Chapter 3
Application of Nanobiosensors for Food Safety Monitoring

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Abstract Dairying is a major sector for the development of socioeconomic conditions in India. The milk production in India mainly comes from millions of small farmers, and 35% of milk produced in India is pasteurized predominantly by state cooperatives, multinational companies, or government dairy plants. There are many factors that may affect the quality and safety of milk including pathogen contamination and growth, chemical contaminants, and nutrient degradation. FSSAI has

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established a regulatory standard for microbial and non-microbial contaminants in milk and milk products. Therefore, dairy industries or food business operators (FBOs) are needed to follow these standards during the manufacture, marketing, retails, and distribution of various dairy products. Since consumption pattern of dairy foods by the consumers and the demand for quality and safe food is increasing, the industries are under tremendous pressure to meet the requirement in one working day. Hence the need of the hour is to develop novel methods which are real-time, accurate, cost-effective, selective, no interference with other contaminants, etc. Many studies have revealed the various applications of biosensors, including environmental and bioprocess control and quality and safety control of dairy products. At present, the biosensors are applied to a large variety of samples including dairy products, food, environmental samples, etc. Further, these biosensors are integrated into nano-molecules for the development of nanobiosensor in order to improve the performance of the system in both the existing and potential sensing applications. We reviewed that the nanobiosensors are naturally sensors which are made up of nanomaterials and interestingly these are not the specialized sensors which can detect the nanoscale events and happenings. The nanobiosensors are developed by using specific recognition molecules which are integrated on a surface of the nanowire/nanotube for making a specifically sensitive to the target. The Wide spectrum of recognition molecule like single-stranded DNA, an antibody, aptamer, enzymes, protein which shows an affinity toward a target, or a protein that specifically interact with another biological molecule. These nanobiosensors are having wide application in the field of microbial quality and safety monitoring in dairy industry including antibiotics, pesticides, heavy metals, aflatoxin, and adulterants, microbial contamination including foodborne pathogens, *and* packaging material integration with nanobiosensor as an indicator of quality and safety of the products. Furthermore, the development of lab-on-a-chip technique by integration of analyte onto a microfluidic chip to develop an electromechanical system would provide new avenue field of nanobiosensor. However, there are still several challenges to overcome, which limit the progress of technology transfer and commercialization, mainly related to the difficulties in the integration of all the components into a single portable platform. Yet, there is still a long road ahead for this emerging technology to be fully adapted to a filed application.

Keywords Nanobiosensor · Food safety · Detection · Chemical and microbial

3.1 Introduction

Dairying is one of the finest instrumentals for the development of socioeconomic condition in India. In India, there are 400 million milk-producing animals (FAOSTAT, 2005) providing 146.3 million tons of milk per year as per economic survey in 2014–2015. Among the total milk productions in India, around 54.5% comes from Buffalo followed by 41% from cow and remaining 4.5% from goats

(Hemme et al. 2003). The milk production in India mainly comes from millions of small farmers, dispersed throughout the rural areas, and these farmers are holding average herd size of one or two milch animals which comprises of cow and/or buffaloes. About 35% of milk produced in India is pasteurized predominantly by state cooperatives, multinational companies, or government dairy plants (India in Business 2008). There are many factors that may affect the quality and safety of milk including pathogen contamination and growth, chemical contaminants, and nutrient degradation. Among them, biological hazards are of major concerned in dairy sector due to the fact that milk is an ideal medium for the growth and activity of bacterial pathogens including zoonotic pathogens such as *Salmonella*, *Escherichia coli* O157: H7, *Listeria monocytogenes*, *Staphylococcus aureus*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Bacillus cereus*, *Clostridium botulinum*, *Mycobacterium bovis*, *Brucella abortus*, and *Brucella melitensis*.

Chemical hazards can be unintentionally introduced into milk and milk products, making them unsafe and unsuitable for consumption. One possible way of getting chemical contamination is by milking the animals which consume feed and/or water that contain chemicals. Chemical contaminants in milk comprise chemical hazards that may introduce during milk production, dairy processing, or packaging. Antibiotic residues, aflatoxins, pesticides, heavy metals, and radionuclides are some chemical contaminants that can come into animal foodstuffs and secreted as residues in milk. Among these, the most combative residues that occur in milk are antimicrobial drugs that may cause risks to the consumers (Khiniki 2006).

In the year 2008, the Government of India has established an authority known as FSSAI (Food Safety and Standards Authority of India) for providing quality and safe food to the consumer. Accordingly, FSSAI has developed a regulatory standard for microbial and non-microbial contaminants in milk and milk products. Indian dairy industries or food business operators (FBOs) are needed to follow these standards during the manufacture, marketing, retails, and distribution of various dairy products. In recent years, consumer preferences and awareness's regarding quality and safety issues in dairy products are also increasing. Therefore, industries are under tremendous pressure to provide these dairy products, within a period of 24 h. or one working day with utmost care regarding quality and safety. Hence the need of the hour is to develop novel methods which are real-time, accurate, cost-effective, selective, no interference with other contaminants, etc. Many studies revealed the various applications of biosensors, including environmental and bioprocess control and quality and safety control of dairy products. At present, the biosensors are applied to a large variety of samples including dairy products, food, environmental samples, etc. Further, these biosensors are integrated into nano-molecules for the development of nanobiosensor in order to improve the performance of the system in both the existing and potential sensing applications. Therefore in this chapter, we have been extensively discussing the applications of nanobiosensors in the dairy industry for the monitoring of dairy processing, shelf-life extension, quality and safety of dairy products, etc.

3.2 Quality and Safety Issues

3.2.1 Chemical Contaminants

Milk is a perishable food commodity having rich source of readily available nutrient including lactose, fat, proteins, mineral, vitamins, etc. If milk is not handled properly, it may lose its natural quality during production, processing, and distribution (Awasthi et al. 2012). The major contaminants that come across in milk and milk products during milk production, dairy processing, or packaging are veterinary drugs/drug residues, heavy metals, radionuclides, mycotoxins, pesticides, etc., which may enter through water, animal feed, and other environmental sources.

