle dissolution kinetics and solubility are size dependent, nanoscale particles materials can dissolve more quickly, and theoretically, to a greater extent than macroscopic particles of the same material. The role of dissolution in the biological fate of nanoscale particles is reviewed in [10].

In the context of oral ingestion in foods, the toxicity of water or lipid soluble, or biodegradable, food materials is expected to be attributable mainly to the constituent ions or monomers and be similar to that of larger forms of the same substance. As most food additives are present in foods in a dissolved form, their preparation as nano-scaled powders to facilitate dispersion and dissolution would present neither novelty nor additional regulatory concern. These materials will therefore be assessed according to a conventional risk assessment pathway. Conversely, poorly soluble (water and lipid), non-biodegradable particles (nanoscale or micron-sized), particularly any that are not readily excreted, may require additional regulatory scrutiny where they remain particulate in nature in the final food.

Much of the greatly expanding literature on the toxicity of nanoscale materials is directed primarily at occupational health and safety issues [11, 12, 13]. The importance of particle size and aspect ratio (length to width ratio) in inhalation toxicology has been well understood for many years for a range of fibrous and non-fibrous particles [14]. In addition, carbon nanotubes have raised concern more recently due to their potential to induce pulmonary lesions in some animal models [15, 16]. Carbon nanotube exposure was also associated with inflammation and granuloma formation in the mesothelial lining of the mouse chest cavity [17], and after intraperitoneal administration to P53 heterozygous mice caused mesothelioma [18]. However, these results are of questionable relevance in assessing health risks

associated with oral ingestion of particulate materials in food. In contrast to inhalation studies, a relationship between oral ingestion of particulate material and disease has not been convincingly demonstrated in laboratory animals or humans. In fact, humans have been exposed to dietary microparticles and nanoparticles as a normal occurrence throughout evolution without significant evidence of adverse effect due to the particulate nature of the materials. This apparent difference is consistent with evidence that the gastrointestinal mucosa is a key barrier to systemic exposure of orally ingested fine particulates. The intestinal mucosa, although consisting of only a single layer of cells, is permeable to substances of low molecular weight including monomers of nutrients such as amino acids, fatty acids and saccharides, but relatively impermeable to macromolecules and particles. This low permeability means that most insoluble material has poor oral bioavailability and passes through the gastrointestinal tract and is eliminated from the body unchanged. Nevertheless, evidence has accumulated in the literature over the past 40 years demonstrating some, albeit generally low, absorption of certain nanoscale and microscale particulates across the intestinal mucosa, via M-cells to underlying lymphoid follicles, and also through normal columnar epithelia (reviewed in 19, 20, 21, 22, 23]. Tissue disposition studies have also found low levels of particulates distributed to the mesenteric lymph nodes and phagocytic cells in the liver and spleen following intestinal exposure. This tissue distribution profile is consistent with that for nanoscale particles administered intravenously, in which blood pharmacokinetic parameters are dominated by interaction with the reticuloendothelial system. Some studies have also shown that non-biodegradable material (nanoscale or microscale) may be retained in certain cells or tissues for extended time periods following oral administration [24, 25]. A detailed consideration of the pharmacokinetics of nanoscale materials following oral ingestion will be published in future issues.

Assessment of the safety of a new material (nanoscale or non-nanoscale) under current regulatory requirements generally includes an evaluation of the toxicokinetics and metabolism of the substance as well as the toxicity of the substance in a number of appropriate *in vitro* and *in vivo* tests in animals, and including, where available, evidence of safety in humans. Further work including classical pharmacokinetic studies following oral ingestion, using suitably radiolabelled particles as well as other combination techniques that can differentiate solubilised material from particulate material in biological matrices, will further facilitate the health and safety assessment of particulates that may be used in food products or food contact materials.

7. Keeping up with current practices and advances

No area of science or technology is static in nature. FSANZ has developed a range of strategies in conjunction with a whole of Government approach in Australia under the National Nanotechnology Strategy and more recently, the National Enabling Technologies Strategy, to ensure it is aware of new developments in nanotechnologies relevant to food. The agency has pursued extensive engagement with international regulators to encourage consistency of approach, gain advance notice of new applications in the food industry, contribute to the utilization of the scientific knowledgebase to test the ongoing utility of test and assessment methodologies, and to provide a basis for rapid response to emerging health related issues. Other initiatives include; linkages with, and support of, key international agencies such as WHO and FAO, scientific reviews of key areas relevant to risk assessment, most particularly the pharmacokinetics of nanoscale materials, and establishment of linkages with other Australian regulators through a Government Health Safety and Environment Working Group on nanomaterials covering commodities closer to the cutting edge of the emerging nanotechnologies. In New Zealand, FSANZ also participates in an intergovernmental nanotechnology regulators group which is considering regulatory approaches to nanomaterials in foods, consumer products, the environment, medicines and other applications.

