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Food Nanotechnologies: Purchasing a Double Edge Sword

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ABTRACT

Rapid development of nanotechnology has revolutionsed various areas of conventional food science and food industry. The novel properties of nanoparticles (NPs) have led to increasing application of nanotechnology in food industry. Nanofood market have a variety of products like the creamy ice-cream, drinks with no fat, enhanced flavour with nutrients and better textured, coloured and fresh looking food. Continuous monitoring for food spoilage or contamination is possible too. Nanotechnology has transformed the food industries which claim health benefits along with better taste. With the increasing use of NPs especially in food products, where humans are in close contact of the engineered nanomaterials (NMs), it is important to ensure safety before use. Bio-nano interactions often result in novel reaction and formation of products leading to toxicity. NPs mediated toxicity mainly includes inflammation, oxidative damage and genotoxicity. Prolong use of these particles can cause detrimental effects on health. Presently, due to lack of appropriate guidelines and regulations for food nanotechnology there are uncertainties regarding risk identification. Hence, it is essential to evaluate the consequences of this technology in terms of general public and occupational health risks associated with the manufacture, use and disposal of NMs, before instigating the same in day to day use.

Keywords: Nanotoxicology; Food nanotoxicology; Bio-Nano interaction; Regulations; Public concern

1. INTRODUCTION

Nanotechnology can be defined as "the understanding and control of matter at dimension of roughly 1 nm to 100 nm, where unique phenomena enable novel applications"[1-3]. The untapped potential of this upcoming endeavour is that, at nanoscale the particles obey quantum mechanism and possess novel properties which are different from the macro counterpart[4]. With nanotechnology, a scientist can not only calculate but also manipulate matter at nanoscale for novel inventions[5].

Nature itself has beautifully well designed nanomaterials (NMs) like vital biological molecules which govern the very existence of human beings[6]. The science of nanotechnology dated to the ancient era, has now revolutionised the modern day world. Nanotechnology has unlocked new avenues in different area like medicine, agriculture, electronics, cosmetics and daily utilities[7]. The consumer market is flooded with nano based applications in medicine, water purification system, commercial products and food industry. The upcoming applications of nanotechnology are implementation of the novel mechanism at nano level with precision, and "Food –Nanotech" is one of it. With the increasing trend of nano products there is an intentional (engineered) or unintentional (Incidental/waste NPs/environmental) exposure to nanoparticles (NPs)[8,9] and human are coming in close contact with NMs, however their interaction with the bio molecular counterpart is still not clear. Nanotechnology has applications that noteworthy have ethical, legal and social implications (ELSIs)[10].

This article overviews the applications of nanotechnology in food industry drawing attention towards the safety issues, mechanism of nano induced toxicity, current regulations, guidelines and public acceptance of nano based applications in the food industry.

2. FOOD NANOTECHNOLOGY

Nano technological applications can be classified into two forms: passive nanotechnology which includes paints, colloids, polymers and ceramics or active nanotechnology that include drug delivery and robotics. Food nanotechnology comprises both forms; "passive nanotechnology" as the NPs are used in packing material and "active nanotechnology" as in Nano-Food ingredients[11]. Applications of nanotechnology in food industry can be collectively termed as Food Nanotechnology.

For Nano food applications usually two different approaches are integrated "Top down approach" and "Bottom up approach"[12]. Top down approach includes physical processing which mainly involves grinding and milling e.g. grinded green tea with improved antioxidant properties[13]. Bottom up approach is based on self-assembly and self-organisation. The process of self-assembly can be regulated by governing different non covalent forces. An example to bottom up approach is casein micelles and starch.

Nanotechnology has revolutionised many technological

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frontiers and food nanotechnology is one of it[14,15.] Convergence of nanotechnology with other industries has improved vital steps which include production, processing, transportation, safety and storage. The four vital "Ps" where nanotechnology play a role in the food industry: are processing, product development, packing and prevention from damage. Various nano formulations are used in food nanotechnology like nano-emulsions, colloids, NPs and nanocomposites[5]. Nano formulations are used for better quality food with enhanced nutrition, food packaging to prevent damage and also detection of different microbial infections. This industry utilises the benefits of this technology in nano based delivery system (liposomes, nanocapsule, nanosphere, emulsions, cubosomes, biopolymeric NPs, food safety through biosensors to detect microbial contamination and in nano packaging. Many metal oxide NPs are widely used in food industries; silver NPs as antimicrobial agents, zinc oxide NPs in packing to improve shelf-life, silica oxide NPs as carrier molecules for aroma and flavouring agents and titanium dioxide NPs are effectively used for colouring agents. Many food industries are effectively using these NPs in plentiful products. Kraft^{Tm} foods was the first to start a nanotechnology laboratory. In the current scenario, around the world nano application in food industry are increasing exponentially, and many more companies have come up with nano based products as shown in Table 1. Food nanotechnology is not only confined to food packing but also enhanced food texture, taste, colour, availability of nutrients, sensations through novel taste and creamier texture. Moreover, nano applications as biosensors can enable us to track contamination and spoilage while transportation and storage of food. Along with improved taste and texture, nano foods also guarantee health, nano based ice creams and mayonnaise are far more creamier, and at the same time, are also made from low fat nano formulations. Nano encapsulated products can deliver and distribute nutrients at the cellular level[16,17]. Futuristic prospective of nano food applications include smart packing which indicate food spoilage and expiry that are indicated by change in colour code change. Nano based application in food industry is increasing day to day different nano formulations and their use in food industry are summarised in Table 2[18].