Antibiotic Residues

The most combative residues that arise in milk are antibiotic residues that may have both technological and public health importance. Many of the antibiotic residues were used in the treatment of dairy cattle which involves intra-mammary infusion as well as the parenteral route of administering drugs to control mastitis, metritis, etc. In addition, some drugs are administered to control endo- and ectoparasites and several illnesses and to boost milk production (Korsrud et al. 1998). In animal husbandry, antibiotics are extensively used for therapeutics, prophylaxis, and metaphylaxis and as a growth promoter (Woolhouse et al. 2015; Rushton et al. 2014). Antibiotics which are commonly used as feed additives include tetracycline, nitrofurans, and sulfonamides (DeVries 1997). Many biologically active metabolites of antimicrobial in milk and dairy products could result in anaphylaxis and allergic shock in sensitized individuals (Gustafson 1991). The most commonly used antimicrobials in dairy cattle include β-lactams, tetracyclines, amino glycosides, macrolides, and sulfonamides (Mitchell et al. 1998). These drugs are also administered to animals through different routes such as parenteral (intravenous, intramuscular, subcutaneous, intramammary, intrauterine, etc.), oral (in the food/water), topical (on the skin), inhalation, and rectal. Theoretically, in lactating cow administration of drugs through all of the above routes may lead to an appearance of residues in milk and dairy products (Mitchell et al. 1998). These measurable levels of the antibiotic are usually detectable in the milk for a few days after the last administration of the drug (EU/Codex Alimentarius commission). Regulations have recommended the maximum residues limits (MRLs) for some/many drugs in milk (European Commission 1997). Primary concerns associated with antimicrobial residues in milk and dairy products are expressed by the dairy processors who found that contaminated milk inhibits the starter cultures used in the production of cheeses, yogurt, and other fermented dairy products as well as it influences the results of the dye reduction tests used for milk quality at the time of reception of raw milk (Jensen 1995). The main apprehension of veterinary drug residues is the possible transmission of antibiotic resistance gene-containing bacteria from milk and dairy products to human population (Hao et al.

2014). On the other hand, plants and agricultural products serve as a reservoir for many microbes which are nonpathogenic to plants whereas pathogenic to animals and humans (Schikora et al. 2012; Gu et al. 2011). Antibiotics can cause some disruptions like aplasia of the bone marrow (e.g., chloramphenicol) (Mitchell et al. 1998) and carcinogen (e.g., oxytetracycline and furazolidone). Therefore, the use of antibiotics in livestock sector may accelerate the development of antibiotic-resistant microbial pathogens, leading to potentially muddling treatment for both animals and humans diseases.

Pesticides

Pesticides are widely used in agriculture to protect the crop from insects/pests, but, through water, forages, and the environment, they become a part of the milk causing contamination and thus confer a health risk (Bo et al. 2011). Chlorinated pesticides, organophosphate, carbaryl, and related compounds such as DDT, endosulfan, polychlorinated biphenyls (PCBs), and dioxins are some of the pesticides that can enter milk and dairy products (Mukerjee 1998). On ingestion, around 20% of an ingested chlorinated hydrocarbon is excreted in milk, adhering to milk fat and butter (Hubbert et al. 1996). DDT is a lipophilic compound; hence it can accumulate in fatty tissues and can transfer into milk and dairy products. Pesticides, such as hexachlorocyclohexane (HCHs), can cause damage to central nervous system, reproductive system, and endocrine system (Alvarado and Perez 1998). Universally, all organochlorine pesticides are characterized by their high lipophilicity and long elimination half-lives. Disruption of normal endocrine-regulated functions by these chemicals represents an important consideration in risk assessment (Mukerjee 1998). In view of the potential health hazards, there are around 13 pesticides which are restricted for use in India since 1997 such as DDT, lindane, methyl parathion, endosulfan, monocrotophos, aluminum phosphate, dieldrin, etc. Residues of such compounds may persist in the environment and cause contamination through the food chain (Wong and Lee 1997).

Aflatoxin M1

Aflatoxins are a group of highly toxic secondary metabolic products of molds such as *Aspergillus flavus and Aspergillus parasiticus*, which infect the cereals and oil seeds, the major constituents of dairy cattle feed, during their pre- and postharvest management. Molds occur in these agro-products, during the growth of plants, maturity, harvesting, and processing of grains. Their presence is influenced by various factors like temperature, relative humidity, oxygen availability, and damaged or broken grain kernels (Lanyasunya et al. 2005). Aflatoxin M1 (AFM1) may be found in the milk of animals that are fed with aflatoxin B1 (AFB1)-contaminated feed (Kangethe and Langa 2009). The concentration of AFM1 in milk is entirely dependent on the presence of the precursor AFB1 in the

ration of dairy cattle, and it can numerically express as a feed to milk ratio. The AFM1 in milk is a carcinogenic metabolite of aflatoxin B1. The generation of AFM1 by the metabolites of AFB1 occurs in the liver and its secrets into milk in the mammary gland of dairy cows (Khiniki 2006) may lead to increase in the risk of liver cancer. The International Agency for Research on Cancer (IARC) of WHO included AFB1 as primary and AFM1 as secondary groups of carcinogenic compounds. Heat treatments like pasteurization, boiling, and UHT treatment were not effective in lowering the development of AFM1 (Khiniki 2006). These findings indicated that AFM1 with altered levels could be available in dairy products made from unclean milk. Consequently, this subject is a serious problem for the public health for all the age groups, including infants and children who consume the milk-containing products worldwide. For this reason, milk and dairy products have to be evaluated uninterruptedly for AFM1 contamination at least twice a year. Beside this, it is important to have low levels of AFM1 in the feeds of dairy animals, and in order to achieve this purpose, feeds of dairy cows should be kept away from contamination as much as possible (Bakirci 2001; Khiniki 2006). Due to the potent carcinogenicity of aflatoxin, most countries regulate the presence of aflatoxin in both feed and milk. The tolerance level for AFM1 in milk varies among countries from 0.05 μg kg^{-1} in Europe to 0.5 μg kg^{-1} in the USA (Saitanu 1997; WHO 2002). In India, FSSAI has also established a standard for aflatoxin M1 (0.5 ppb) in milk.