8. Testing assumptions and reviewing practices

Test methodologies and data requirements for risk assessment are under constant review. Nanotechnologies add additional challenges which need to be weighed against the current practices to ensure those challenges are adequately addressed. Major international regulatory bodies including FSANZ and a recent FAO/WHO expert consultation on nanotechnology in food and agriculture have examined this issue closely and whilst acknowledging further work is necessary, have concluded that the current risk assessment approaches remain appropriate. As nanotechnologies advance in sophistication this conclusion will need to be revisited to ensure the conclusion remains valid. FSANZ has an ongoing program of work to review and revise where necessary existing arrangements for the regulation of nanotechnologies in food.

9. Facilitating informed debate

Of all the challenges presented by nanotechnologies perhaps the greatest is the need to facilitate balanced and informed debate around the management and consequences of new technologies in the food industry (recently reviewed in [26]).

FSANZ recognises that consumer's perception of risk can be influenced by many factors, including their level of knowledge, values and understanding of the issue, as well as an individual's level of acceptance of the potential perceived benefit. These factors may be influenced by the way in which scientific reports are reported in the media and the presence or absence of non-governmental organisation campaigns. In addition, perceptions regarding food risks can also change slowly over time as new information becomes available. Thus, studies which investigate the linkages between food and health outcomes can be important in changing perceptions and in providing reassurance regarding the safety of food. FSANZ has sought to inform the public debate through the development of fact sheets, web videos, presentations at international conferences outlining the FSANZ regulatory strategy on nanotechnologies, informed media comment and participation in public discussions. The current regulatory review provides further opportunity for industry, non-government organisations and public to comment on FSANZ's approach to regulating nanotechnologies and its view of the current state of the science.

10. Conclusions and future directions

FSANZ has adopted a range of strategies to manage potential risks associated with nanotechnologies in foods with the aim of ensuring the protection of public health and safety and having regard for the best available scientific evidence. The FSANZ strategy has involved:

- A conservative interim risk management approach through amendments to its Application Handbook to support food regulatory measures and ensure that an applicant provides appropriate information for FSANZ to conduct a risk assessment;
- Detailed assessment of the pharmacokinetics of nanoparticles as a potential determinant of novel toxicity to underpin the risk assessment of novel nanoparticulates in food should FSANZ receive an application to amend the Code;
- Providing advice to the food industry on FSANZ's regulatory activities in response to nanotechnologies, particularly the amendments to the Application Handbook; and seeking information from industry on proposed food applications for nanotechnology;
- Engagement with international food regulatory partners to share experiences and information and ensure a consistent regulatory response;
- Engagement with other key national regulatory agencies through a whole of Government Health Safety and Environment Working Group; and
- Engagement with industry, non-governmental organisations and the public through various forums including fact sheets, web videos and presentations at international conferences/workshops outlining FSANZ's regulatory response to nanotechnologies.

Under the current regulatory arrangements the level of risk posed by products of nanotechnologies in food and food packaging is considered low and FSANZ's conservative risk management strategy is considered generally sufficient to maintain an acceptable level of health protection. However, FSANZ recognises that nanotechnologies are a rapidly evolving area with potential current and projected applications in the food and food packaging sector. In order to ensure FSANZ's capacity to undertake best practice risk assessment of foods incorporating nanotechnologies, FSANZ has an ongoing program of work to review and revise, where necessary, existing arrangements for regulation of nanotechnologies in food, including:

- An assessment of existing food additives and processing aids for which permissions exist in the Code where those materials are particulate in nature in the final food, and where the material is poorly soluble, non-biodegradable, or has a potential for poor excretion. This information will be used to establish whether specifications for particle size need to be established in the Code for existing food additives and processing aids that may be manufactured to have nanoscale dimensions.
- FSANZ will also further consider the potential impacts of nanotechnologies on the safety of food packaging as part of a broader review of the standard regulating articles and materials in contact with food, and continue to work with the food packaging industry to ensure FSANZ is aware of developments in this area.
- FSANZ will continue to monitor the rapidly developing scientific literature with respect to nanotechnologies to ensure that FSANZ conclusions remain valid in light of the emerging state of the science in order to inform the need for further regulatory or non-regulatory response by FSANZ.

11. Acknowledgements

The authors would like to thank Professor Brian Priestly, Director, Australian Centre for Human Health Risk Assessment (ACHHRA) at Monash University for his helpful comments on the manuscript.

12. References

- [1] J. Weiss, P. Takhistov, J. McClements, "Functional materials in food nanotechnology," *J Food Sci*, vol. 71(6), pp. 107-116, 2006.
- [2] Q. Chaudhry, M. Scotter, J. Blackburn, B. Ross, A. Boxall, L. Castle, R. Aitken, R. Watkins, "Applications and implications of nanotechnologies for the food sector," *Food Addit Contam*, vol. 25(3), pp. 241-258, 2008.