3. HOW SAFE IS NANO PARTICLES BASED FOOD PRODUCTS

There are considerable debates regarding how the novel properties of NMs could lead to adverse biological effects, with the potential to cause toxicity. Some of the crucial questions asked are: 1) Whether NMs are more toxic than their non-nano counterparts? 2) Will NPs transform in the environment into more toxic forms? Graphite is approved by FDA, and considered as non-toxic, however the nano counterpart bucky balls are reported to show toxicity. Before NMs are allowed to be used in daily life activities, it is important for nanotoxicology research to uncover and understand how these materials influence the environment so that their undesirable properties can be eliminated. While nearly anything can be toxic at some particular dose, the more relevant question is: how toxic are NMs at the potential concentrations at which they might be used? Nanotoxicology is the study of negative side of the

Table 1. Nano products in market

Nano based food products	Companies in food Industry
Nanoceuticals slim shake	Assorted Flavor, RBC Life Sciences, Irving, USA
Oat nutritional drink	Assorted Flavor, Toddler Health, Los Angeles, USA
Canola active oil	Shemen, Israel
Nanotea	Shenzhen Become Industry Trading Co. Guangdong, China
Fortified fruit juice	High Vive.com, USA
Nanoslim beverage	NanoSlim, Canada
Daily vitamin boost	Jamba Juice, Hawaii
Tiptop up bread (Tuna fish oil)	Enfield, Australia
Nestle original coffee creamer	Nestle, USA
Trix cereal	General Mills, USA
Mentos fresh mint	Mentos, USA

Table 2. Nano formulations and applications in food Industry

Types	Applications	Examples
Nano encapsulation	Include nano composite, nano emulsification and nano structure for control release of active ingredient.	Colloidosomes, NovaSOL
Nano composites	Improve mechanical strength, reduce weight, increase resistance to heat, and act as barrier against oxygen, carbon-dioxide, UV, moisture and degradation of ripening gas, e.g. ethylene.	Durethan, Nanocor
Nano emulsions	Decontamination of food packaging equipment and packaging	Megace ES (MA-ES) (Megastrol acetate oral suspension)
Polymeric NPs	Controlled release and targeted delivery.	Vitamin E, Itraconazole, beta carotene.
Nano sized self-assembly liquid structure	Vehicle to targeted nutraceuticals.	Lycopene, beta-carotene, CoQ10, omega-3 fatty acids, phytosterols and isoflavones.

nanotechnology revolution brought into concern since 1990. Nano toxicity is reported through many research proposals, and the use of NPs becomes a question. With the extended use of NPs in food industry the primary concern would be "How safe are these applications"? Use of NPs in food industry may result in NPs mediated toxicity at different levels as shown in Fig. 1.

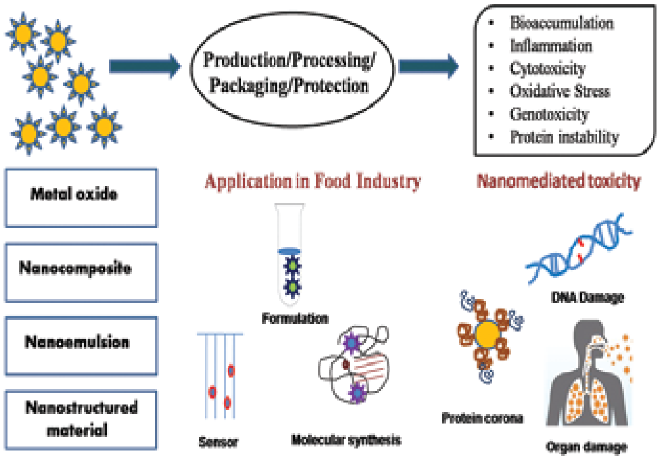

Figure 1. Nanotechnology in food industry and toxicity issues.

3.1 Occupational Health Risks in Food Industry

A major group of population exposed to NPs are those involved in processing, packaging and transportation of products containing NPs. The prime route of exposure to NPs include inhalation and dermal absorption which can cause respiratory disorders and skin diseases. Currently there are no well-defined regulatory guidelines for manufacturing units to ensure safety while handling NPs. Also there is lack of knowledge as far as lethal dose of exposure, is concerned.