Heavy Metals

Heavy metals enter the human and animal body mainly through inhalation and ingestion. Heavy metals produce toxic effects by replacing essential metal ions existing in the chelates present in the body. The intake via ingestion depends upon food habits (Aytenfsu et al. 2016). The metals, namely, copper (Cu) and zinc (Zn), are essential micronutrients and have a variety of biochemical functions in all living organisms (Licata et al. 2004). While Cu and Zn are essential, they can be toxic when taken in excess; both toxicity and necessity vary from element to element. It is well established that lead (Pb) and cadmium (Cd) are toxic for human especially children who are more sensitive to these metals than adults. Milk is the fundamental food for infants, and the daily intake of the heavy metals Pb, Cd, Cu, and Zn can be determined by different age groups of infants through different milks and baby foods. Heavy metals can enter to milk and dairy products and affect the health of people who have consumed contaminate milk and dairy products. The health implications from heavy metals lead to kidney damage, cardiovascular diseases, and induction of hypertension, growth inhibition, and interference in hemoglobin synthesis and irreversible changes in the brain and nerve cells, and also some of these residues are known to be carcinogenic in nature. The pulmonary and nervous systems and skins are the main target organs of arsenic contamination. Cadmium is associated with kidney damage, and lead is considered to be associated with learning deficits in children. Copper and zinc are essential micronutrients but in higher amount may influence metallic taste to the product resulting unacceptability

of the product (Raghunath et al. 1997). With increasing environmental pollution, a heavy metal exposure assessment study is necessary (Ikeda et al. 1996, Raghunath et al. 1997)

3.2.2 Microbiological Contaminants

The presence of foodborne pathogens in milk and milk products is due to direct contact with contaminated sources in the dairy farm environment, infected animals, and improper personnel hygiene (Zeinhom and Abdel-Latef 2014). The microbiological quality of milk and dairy products is influenced by the initial flora of raw milk, the processing conditions, and post-heat treatment contamination (Rajagopal et al. 2005). Today's context, food spoilage is a big economic problem worldwide. Undesirable microbes in the milk can cause spoilage of dairy products which include Gram-negative psychrotrophs, coliforms, lactic acid bacteria, yeasts, and molds. In addition, various bacteria of public health concern such as *Salmonella* spp., *L. monocytogenes*, *C. jejuni*, *Y. enterocolitica*, pathogenic strains of *E. coli*, and enterotoxigenic strains of *S. aureus* may also be found in milk and dairy products. In industrialized countries like India, the percentage of the population suffering from foodborne diseases each year has been reported to be up to 30%. Though there are various foodborne pathogens that have been identified for foodborne illness, *Campylobacter*, *Salmonella*, *L. monocytogenes*, *and E. coli* O157:H7 have been generally found to be responsible for the majority of foodborne outbreaks (Alocilja and Stephen 2003; Chemburu et al. 2005). In the last two decades, other infectious agents have been either newly defined or newly concomitant with foodborne transmission. *L. monocytogenes*, *E. coli* O157:H7, *C. jejuni*, *Staphylococcus intermedia*, *Enterobacter sakazakii*, and *Salmonella enteritidis* are examples of newly described pathogens that often are foodborne. The most dangerous among them are enterohemorrhagic *E. coli* strains, especially serotype O157:H7. *E. coli* O157:H7 has become a pathogen of major concern in dairy industries, and to the public, because of its ability to cause severe illness, in particular hemorrhagic colitis, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura (Picozzi et al. 2005 and Reuben et al. 2013). Foodborne salmonellosis has been recognized due to consumption of raw or improperly pasteurized milk and milk products (Karshima et al. 2013). Recently CDC has reported an incidence of *L. monocytogenes* in pasteurized milk, Mexican cheeses, and pasteurized cheeses (FDA 2010; CDC 2012/2013/2014; CDC NORS 2012), *Salmonella braenderup* (OHA 2010) and *Salmonella java* in pasteurized cheddar cheese, *Salmonella Montevideo* in pasteurized shredded cheeses, *Salmonella newport* in pasteurized milk, *Salmonella typhimurium* in pasteurized milk, *Campylobacter jejuni* in pasteurized milk and cheese curd, and *Staphylococcus aureus* in powdered milk and pasteurized cheese (CDC NORS 2012).

3.3 Detection

3.3.1 Chemical Contaminants

The accessibility of rapid and sensitive approaches to determine chemical contaminants in dairy products is critical in food safety control laboratories. In countries like the USA, there is a practice to analyze individual farm milk supply for chemical contaminants before allowing to pool with the bulk milk (Kumar et al. 2012). To detect contaminants in milk, different methods have been developed which include screening methods and chromatographic techniques to detect as many contaminants as possible. The screening methods are based on the susceptibility of bacteria to different contaminants including antibiotics (Mitchell et al. 2002). They are very cost-effective, and in contrast to, for example, immunological or receptor-based tests, they have the potential to cover the entire spectrum within one test. However, these methods have their drawbacks as they do not enable specific identification that limits their use. They are highly sensitive to specific groups of contaminants but evidently less sensitive (Navratilova´ 2008). Quantitative confirmatory methods such as high-performance liquid chromatography (HPLC) (Zhou et al. 2009), gas chromatography–mass spectrometry (GC–MS) (Azzouz et al. 2010, 2011), thin-layer chromatography (TLC) (Grzelak et al. 2009), and mass spectrometry (MS) (Blascoa et al. 2009) have been commonly used for the detection of contaminants having safety concern. However, again each method has one or more limitations in terms of precision, accuracy, sensitivity, infrastructural requirement, and ease of method (Kumar et al. 2012).

3.3.2 Microbial Contaminants

Presently, the conventional testing methods that are considered as gold standard tests are among the first choice of the quality control laboratory. These conventional methods generally involve isolation and confirmation procedures for the detection of the microbes and other platform tests that are carried to determine non-microbial contaminants of the milk which are often time-consuming and laborious to perform. The other associated problem with such tests is that the product needs to be hold till the results come. This adds up to working capital of the industry because the holding infrastructure has to be created. Moreover, the perish ability of the milk and milk products further adds up to the problem of storage of these products. In such circumstances the milk and milk products are often pushed into the market without screening. The only thing the industry can do is banning the product and recalling the product. To overcome this unmanageable situation, dairy industry is looking for alternatives to conventional methods. The methods that are rapid, cost-effective, and easy to perform and significantly validated with approved standard methods are the need of the hour (Thakur et al. 2013).