- [3] D.J. McClements, J. Rao, "Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity," *Critical Reviews in Food Science and Nutrition*, vol. 51, pp. 285-330, 2011.
- [4] B.A. Magnuson, T.S. Jonaitis, J.W. Card, "A brief review of the occurrence, use, and safety of food-related nanomaterials," *Concise Reviews in Food Science*, vol. 76(6), pp. R126-R133, 2011.
- [5] FAO/WHO, "FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications: Meeting Report. Rome," pp. 1-103, 2009. Available online from http://www.fao.org/ag/agn/agns/files/FAO_WHO_Nano_Expert_Meeting_Report_Final.pdf
- [6] EFSA, "Scientific Opinion Scientific Opinion of the Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on 21st list of substances for food contact materials," *The EFSA Journal*, vol. 888-890, pp. 1-14, 2008.
- [7] EFSA, "Scientific Statement of the Panel on Food Additives and Nutrient Sources added to Food on a request from the Commission on Silver hydrosol as a source of silver added for nutritional purposes to food supplements," *The EFSA Journal*, vol. 884, pp. 1-3, 2008.
- [8] A.D. Maynard, "Don't define nanomaterials," *Nature*, vol. 475, pp. 31, 2011.
- [9] EFSA, "Scientific Opinion of the Scientific Committee on a request from the European Commission on the Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety," *The EFSA Journal*, vol. 958, pp. 1-39, 2009.
- [10] P. Borm, F.C. Klaessig, T.D. Landry, B. Moudgil, J. Pauluhn, K. Thomas, R. Trotter, S. Wood, "Research strategies for safety evaluation of nanomaterials, Part V: Role of dissolution in biological fate and effects of nanoscale particles," *Toxicol Sci*, vol. 90(1), pp. 23-32, 2006.
- [11] A.D. Maynard, E.D. Kuempel, "Airborne nanostructured particles and occupational health," *J Nanopart Res*, vol. 7, pp. 587-614, 2005.
- [12] A.D. Maynard, D.B. Warheit, M.A. Philbert, "The new toxicology of sophisticated materials: nanotoxicology and beyond," *Toxicol Sci*, vol. 120(S1), pp. S109-S129, 2011.
- [13] A. Seaton, L. Tran, R. Aitken, K. Donaldson, K. "Nanoparticles, human health hazard and regulation," *J R Soc Interface*, vol. 7, pp. S119-S129, 2010.
- [14] Hayes, AW "Principles and Methods of Toxicology," Fourth Edition. Taylor and Francis, Philadelphia, USA, 2001
- [15] C.W. Lam, J.T. James, R. McCluskey, R.L. Hunter, "Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation," *Toxicol Sci*, vol. 77, pp. 126-134, 2004.
- [16] D.B. Warheit, B.R. Laurence, K.L. Reed, D.H. Roach, G.A.M. Reynolds, T.R. Webb, "Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats," *Toxicol Sci*, vol. 77, pp. 117-25, 2004.
- [17] C.A. Poland, R. Duffin, I. Kinloch, A. Maynard, W.A. Wallace, A. Seaton, V. Stone, S. Brown, W. MacNee, K. Donaldson "Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study," *Nat Nanotechnol*, vol. 3(7), pp. 423-428, 2008.
- [18] A. Takagi, A. Hirose, T. Nishimura, N. Fukumori, A. Ogata, N. Ohashi, S. Kitajima, J. Kanno "Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube," *J Toxicol Sci*, vol. 33(1), pp. 105-116, 2008.
- [19] A. des Rieux, V. Fievez, M. Garinot, Y.J. Schneider, V. Preat, "Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach," *J Control Release*, vol. 116(1), pp. 1-27, 2006.
- [20] A.T. Florence, N. Hussain, "Transcytosis of nanoparticle and dendrimer delivery systems: evolving vistas," *Adv Drug Deliv Rev*, vol. 50 Suppl 1, pp. S69-S89, 2001.
- [21] N. Hussain, V. Jaitley, A.T. Florence, "Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics," *Adv Drug Deliv Rev*, vol. 50(1-2), pp. 107-142, 2001.
- [22] D.T. O'Hagan, "The intestinal uptake of particles and the implications for drug and antigen delivery," *J Anat*, vol. 189 (Pt 3), pp. 477-482, 1996.
- [23] M. Shakweh, G. Ponchel, E. Fattal, "Particle uptake by Peyer's patches: a pathway for drug and vaccine delivery," *Expert Opin Drug Deliv*, vol. 1(1), pp. 141-163, 2004.
- [24] D.D. Joel, J.A. Laissue, M.E. LeFevre, "Distribution and fate of ingested carbon particles in mice," *J Reticuloendothel Soc*, vol. 24(5), pp. 477-487, 1978.
- [25] M.E. LeFevre, R. Olivo, J.W. Vanderhoff, D.D. Joel, "Accumulation of latex in Peyer's patches and its subsequent appearance in villi and mesenteric lymph nodes," *Proc Soc Exp Biol Med* vol. 159(2), pp. 298-302, 1978.
- [26] T.V. Duncan "The communication challenges presented by nanofoods," *Nature Nanotechnology* vol. 6, pp. 683-688, 2011.