3.2 Nano Flavour: Adding Taste can be Risky

Nano ingredients are profoundly used in food industry to alter food in various prospects. Most of the nano supplements are used to enhance taste and nutritional value. Various vitamins are available in the food market at nano level however, the major concern is that at nano level these food ingredients can be toxic, specifically at higher doses[19]. Consumption of vitamins at nano level may result in excessive, unmonitored absorption of vitamins by the body which could be detrimental and possibly result in various neurological disorders[19]. It is unpredictable that nano fortification food, claim to meet the dietary requirement could replace the natural varied diet.

3.3 Nano Packing and Toxicity

Use of NPs in food packaging is considered safe, as NPs are not a food component and usually accepted by the public; however, leaching of nano substituent of packing materials is quite possible. NPs are used in packing material like wraps, container, beer bottle, chopping board, cooking utensils etc, where NPs can leach out and contaminate the food. Metal oxide NPs like zinc oxide, silver oxide, copper oxide and magnesium are used for making packaging material as these ensure long term storage of food items. However, it is quite possible that these NPs can adhere or blend to the packed food materials and result in toxicity[20-23]. Considering the harmful effects of NPs all the benefits of this technology get annulled. NPs are used in various sensors to monitor and eliminate microbial contamination and toxins from food. NPs can contaminate food during this process and result in toxicity as food comes in contact with NPs. *In-vivo* and *in-vitro* studies have highlighted the lethal effect of these metal oxide NPs. In the current scenario there is no relevant data about release of NPs from the packing material in food, therefore indepth studies are required in cases where metal oxide are used in packaging. It is also important to understand how these particles move into the food chain and environment on disposable of these packaging materials[23].

Alternative to metal oxide is hybrid organic inorganic system which comprise of organic and biodegradable NMs. Zein, a component of corn protein in nano form can be used for making biodegradable plastic which is more tensile. Nano fillers made up of silicate e.g. nylon clay hydrid and mess network of silicate are quite promising for safer manufacture of nano made packing material in food industry, however these NPs can mildly interact with food and toxicity studies are required to implement their use[24]. These packaging materials ensure quality of the food item by control oxidation, release active components and maintain the texture of food. Commonly used food additives like gelatin, polyglycolic acid, polylactic acid, aliginate are effectively used in nanoenacapsulation for food packaging and application in relative to food industry. Organic and biocompatible nano formulation can certainly ensure better packaging as well as safety of the food items[25].

3.4 Oral Consumption of NPs and Toxicity at Cellular Level

Recent research has showed that NPs present toxic effects when in contact with biological interface. After ingestion these particles are diffused to the blood and lymph through which these can reach vital organs like heart, spleen, lungs, liver and possibly to brain with the ability to cross blood brain barrier. Nanoscale formulations are biologically more available, as they can penetrate deep into the tissue and cell, resulting in enhanced interaction with various biological molecules culminating toxicity. The toxicity mediated by the NPs greatly depends on size, composition, properties and aggregation[26]. With reduction in size the surface area increases, which results in offering more space for any interaction to occur. These nano bio interactions can trigger novel toxicological pathways. NPs are reported to stimulate inflammation, increased ROS production, immunological reactions, protein denaturation and DNA damage[27]. Most of toxicological studies focus on exposure to NPs through inhalation, ingestion, injection and dermal absorbtion however, considering food nanotechnology, oral route of exposure should be administered and bio-kinetic profile of NPs and biodistribution in different organs should be determined[28,29]. The gut wall executes the natural process of blocking larger material and absorbing small size particles with great efficiency. The NPs used in food nano industry are efficiently absorbed by the mammalian gut and accumulate in various organelles[30]. According to a research at Cornell University, led by Dr. Miceal Shuler it was reported that large dose intake of polystyrene NPs, blocks iron absorption and its long term utilisation may result in intestinal structure changes. NPs can also result in gut related ailments like Cron Disease. Increased absorption of NPs may result in altered nutritional profile and intrusion of foreign substances in the blood[31]. When ingested, these nano particles can disturb the gut microbial flora which also determines the health of an individual. It is important to study the fate of NPs that include absorption, distribution, metabolism and excretion by the human body[32]. The body can breakdown these NPs into more toxic metabolites e.g. metal oxide NPs into metal ions.

The intensely used nano formulations in food industry which include aluminium, silicon and titanium are commonly seen to aggregate in lymphoid tissue. Biological entities like nucleus of the cell are easily reached by these particles. NPs are reported to cross the placental barriers[33,34]. The increased surface to volume ratio enable more interaction with cellular bodies[35]. The change in physio chemical properties, ruled by the increased surface area influence cellular uptake and interactions[36,37].