3.4 Biosensors

The biosensor can be defined as "a sensing device or a measurement system designed specifically for the estimation of a material using the biological interactions and then assessing these interactions into a readable form with the help of a transduction and electro-mechanical interpretation" (Malik et al. 2013). In general, three different assay formats are used in biosensors – the direct and the indirect (competitive or noncompetitive) assay. In the case of the direct assay, the analyte is bound by its biorecognition element, which is detected directly (Vasilescu et al. 2016). This can be an antigen binding to its antibody, a hormone binding to a receptor, or a substrate reacting with its enzyme and producing a product (Eijkelkamp et al. 2009). The detection of these binding events is limited to the event itself and can be changed in mass, refractive index, impedance, pH, etc. (Griffin et al. 2014). In contrast, in indirect format, an additional reaction has to occur in order to detect the binding of analyte and biorecognition element. This additional reaction can either be competitive or noncompetitive. In both cases, a label is typically used for subsequent detection and quantification (Ramírez et al. 2009). The detection scheme is much less limited than in the case of the direct approach and depends on the nature of the label. This label can be optical, electrochemical, or mass related and thus permits the use of any transduction principle with indirect assay formats in contrast to the constraints given by the direct assay, which is limited by the nature of the analyte itself (Baeumner 2003). Based on the publication in reputed science journals, different methods which are applied in detection of many foodborne bacterial pathogens were compared by Lazcka et al. (2007) as shown in Fig. 3.1. The most popular methods are, by far, those based on culture and colony counting methods (Leoni and Legnani 2001) and the polymerase chain reaction, PCR (Bej et al. 1991). This can be explained on the grounds of selectivity and reliability of both techniques. Culture and colony counting methods are much more time-consuming than PCR methods, but both provide conclusive and unambiguous results. On the other hand, recent advances in PCR technology, namely, real-time PCR (Levi et al. 2003), now enable obtaining results in a few hours.

Biosensor technology comes with promises of equally reliable results in much smaller times, which is perhaps why they are currently drawing a lot of interest. However, there is still much work to do before biosensors become a real alternative. Figure 3.1 suggests that biosensor technology may soon move ahead of traditional ELISA-based methods and their potential market (Alocilja and Stephen 2003) is very encouraging too. Many biosensors rely on either specific antibodies or DNA as biomolecules to provide specificity.

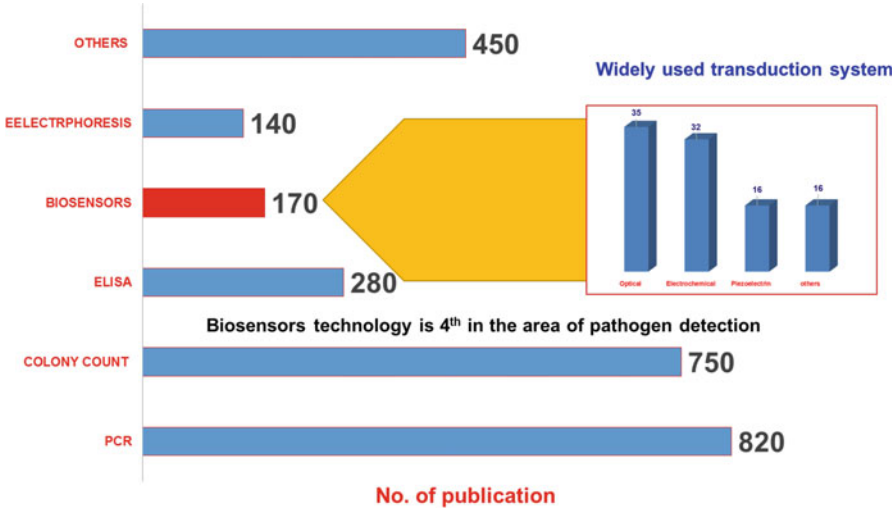

Fig. 3.1 Number of articles using different techniques to detect and identify pathogenic bacteria. Time series of the number of works published on detection of pathogen bacteria over the last 20 years. (Source: ISI web of science, Adapted from Lazcka et al. 2007)

3.5 Nanobiosensors

Nanotechnology is a new branch of science that deals with the generation and alteration of materials to nanosize (10^{-9} m) (Sagadevan and Periasamy 2014). Nanobiosensor is basically the sensors which are made up of nanomaterials, and interestingly these are not the specialized sensors which can detect the nanoscale events and happenings (Malik et al. 2013). A specific recognition group can be used to coat the surface of the nanowire/nanotube, making the device specifically sensitive only to a particular target. This recognition group could be a single-stranded DNA (capable of recognizing its complementary strand), an antibody (that recognizes a particular antigen), an aptamer that shows an affinity for a unique target, or a protein that specifically interacts with another biological molecule. The presence of this recognition group on the nanowire surface gives to the device high specificity and exclusivity toward its target (Thompsons Research Groups) (Fig. 3.2).

Nanomaterials are intended to be used in making biosensors which are going to drive a significant difference in the nanobiosensors technology. The physical properties of nan-materials used during the preparation of sensor will make them a very special due to their constituent atoms located at or near their surface increases the surface area for the interaction of biomolecule with the target material. These nanomaterials having all the vital physicochemical properties (Gatoo et al. 2014) such as size, surface area, surface chemistry, surface roughness, the dispersion medium, and ability to agglomerate will play a vital role in nanobiosensor. Metallic and inorganic nanomaterial having nanoscale in size may demonstrate new research avenue for scientists and researchers working the field of biosensors. Nanomaterials

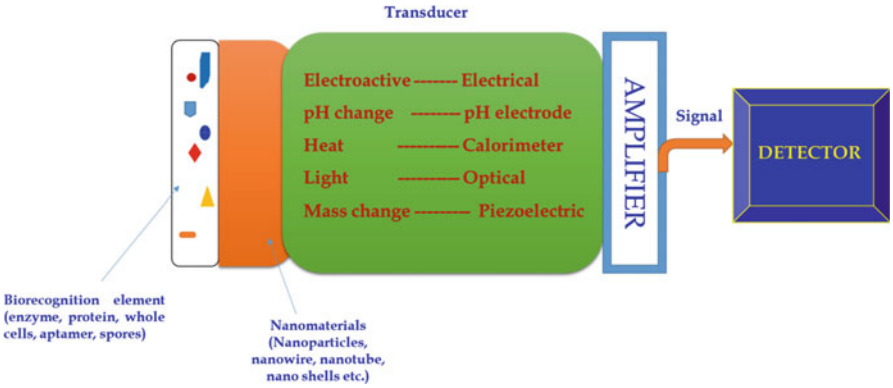

Fig. 3.2 Nanobiosensors

or nanoparticles reveal unique properties in terms of particle aggregation; photoemission; electrical, magnetic, and luminescent activity, heat conductivity; and catalytic activity (Rai et al. 2012). These properties have recently been applied in different biological studies like foodborne pathogen detection, biomolecule detection, sample separation, purification and concentration, signal transduction, and amplification (sensors) (Jain 2007). These nanoparticles further enhance the detection sensitivity of microbial monitoring, degradation, and recovery efficiency of chemicals (Urban and Meas 2008).