ROS generation is a common phenomenon on exposure to NPs. Cells have defensive machinery to overcome ROS generations, however failure in this, results in toxicity[38,39]. Increased surface area of the NPs results in extensive ROS generations. The interaction of these particles may result in altered cellular morphology and cytoskeleton[40,41]. Wu[42,43], *et al.* showed that NPs disrupt cytoskeleton networks by changing actin fibers. Though it is reported that NPs effect the cytoskeleton network, the detailed mechanism and the role of cellular pathways involved is yet to be studied.

Inorganic NPs can interfere with the delicate balance of cellular homeostasis and thereby alter complex intracellular signalling pathways, resulting in a cascade of possible effects. These interactions can occur by several mechanisms, such as: genotoxic effects caused by high levels of ROS[44], altered protein or gene expression due to the perinuclear localisation of the particles[35], altered protein or gene expression levels due to leaching of free metal ions[45], altered activation status of proteins by interfering with stimulating factors such as cell-surface receptors[46], and altered gene expression levels in response to the cellular stress that the NPs induce[47].

To date, the effect of NMs on protein or gene expression levels has only scarcely been investigated and sufficient data needs to be generated in order to get a holistic view of the extent NPs can cause alterations to intracellular signalling pathways. Studies on genotoxicity induced by these NPs lacks detailed data and real harm caused by these NPs is yet not clear. The effect of chronic exposure and subsequent lethal damage of the genetic material has not been investigated conclusively.

Because of the high surface to charge density, pH at NPs surface is different from their surrounding[48]. NPs are also exposed to various enzymatic degradation resulting in generation of free ions and disruption in cellular homeostasis[49,50]. The surface charge enables NPs to bind with various proteins, leading to formation of protein corona[51,52]. Even the presence of proteins will result in strong bonding between the NPs and proteins[53] which can be prevented by protective coating.

It is clearly demarked that bio nano-interaction can mediate toxicity at different level of cellular organisation. Not only this, there is a dual concern of toxicity effecting human health as well as environment. These NPs inadvertently get built up at different level in the food chain during the manufacturing, utilisation and disposable process. At different levels these NPs may behave different with different unexpected surrounding, resulting in novel reactions and formation of lethal substances. It is important to effectively evaluate and put forward standard guidelines before the nano food market flourish.

4. REGULATIONS: ELSIS

The need of the hour is to develop considerable ethical, legal and social implications (ELSIs) before nano food products are introduced in the market[10]. Till date, there are no specific guidelines to evaluate toxicity related to nano food. The monitoring agencies like FDA regulate food products not technologies, thus multiple regulatory bodies are required to deliver safe nano food products in market. Combitorial system comprising of toxicologist and food technologist is required before implementing nanotechnology to human health[54]. Another aspect by the Institute of Food Science and Technology is that when nano material is a component of food additive then conventional E-numbering system should be implemented along with subscript “n”[55]. Despite of the lack of concrete rules and regulations and incomplete knowledge nano food market is flourishing by the day, ignoring the detrimental effects. In European Union, “Scientific Committee on Emerging and Newly Identified Health Risks” risk assessment related to nanotechnology and defining recognised terminology to evaluate toxicity mediated by NPs is emphasised. Standard analytical methods must be developed for effective detection of NPs in food[56]. Regulations related to nanotechnology can be framed well defined horizontal and vertical legislation. The horizontal legislation is very broad and includes aspect of nanotechnology but does not specifically state methodologies to do so. On the other hand the vertical legislation is well defined, explanatory and most recent. Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and General Product and safety Directive (GPSD) in European countries regulate nano technologies under horizontal legislation. Both define safety through gathering adequate information that whether the substance used is safe on production and well explained on labelling[57]. The Food Additives Directive (89/109/EEC) was the first legislation to include nano technologies in specific[58].

5. PUBLIC ACCEPTANCE TO NANO-FOOD TECHNOLOGY

The prime concern is public acceptance, trust and willingness to pay for nano technologies in food industry. The public is willing to buy food with nano packaging but nano food where a NM is a part of ingredient are less acceptable and considered to be less safe and compared to the nano based packaging[59]. In a study by Siegrist[60], *el al.* it was found that the public is reluctant to accept nanotechnology related foods or food packaging with nano composition. Thus the big question is will this novel technology be accepted or rejected? In a research it was found that public perception on food nano technologies is not simple but complex, and influenced by multiple factor e.g.

when product is less beneficial, consumers are more concerned about risk as compared to, when benefits are high[61]. Research on public perception on nano technologies also indicates that there is lack of information about nano food application and their impact on health and environment. Due to the unexpected outcome of the genetically modified food, public is reluctant to accept something which is artificially synthesised. However, a change in this notion can be brought through transparency, education, implementation and assurance of safety.

6. FUTURE OF FOOD NANOTECHNOLOGY

Considering the current scenario, the conflict between benefits and risk will last long before a proper regulatory authority would be constituted and guidelines will be framed; however, despite the safety concerns the benefits of food nanotechnology cannot be ignored. It is therefore essential to maintain a balance between "too strict" and "too loose" in scheming the standards and guidelines for food nanotechnologies[62]. Updated research on toxicity correlated with innovative upcoming nanotechnologies is essential for their safe application in food industry. Safety of NPs applications in food industry can be ensured only by evaluating their physio-chemical properties in the corresponding surrounding[63]. Benefits of nanotechnology in food industry can be harnessed by using NPs of biological and organic origin. Based on the research information, implementation of a well designed safety guideline in consideration to the food based applications of NPs is a prerequisite. Public acceptance of this novel technology can be achieved if the benefits are worth paying and more as out weights its drawbacks. Public awareness about both pros and cons of this application is required, by proper labelling and advertisement of such applications in food industry[64]. Though, demanding practical implementation of this technology in food industry is a far off dream, yet nanotechnology can certainly modernise the food industry.

7. CONCLUSIONS

Every technology comes with a pros and cons. The Janet facet of nanotechnology cannot be ignored. On one hand nanotechnology has made our lives much easier on the other hand there can be severe harmful drawbacks of this technology. Currently scientific research is at the very benign state, and many mysteries of the nanotechnology are yet to be known before wide spread diaspora of these in the surrounding. Application of nano based products can certainly be used in food industry under well defined regulatory guidelines.

REFERENCES

1. Tarver, T. O. N. I. Food nanotechnology. *Food Technology-Champaign*, 2006, **60**(11), 22–26.
2. Donaldson, K. & Stone, V. Technical opinion. *Communications ACH*, 2004, 47.
3. Masciangioli, T. & Zhang W. X. Peer reviewed: environmental technologies at the nanoscale. *Environmental Sci. Technol.*, 2003, 102-108.
4. Karmakar, A.; Zhang, Q. & Zhang Y. Neurotoxicity of nanoscale materials. *J. Food Drug Anal.*, 2014, **22**(1), 147-160. doi: org/10.1016/j.jfda.2014.01.012
5. Weiss, J.; Takhistov P. & McClements, D. J. Functional materials in food nanotechnology. *J. Food Sci.*, 2006, **71**(9), 107-116. doi: 10.1111/j.1750-3841.2006.00195.x.
6. German, J. B.; Smilowitz, J. T. & Zivkovic, A. M. Lipoproteins: When size really matters. *Current opinion Colloid Interface Sci.*, 2006, **11**(2-3), 171-183. doi: 10.1016/j.cocis.2005.11.006.
7. Zhang, F.; Ali, Z.; Amin, F.; Feltz, A.; Oheim, M. & Parak W. J. Ion and pH sensing with colloidal nanoparticles: influence of surface charge on sensing and colloidal properties. *Chem. Phys. Chem.*, 2010, **11**(3), 730-735. doi: 10.1002/cphc.200900849.
8. Ai, J.; Biazar, E.; Jafarpour, M.; Montazeri, M.; Majdi, A.; Aminifard, S.; Zafari, M.; Akbari, H. R. & Rad, H.G. Nanotoxicology and nanoparticle safety in biomedical designs. *Int. J. Nanomed.*, 2011, **6**, 1117-1127. doi: 10.2147/IJN.S16603
9. Lison, D., Vietti, G. & Van den Brule, S. Paracelsus in nanotoxicology. *Particle Fibre Toxicol.*, 2014, **11**(1), 35. doi: 10.1186/s12989-014-0035-7
10. Dudo, A.; Choi, D.H. & Scheufele, D.A. Food nanotechnology in the news : Coverage patterns and thematic emphases during the last decade. *Appetite,* 2011, **56**(1), 78-89. doi: 10.1016/j.appet.2010.11.143
11. Das, M., Saxena, N. & Dwivedi, P.D. Emerging trends of nanoparticles application in food technology*:* Safety paradigms. *Nanotoxicology*, 2009, **3**(1), 10-18. doi: 10.1080/17435390802504237
12. Silva, P.T.D.; Fries, L.L.M.; Menezes, C.R.D.; Holkem, A.T.; Schwan, C.L.; Wigmann, É.F.; Bastos, J.D.O. & Silva, C.D.B.D. Microencapsulation: Concepts, mechanisms, methods and some applications in food technology. *Ciência Rural*, 2014, **44**(7), 1304-1311.
13. Shibata, T. & Kaiken K.K. Method for producing green tea in microfine powder. United States Patent US6416803, B1, 2002
14. Arora, A. & Padua, G.W. Nanocomposites in food packaging. *J. Food Sci.*, 2010, **75**(1). doi: 10.1111/j.1750-3841.2009.01456.x
15. Berube, D.M. Nano-hype: the truth behind the nanotechnology buzz. Prometheus Books. 2006.
16. Kuzma, J. & VerHage, P. Nanotechnology in agriculture and food production: Anticipated applications. Project on Emerging Nanotechnologies. 2006
17. Scrinis, G. & Lyons, K. The emerging nano-corporate paradigm: Nanotechnology and the transformation of nature, food and agri-food systems. *Int. J. Sociol. Agric. Food*, 2007, **15**(2), 22-44.
18. Sekhon, B.S. Food nanotechnology–an overview. *Nanotechnology, science and applications*, 2010, **3**(1), 1.
19. Friends of the Earth, Out of the laboratory and on to our plates Nanotechnology in Food and Agriculture. http://www.foeeurope.org/activities/nanotechnology/Documents/Nano_food_report.pdf; www.scribd.com/doc/9197096/Nano-Food. 2008