3.5.1 Nanomaterials

A nanosized material having at least one external dimension in the size ranges from 1 to 100 nanometers. Nanoscale materials are defined as a set of substances where at least one dimension is less than approximately 100 nanometers. Nanomaterials (NMs) are of interest because at this scale unique optical, magnetic, electrical, and other properties emerge (Alagarasi 2011). NMs include nanoparticles (NPs), nanostructured materials and ultrafine particles, and their agglomerates and aggregates. According to US EPA (USEPA 2007), there are four main types of nanomaterials including carbon-based, metal-based, dendrimers and composites.

Carbon-based nanomaterials are composed mostly of carbon, most commonly taking the form of hollow spheres, ellipsoids, or tubes. Spherical and ellipsoidal carbon nanomaterials are referred to as fullerenes, while cylindrical ones are called nanotubes (Roy and Jayanta 2015). These particles have many potential applications, including improved films and coatings, stronger and lighter materials, and applications in electronics. Metal-based nanomaterials include quantum dots, nanogold, nanosilver, and metal oxides, such as titanium dioxide (Ranganathan 2015). A quantum dot is a closely packed semiconductor crystal comprised of hundreds or thousands of atoms and whose size is on the order of a few nanometers to a few

hundred nanometers. Changing the size of quantum dots changes their optical properties. Dendrimers are nanosized polymers built from branched units. The surface of a dendrimer has numerous chain ends, which can be tailored to perform specific chemical functions. This property could also be useful for catalysis. Also, because three-dimensional dendrimers contain interior cavities into which other molecules could be placed, they may be useful for drug delivery. Composites combine the nanoparticles with other nanoparticles or with larger, bulk-type materials. Nanoparticles, such as nanosized clays, are already being added to products ranging from auto parts to packaging materials, to enhance mechanical, thermal, barrier, and flame-retardant properties.

Physicochemical Properties

The physicochemical properties of these nanomaterials are electrical, optical, catalytic, magnetic, mechanical, thermal, or imaging features that are highly desirable for applications in commercial, medical, food science, food safety, military, and environmental sectors.

The main parameters of interest with respect to nanoparticle safety are:

1. Physical properties
   (a) Size, shape, specific surface area, aspect ratio
   (b) Agglomeration/aggregation state
   (c) Size distribution
   (d) Surface morphology/topography
   (e) Structure, including crystallinity and defect structure
   (f) Solubility
2. Chemical properties
   (a) Structural formula/molecular structure
   (b) Composition of nanomaterial (including degree of purity, known impurities or additives)
   (c) Phase identity
   (d) Surface chemistry (composition, charge, tension, reactive sites, physical structure, photocatalytic properties, zeta potential)
   (e) Hydrophilicity/lipophilicity

The principal parameters of nanoparticles are their shape (including aspect ratios), size, and the morphological substructure of the substance (Williams 2014). Nanoparticles are presented as an aerosol (mostly solid or liquid phase in air), a suspension (mostly solid in liquids) or an emulsion (two liquid phases) (Scientific Committee on Emerging and Newly-Identified Health Risks (Sutariya and Pathak 2014; SCENIHR 2006). In the presence of chemical agents (surfactants), the surface and interfacial properties may be modified. Indirectly such agents can stabilize against coagulation or aggregation by conserving particle charge and by modifying

the outmost layer of the particle. Depending on the growth history and the lifetime of a nanoparticle, very complex compositions, possibly with complex mixtures of adsorbates, have to be expected. In the typical history of a combustion nanoparticle, for example, many different agents are prone to condensation on the particle, while they cool down and are exposed to different ambient atmospheres (Singh et al. 2011). Complex surface chemical processes are to be expected and have been identified only for a small number of particulate model systems. At the nanoparticle–liquid interface, polyelectrolytes have been utilized to modify surface properties and the interactions between particles and their environment. They have been used in a wide range of technologies, including adhesion, lubrication, stabilization, and controlled flocculation of colloidal dispersions (Liufu et al. 2004).

3.6 Applications of Nanobiosensors

3.6.1 Antibiotic Residues

Nanobiosensors for the detection of antibiotic residues in milk by different biomolecules such as antibody, aptamer, enzymes, etc. are in conjugation with gold, silver, or iron nanoparticles based on their change in SPR properties (LSPR, localized surface plasmon resonance) reinforcing the signal by means of electronic coupling of surface and the NP plasmons (Lyon et al. 1998). A gold nanoparticle label is an ideal one in biotechnological systems due to its inherent advantages, such as easy preparation, good biocompatibility, and so on (Sapsford et al. 2013). As far back as the 1970s, colloidal gold particles were used as an immune-staining and contrast agent for electron microscopy (Faulk and Taylor 1971). Nowadays, gold nanoparticles have been extensively employed as the labels for different biological receptors, e.g., enzyme, DNA, antigen/antibody, and other biomolecules (Ghosh et al. 2008; Ambrosi et al. 2007). More significantly, gold nanoparticles can be also used as catalysts in a number of chemical reactions. Yang and Tang (Tang et al. 2011) designed two types of ultrasensitive electrochemical immunoassay using nanometer gold labels as catalysts. The catalytic properties mainly derived from the catalytic reduction of 4-nitrophenol by gold nano-labels (Zhang et al. 2013). Based on the characteristic of surface plasmon resonance absorption of gold nanoparticles, Zhu et al. (2011) constructed an optical sensor for detection of antibiotics by using UV–vis absorbance spectrometry.