20. Von Moos, L.M.; Schneider, M.; Hilty F.M., Hilbe, M.; Arnold, M.; Ziegler, N.; Mato, D.S.; Winkler, H.; Tarik, M.; Ludwig, C. & Naegeli, H. Iron phosphate NPs for food fortification: Biological effects in rats and human cell lines. *Nanotoxicology*, 2017, **11**(4), 496-506
21. Wittig, A.; Gehrke, H.; Del Favero, G.; Fritz, E.M.; Al-Rawi, M.; Diabaté, S.; Weiss, C.; Sami, H.; Ogris, M. & Marko, D. Amorphous silica particles relevant in food industry influence cellular growth and associated signaling pathways in human gastric carcinoma cells. *Nanomaterials*, 2017, **7**(1), 18.
22. Bouwmeester, H.; Van Der Zande, M. & Jepson, M.A. Effects of food-borne nanomaterials on gastrointestinal tissues and microbiota. *Wiley Interdisciplinary Reviews: Nanomed. Nanobiotechnol.* 2017. **10**(1)
23. Servin, A. D.; Pagano, L.; Castillo-Michel, H.; De la Torre-Roche, R.; Hawthorne, J.; Hernandez-Viezcas, J. A.; Loredo-Portales, R.; Majumdar, S.; Gardea-Torresday, J.; Dhankher, O.P. & White, J.C. Weathering in soil increases nanoparticle CuO bioaccumulation within a terrestrial food chain. *Nanotoxicology*, 2017, **11**(1), 98-111.
24. Go, M. R.; Bae, S. H.; Kim, H. J.; Yu, J. & Choi, S. J. Interactions between food additive silica NPs and food matrices. *Frontiers Microbio.*, 2017, **8**, 1013.
25. Sozer, N. & Kokini, J.L. Nanotechnology and its applications in the food sector. *Trends Biotechnol.*, 2009, **27**(2), 82-89.
doi: 10.1016/j.tibtech.2008.10.010
26. Oberdörster, G.; Oberdörster, E. & Oberdörster, J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environmental Health Perspectives*, 2005, **113**(7) 823-839.
doi: 10.1002/jbm.a.32530.
27. Soenen, S.J.; Rivera Gil, P.; Montenegro J.M.; Parak, W.J.; De Smedt S.C. & Braeckmans K. Cellular toxicity of inorganic NPs: common aspects and guidelines for improved nanotoxicity evaluation. *Nano Today*, 2011, **6**(5), 446-465.
doi: 10.1016/j.nantod.2011.08.001.
28. Choi, S.J. & Choy, J.H. Biokinetics of zinc oxide NPs: toxicokinetics, biological fates, and protein interaction. *In. J. Nanomed.*, 2014, **9**(Suppl 2), 261.
doi: 10.2147/IJN.S57920
29. Geiser, M. & Kreyling, W.G. Deposition and biokinetics of inhaled NPs. *Particle Fibre Toxicol.*, 2010, **7**(1), 2. 1-17.
doi: 10.1186/1743-8977-7-2
30. Hillyer, J.F. & Albrecht, R.M. Gastrointestinal persorption and tissue distribution of differently sized colloidal gold NPs. *J. Pharm. Sci.*, 2001, **90**(12), 1927-1936.
doi: 10.1016/j.tibtech.2008.10.010
31. Chaudhry, Q.; Scotter M.; Blackburn, J.; Ross, B.; Boxall, A.; Castle, L.; Aitken, R. & Watkins R. Applications and implications of nanotechnologies for the food sector. *Food Additives Contaminants*, 2008, **25**(3), 241-258.
doi: 10.1080/02652030701744538
32. Handy, R.D. & Shaw, B.J. Toxic effects of NPs and nanomaterials: Implications for public health, risk assessment and the public perception of nanotechnology. *Health, Risk & Society* , 2007, **9**(2), 125-144.
doi: 10.1080/13698570701306807.
33. Gu, Y. J.; Cheng, J.; Lin, C. C.; Lam, Y. W.; Cheng, S. H. & Wong, W. T. Nuclear penetration of surface functionalised gold NPs. *Toxicology and applied Pharmacology*, 2009, **237**(2), 196-204.
doi: 10.1016/j.taap.2009.03.009.
34. Chu, M.; Wu; Q.; Yang H.; Yuan R.; Hou S.; Yang, Y.; Zou Y.; Xu, S.; Xu, K. & Ji, A. & Sheng, L. Transfer of quantum dots from pregnant mice to pups across the placental barrier. *Small*, 2010, **6**(5), 670-678.
doi: 10.1002/smll.200902049
35. Pisanic II, T. R.; Blackwell, J. D.; Shubayev, V. I.; Fiñones, R. R. & Jin, S. Nanotoxicity of iron oxide nanoparticle internalisation in growing neurons. *Biomaterials,* 2007, **28**(16), 2572-2581.
doi: 10.1016/j.biomaterials.2007.01.043.
36. Adler, A. F. & Leong, K. W. Emerging links between surface nanotechnology and endocytosis: impact on nonviral gene delivery. *Nano Today*, 2010, **5**(6)553-569.
doi:10.1016/j.nantod. 2010.10.007
37. Verma, A. & Stellacci F. Effect of surface properties on nanoparticle–cell interactions. *Small*, 2010, **6**(1), 12-21.
doi: 10.1002/smll.200901158
38. Jain, K.; Kohli, E.; Prasad, D.; Kamal, K.; Hussain, S. M. & Singh, S. B. In Vitro Cytotoxicity Assessment of Metal Oxide NPs. *Nanomedicine and Nanobiology,* 2014, **1**(1), 10-19.
doi: 10.1166/nmb.2014.1003
39. Diaz, B.; Sanchez-Espinel, C.; Arruebo, M.; Faro, J.; de Miguel, E.; Magadán, S.; Yagüe, C.; Fernández-Pacheco, R.; Ibarra, M.R.; Santamaria, J. & González-Fernández, Á. Assessing methods for blood cell cytotoxic responses to inorganic nanoparticles and nanoparticle aggregates. *Small*, 2008. **4**(11), 2025-2034.
doi: 10.1002/smll.200800199.
40. Soenen, S. J.; Illyes, E.; Vercauteren, D.; Braeckmans, K.; Majer, Z.; De Smedt S. C. & De Cuyper, M. The role of nanoparticle concentration-dependent induction of cellular stress in the internalisation of non-toxic cationic magnetoliposomes. *Biomaterials*, 2009, **30**(36), 6803-6813.
doi:10.1016/j.biomaterials.2009.08.050.
41. Soenen, S.J.; Nuytten, N.; De Meyer, S.F.; De Smedt, S.C. & De Cuyper, M. High Intracellular Iron Oxide Nanoparticle Concentrations Affect Cellular Cytoskeleton and Focal Adhesion Kinase-Mediated Signaling. *Small*. 2010. **6**(7), 832-842.
42. Wu, X.; Tan Y.; Mao H. & Zhang M. Toxic effects of iron oxide NPs on human umbilical vein endothelial cells. *In. J. Nanomed.*, 2010, 5, 385.
43. Buyukhatipoglu, K. & Clyne A. M. Superparamagnetic iron oxide NPs change endothelial cell morphology and mechanics via reactive oxygen species formation. *J. Biomed. Mater. Res.*, 2011, **96**(1): 186-195.
doi: 10.1002/jbm.a.32972.
44. Singh, N.; Manshian, B.; Jenkins, G.J.; Griffiths, S.M.;