Natan's group was one of the first research teams demonstrating the potential of nano-gold probes for signal enhancement. They employed *secondary nano-gold probes* (anti-IgG coupled to AuNP) to detect human IgG in a sandwich format (Lyon et al. 1998). Regarding low molecular weight analytes, few papers report signal enhancement using 10–40 nm *secondary nano-gold probes*. The enhancement allowed reducing the concentration of primary antibody (i.e., from 10 to 1 μg mL^{-1}) and improved the detectability (i.e., LOD from 0.1 to 0.007 μg L^{-1} for benzaldehyde) (Yuan et al. 2007, 2008; Mitchell and Lowe 2009). Jiang et al.

conjugated the primary antibody to AuNP allowing to improve the LOD of estriol from 0.2 to 0.03 μg L^{-1}, but no data is shown comparing the performance of this strategy in respect to the use of *secondary gold probes.*

Frasconi et al. (2010) functionalized the Au nanoparticles (NPs) with thioaniline electropolymerizable groups and (mercapto-phenyl) boronic acid wherein antibiotic substrates neomycin (NE), kanamycin (KA), and streptomycin (ST) include vicinal diol functionalities which were specifically bound to the boronic acid ligands leading to electropolymerization of the functionalized Au NPs onto Au surfaces yields bisaniline-cross-linked Au-NP composites that, after removal of the ligated antibiotics, provide molecularly imprinted matrixes which reveal high sensitivities toward the sensing of the imprinted antibiotic analytes (detection limits for analyzing NE, KA, and ST correspond to 2.00 ± 0.21 pM, 1.00 ± 0.10 pM, and 200 ± 30 fM, respectively).

Another researcher has discovered a selective kanamycin-binding single-strand DNA (ssDNA) aptamer (TGGGGGTTGAGGCTAAGCCGA) through in vitro selection using affinity chromatography with kanamycin-immobilized sepharose beads (Song et al. 2011). The SS DNA Aptamer linked with gold nanoparticle for the selective detection of kanamycin and its derivatives such as kanamycin B and tobramycin with a detection limit of 25 nM by visual observation or by colorimetric method. A colorimetric and fluorescence quenching aptasensors for detection of streptomycin in milk based on double-stranded DNA and gold nanoparticles have been attempted by Emrani et al. (2016). The aptamer/FAM-labeled complementary dsDNA strand is stable, resulting in the aggregation of AuNPs by salt and an obvious color change from red to blue and strong emission of fluorescence in the absence of streptomycin (Emrani et al. 2016). In the presence of streptomycin, aptamer binds to its target, and FAM-labeled complementary strand adsorbs on the surface of AuNPs. Therefore, the well-dispersed AuNPs continue to be stable against salt-induced aggregation with a wine-red color, and the fluorescence of FAM-labeled complimentary strand is efficiently quenched by AuNPs. The colorimetric and fluorescence quenching aptasensors showed excellent selectivity toward streptomycin with the limit of detections as low as 73.1 and 47.6 nM, respectively.

Other efforts by Font et al. (2008) have developed two direct enzyme-linked immunosorbent assays (ELISAs) which have been developed for detection of sulfonamide antibiotic residues in milk samples using magnetic nanoparticles (MNP) for target capture/enrichment (Ab-MNP-ELISA) and further assay performed using microtiter plates. In this assay, selective polyclonal antibodies were raised against 5-[6-(4-amino-benzenesulfonylamino)-pyridin-3-yl]-2-methyl-pentanoic acid (SA1), used in combination with an enzyme tracer prepared with the same hapten, so has to achieve a limit of detection (LOD) lower than 0.5 μg L^{-1} by both ELISA formats. Sulfapyridine, sulfamethoxypyridazine, sulfathiazole, and sulfachloropyridazine are detected below the maximum residue limits established by the European Union for these antibiotics in milk (100 μg L^{-1}). Silver nanoparticle that enhanced the fluorescence of europium (III) for detection of tetracycline in milk has been investigated by Tan and Chen (2012) based on the coordination of Tc with europium functionalized on the surface of AgNPs to become EuTc complex for the

emission of strong fluorescence due to an intramolecular energy transfer from Tc to Eu3+. The fluorescence intensity of this probe displayed a good linear response to Tc concentrations in the range of 10 nM to 10 μM with a detection limit of 4 nM and was applied successfully to determine the levels of Tc in milk with a high selectivity.

3.6.2 Aflatoxin M1

Aflatoxins are secondary metabolites when ingested by animals, and higher vertebrates cause diverse health effects and disease called aflatoxicosis (Adegoke and Puleng 2013). Aflatoxin-contaminated/aflatoxin-containing agricultural and dairy products meet great economic losses (Cleveland et al. 2003). Studies by various researchers have shown that in the storage processes or cultivation of grains showed different levels of contamination, especially with aflatoxin B1 (AFB1) (Caldas et al. 2002). AFB1 is a powerful genotoxic carcinogen for humans and many animal species, including rodents, nonhuman primates, and fish (EC 2012). The main target of this carcinogen is the liver, although tumors may also develop in other organs, such as the lungs, kidney, and colon (Gelderblom et al. 1996). The current maximum residue levels for aflatoxins set by the European community (EC) are 20 μg/kg for AFB1 and 40 μg/kg for total aflatoxins in groundnuts, nuts, dried fruits, and cereals for direct human consumption (EC 2006). Aflatoxin M1 (AFM1), as the hydroxylated metabolite of aflatoxin B1 (AFB1), is usually present in the animal milk contaminated by AFB1. Because of their stronger toxic effects than AFB1 on public health, many governments have provided maximum acceptable limits for residual AFM1 in foodstuffs, especially in milk products (Kadir and Tothill 2010). For example, according to FSSAI standards, aflatoxin M1 content cannot exceed 0.5 μg/kg in milk, whereas the European–USA has higher regulations of 50 ng/kg. Thus, the food administration agencies in almost all countries have dedicated much effort to developing sensitive analytical methods for monitoring ultra-trace levels of AFM1 (<0.05 μg/kg) in foods (Hansmann et al. 2009). Current strategies for ultrasensitive detection of AFM1 are based mainly on thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), or UV light spectroscopy after extraction and clean-up procedures (Amine et al. 2003). These methods are adequately sensitive and accurate; however, they often require sophisticated, expensive, and heavy instruments that may not be available in laboratories with fewer resources; these methods are especially not fit for mass screening (Gan et al. 2013). The Zhang group developed a rapid method for detection of aflatoxin M1 by coupling superparamagnetic beads with gold labels (Zhang et al. 2013). The recent development of nanobiosensors has roused their application also to aflatoxin analysis. Many examples are reported, like DNA biosensor (Tombelli et al. 2009), electrochemical immune sensor (Linting et al. 2012), an electrochemical sensor (Liu et al. 2006), and the fluorometric biosensor (Carlson et al. 2000). Advantages of nanobiosensors techniques are a reduction of extraction, clean-up analytical steps, and global time of analysis (1 min or only a few seconds), the possibility of online

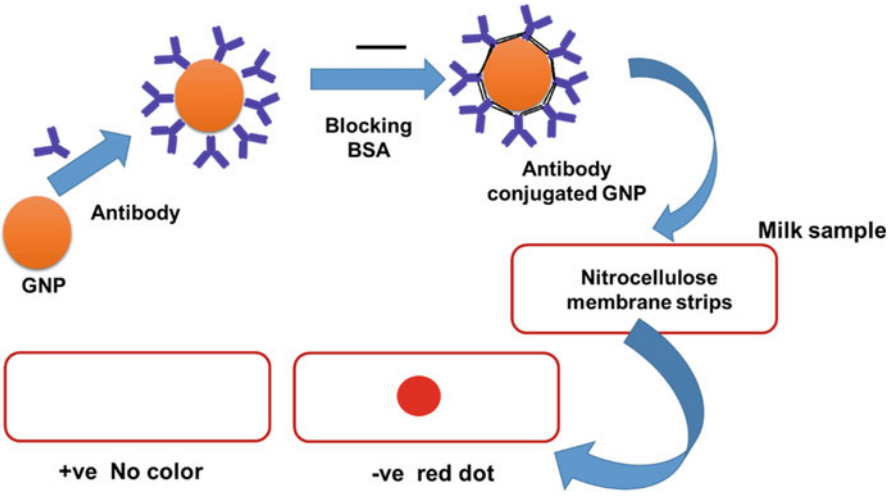

Fig. 3.3 DIGFA sensor for detection of AFB1 in feed

automated analysis, low cost, and no requirement of skilled personnel. On the other side, enhanced sensitivity and their improved stability allow long-term use. Because of the ease of use of these devices, many commercial systems continue to develop not only for aflatoxins but also for all mycotoxins (Eldin et al. 2014).

At the regional center for Food and Feed, ARC, Egypt, by Eldin and coworkers, a dot-immunogold chromatography flow-through assay (DIGFA) was developed for detection of AFB1 in food and feed samples using colloidal gold nanoparticles (AuNPs). AuNPs are being extensively used in various applications due to its stability and controlled geometrical, optical, and surface chemical properties. AuNPs-Anti AFB1 conjugates were designed by physical conjugation wherein AuNPs can be used as a probe for AFB1 detection with acceptable sensitivity and specificity compared to HPLC technique. The FAB1 present in feed and food samples is binding on AuNPs-Anti AFB1 conjugates DIGFA sensor (Fig. 3.3) Constructed DIGFA sensor detects AFB1 with high sensitivity (5 ng/mL) which is validated by HPLC. An assay is rapid (test completion time is 2 min) and reproducible and doesn't require any equipment.

Dynamic light scattering (DLS) coupled with superparamagnetic beads for the detection of AFM1 in milk using gold nanoparticle probe has been developed (Zhang et al. 2013). The nanoprobes were synthesized by the conjugate of AFM and bovine serum albumin (AFM-BSA), BSA, and gold nanoparticles. Magnetic beads-based immunosorbent assay (MBISA) is used to measure the concentration of AFM1 by through competition between AFM1 and nanoprobes. DLS was used to determine the concentration of unattached nanoprobes that was positively proportional to the concentration of AFM in the sample. Compared to conventional ELISA, MBISA could effectively reduce the detection time to 15 min in buffer solution and

completely eliminate the color development step, thus simplifying the analysis of AFM. A linear relationship was observed between the inhibition values and the concentrations of AFM in both buffer solution (0–1000 $ng \cdot L^{-1}$) and spiked milk samples (0–400 $ng \cdot L^{-1}$). The limit of detection was found to be 37.7 $ng \cdot L^{-1}$ for AFM in buffer solution and 27.5 $ng \cdot L^{-1}$ in milk samples.

An ultrasensitive electro-chemiluminescent immunoassay (ECLIA) for aflatoxins M1 (AFM1) in milk using magnetic Fe_3O_4-graphene oxides (Fe-GO) as the absorbent and antibody-labeled cadmium telluride quantum dots (CdTe QDs) as the signal tag (Gan et al. 2013). Firstly, Fe_3O_4 nanoparticles are immobilized on graphene oxides to fabricate the magnetic nanocomposites, which are used as absorbent to AFM1. Secondly, aflatoxin M1 antibody (primary antibody, AFM1 Ab1) is attached to the surface of the CdTe QDs-carbon nanotubes nanocomposite to form the signal tag (AFM1 Ab1/CdTe-CNT). Thirdly, Fe-GO was employed for extraction of AFM1 in milk wherein it can adsorb AFM1 efficiently and selectively within a large extent of pH from 3.0 to 8.0. Adsorption processes reached 95% of the equilibrium within 10 min (Gan et al. 2016). Lastly, the AFM1 with a serial of concentrations absorbed on Fe-GO was conjugated with AFM1 Ab1/CdTe-CNT signal tag based on sandwich immunoassay. The immuno-complex can emit a strong ECL signal whose intensity depended linearly on the logarithm of AFM1 concentration from 1.0 to 1.0×10^5 pg/mL, with the detection limit (LOD) of 0.3 pg/mL (S/N = 3). The method was more sensitive for AFM1 detection compared to the ELISA method.

Pal et al. (2015) have developed a multi-platform detection of AFM1 based on hafnia nanoparticles based on immunochemistry. The fine-grained nanocrystal ceramic powder samples of HfO_2NP_2 were prepared, and they are highly specific to the monoclonal antibody immobilized onto HfO_2 surface using chemical modification and cross-linking chemistry. Further, nanobiosensors were evaluated based on chemiluminescent sandwich enzyme-linked immunosorbent assay followed by photometric measurement of particles with a detection limit of 200–0.5 pg/ml. the multi-platform detection having a good linearity with a limit of detection 6.25 pg/ml, sensitivity, selectivity, and stability.