Williams, P.M.; Maffeis, T.G.; Wright, C.J. & Doak, S.H. NanoGenotoxicology: The DNA damaging potential of engineered nanomaterials. *Biomaterials*, 2009, **30**(23-24), 3891-3914.
doi: 10.1016/j.biomaterials.2009.04.009.

45. Soenen, S.J.; Himmelreich, U.; Nuytten, N.; Pisanic, T.R.; Ferrari, A. & De Cuyper, M. Intracellular nanoparticle coating stability determines nanoparticle diagnostics efficacy and cell functionality. *Small*, 2010, **6**(19), 2136-2145.
doi: 10.1002/smll.201000763.
46. Miller, I.S.; Lynch, I.; Dowling, D.; Dawson, K.A. & Gallagher, W.M. Surface-induced cell signaling events control actin rearrangements and motility. *J. Biomed. Mater. Res.*, 2010, **93**(2), 493-504.
doi: 10.1002/jbm.a.32530.
47. Kedziorek, D.A.; Muja, N.; Walczak, P.; Ruiz-Cabello, J.; Gilad, A.A.; Jie, C.C. & Bulte, J.W. Gene expression profiling reveals early cellular responses to intracellular magnetic labeling with superparamagnetic iron oxide nanoparticles. *Magnetic Resonance Med.*, 2010, **63**(4), 1031-1043.
doi: 10.1002/mrm.22290.
48. Zhang, F.; Ali, Z.; Amin, F.; Feltz, A.; Oheim, M. & Parak, W.J. Ion and pH sensing with colloidal NPs: influence of surface charge on sensing and colloidal properties. *ChemPhysChem*, 2010, **11**(3), 730-735.
doi:10.1002/cphc.200900849
49. Sée, V.; Free, P.; Cesbron, Y.; Nativo, P.; Shaheen, U.; Rigden, D.J.; Spiller, D.G.; Fernig, D.G.; White, M.R.; Prior, I.A. & Brust, M. Cathepsin L digestion of nanobioconjugates upon endocytosis. *ACS Nano*, 2009, **3**(9), 2461-2468.
doi:10.1016/j.biomaterials.2007.01.043 .
50. Sealy, C. Researchers reveal fate of NPs inside cells. *Nano Today*, 2009, **4**(6), 452-453.
doi: 10.1016/j.nantod.2009.10.002
51. Cedervall, T.; Lynch, I.; Lindman, S.; Berggård, T.; Thulin, E.; Nilsson, H.; Dawson, K.A. & Linse, S. Understanding the nanoparticle–protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proceedings of the National Academy of Sciences*, 2007, **104**(7), 2050-2055.
doi: 10.1073_pnas.0608582104.
52. Neagu, M.; Piperigkou, Z.; Karamanou, K.; Engin, A. B.; Docea, A. O.; Constantin, C.; Negrei, C.; Nikitovic, D. & Tsatsakis, A. Protein bio-corona: critical issue in immune nanotoxicology. *Archives Toxicology*, 2017, **91**(3), 1031-1048.
53. Wiogo, H.T.; Lim, M.; Bulmus, V.; Yun, J. & Amal, R. Stabilisation of magnetic iron oxide nanoparticles in biological media by fetal bovine serum (FBS). *Langmuir*, 2010, **27**(2), 843-850.
doi: 10.1021/la104278m
54. Maynard, A. Presentation: nanotechnology and human health impact. A framework for strategic research. Available from http:/www.Nanotech project.org/process/files/2741/18_nanotechnology. Human health impact framework strategic research.pdf. 2010.
55. IFST. Institute of Food Science and Technology. Nanotechnology. http://www.ifst.org/uploadedfiles/cms/store/attachments/nanotechnology, 2006.
56. Tiede, K.; Boxall, A.B.; Tear, S.P.; Lewis, J.; David H. & Hassellöv, M. Detection and characterisation of engineered NPs in food and the environment. *Food Additives Contaminants*, 2008, **25**(7), 795-821.
doi: org/10.1080/02652030802007553
57. Cushen, M.; Kerry, J.; Morris, M.; Cruz-Romero, M. & Cummins, E. Nanotechnologies in the food industry–Recent developments, risks and regulation. *Trends Food Sci. Technol.*, 2012, **24**(1), 30-46.
doi: 10.1016/j.tifs.2011.10.006
58. Eisenberger, I.; Nentwich M.; Fiedeler U.; Gazsó, A. & Simkó M. Nano regulation in the European Union (NanoTrust Dossier No. 017en–November 2010)
59. Roosen, J.; Bieberstein, A.; Blanchemanche, S.; Goddard, E.; Marette, S. & Vandermoere, F. Trust and willingness to pay for nanotechnology food. *Food Policy* , 2015, **52**, 75-83.
doi:10.1016/j.biomaterials.2007.01.043.
60. Siegrist, M.; Cousin, M.E.; Kastenholz, H. & Wiek, A. Public acceptance of nanotechnology foods and food packaging: The influence of affect and trust. *Appetite*, 2007, **49**(2), 459-466.
doi:10.1016/j.appet.2007.03.002
61. Currall, S.C.; King, E.B.; Lane, N.; Madera, J. & Turner, S. What drives public acceptance of nanotechnology? *In* Presenting Futures, 2008, 109-116
62. Chau, C.F.; Wu, S.H. & Yen, G.C. The development of regulations for food nanotechnology. *Trends Food Sci. Technol.*, 2007, **18**(5), 269-280.
63. Mattsson, M.O. & Simkó, M. The changing face of nanomaterials: Risk assessment challenges along the value chain. *Regulatory Toxicol. Pharmacol.,* 2017, **84**, 105-115.
64. Engelmann, W. & Gaymard, S. Consumers health and safety in relation to the use of nanotechnology in food: Challenges and perspectives from the humanities and social sciences. *Canadian Social Sci.,* 2017, **13**(3), 1-6.

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