An electrochemical immune sensor for the detection of ultra-trace amounts of aflatoxin M1 (AFM1) in food products has been developed by Paniel et al. (2010). The sensor was based on a competitive immunoassay using horseradish peroxidase (HRP) as a tag. Magnetic nanoparticles coated with antibody (anti-AFM1) were used to separate the bound and unbound fractions. The samples containing AFM1 were incubated with a fixed amount of antibody and tracer [AFM1 linked to HRP (conjugate)] until the system reached equilibrium. Competition occurs between the antigen (AFM1) and the conjugate for the antibody. Then, the mixture was deposited on the surface of screen-printed carbon electrodes, and the mediator [5-methylphenazinium methyl sulfate (MPMS)] was added. The enzymatic response was measured amperometrically. A standard range (0, 0.005, 0.01, 0.025, 0.05, 0.1, 0.25, 0.3, 0.4 and 0.5 ppb) of AFM1-contaminated milk from the ELISA kit was used to obtain a standard curve for AFM1. To test the detection sensitivity of the sensor, samples of commercial milk were supplemented at 0.01, 0.025, 0.05, or

0.1 ppb with AFM1. Results revealed that the immune sensor has a low detection limit (0.01 ppb), which was under the recommended level of AFM1 [0.05 μg L^{-1} (ppb)], and has good reproducibility.

A new DNA-based biosensor for detection of aflatoxin M1 has been developed by Dinckaya et al. (2011) based on an immobilization of thiol-modified single-stranded DNA (ss-HSDNA) probe that specifically binds to aflatoxin M1, a self-assembled monolayer (SAM) of cysteamine and gold nanoparticles on the SAM on gold electrodes, layer-by-layer. The assembly processes of cysteamine, gold nanoparticles, and ss-HSDNA were monitored with the help of electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) techniques using potassium ferrocyanide as a redox probe for electrochemical measurements. The biosensor provided a linear response to aflatoxin M1 over the concentration range of 1–14 ng/mL with a standard deviation of ±0.36 ng/ml.

3.6.3 Heavy Metals

Heavy metal ions, such as lead, mercury, cadmium, chromium, and arsenic, are hazardous, contributing to water and soil pollution. Through water and soil, these metal residues reach daily foods. Heavy metals are known to cause irreversible changes in protein structures, affecting cell functions. Excessive intake of such substances can result in adverse health conditions including neurological disorders, renal degradation, and bone lesions (Kim et al. 2012). The nanobiosensing methods for the detection of heavy metal ions can be divided into several subcategories according to biorecognition molecule. Chen has developed an AuNPs-based dual-labeling colorimetric method for Hg^{2+} detection using a specific thymine–Hg^{2+}–thymine (T-Hg-T) (Tedsana et al. 2015) as a recognition system and dual-labeling strategy for signal amplification; without using any instruments, they obtained a LOD of 0.025 nM, competitive to other rapid detection methods (Dheng et al. 2015). The target ions aid in assembling AuNPs modified with different Raman labels, leading to different enhancements of Raman signal (Li et al. 2015). Saran and Liu (2016) have used DNAzyme (recognition group and amplifier) for the development of label-free catalytic biosensing platform for the detection of Pb^{2+} and Ag^{+} based on stabilization of AgNCs (signal reporter) with DNA wherein these metals act as a cofactor of DNAzyme activity (Gong et al. 2015). A study by Zhou et al. (2016) for the specific detection of Cd^{2+} and Pb^{2+} by using amino acids because of the functional side chain (like cysteine) wherein graphene oxide nanoparticles were being used based on the change of the electrochemical signal. An approach by Fu et al. (2015) for the detection of heavy metals (Cd^{2+}) by the use of antibody based on core–shell AuNPs/AgNPs enhanced Raman scattering.

Sener et al. (2013) have developed a colorimetric assay based on the aggregation of gold nanoparticles (AuNPs) in the presence of Hg^{2+}. The detection limit of this colorimetric assay is 2.9 nM, which is below the limit value (10 nM) defined by the US Environmental Protection Agency. The colorimetric response of AuNPs in the

presence of lysine is very selective to the Hg^{2+}. Another attempt by Childress et al. (2012) is by the use of dye-doped polymer nanoparticles that are able to detect mercury in aqueous solution at parts per billion (ppb) levels via fluorescence resonance energy transfer (FRET). The polymer NPs are synthesized by re-precipitation of highly fluorescent conjugated polymers in water followed by doping with rhodamine spirolactam dyes that are nonfluorescent until they encounter mercury ions, which promote an irreversible reaction that converts the dyes to fluorescent rhodamines. The rhodamine dyes act as FRET acceptors for the fluorescent nanoparticles, and the ratio of nanoparticle-to-rhodamine fluorescence intensities functions as a radio/ratiometric fluorescence chemodosimeter for mercury. The light-harvesting capability of the conjugated polymer nanoparticles enhances the fluorescence intensity of the rhodamine dyes by a factor of 10, enabling sensitive detection of mercury ions at levels as low as 0.7 ppb.

3.6.4 Adulterants

Some manufacturers and farms engage in food fraud for increasing profit margin, and such ill practices often lead to devastating results. Melamine, a chemical adulterant, is sometimes illegally added to milk powder to improve the apparent protein content (Niu et al. 2015). A melamine aptamer derived from a basic-site-containing triplex molecular beacon (tMB) has been proposed for sensitive recognition of melamine by integrating tMBs and fluorescent AgNCs (Wang et al. 2015). Nitrite is harmful to humans and is widely used as an additive and preservative in food service industry. A biosensor toward nitrite was developed based on the direct electrochemistry of myoglobin on a reduced GOx-multi-walled CNTs-platinum NPs nanocomposite (Mani et al. 2014). ZnO NPs are frequently considered to design biosensing strategies for the detection of bisphenol A, a ubiquitous environmental contaminant found in food products and aquatic ecosystems (Najafi et al. 2014; Zhang et al. 2014). As H_2O_2 is a kind of unlawful decolorizer for food, a biosensing method toward H_2O_2 was developed based on the H_2O_2 enlarging AuNPs that induced significant fluorescence quenching of BSA-AuNCs.

A highly sensitive acetylcholinesterase cyclic voltammetric biosensor based on zinc oxide nanospheres modified Pt electrode has been successfully developed for the simultaneous determination of melamine and urea in cow milk sample (Ezhilan et al. 2017). The fabricated bioelectrode showed 100% permeability to the binary mixture of melamine and urea, which in turn enhanced selectivity. The developed Pt/ZnO/AChE/chitosan bioelectrode detected melamine and urea over a range of 1–20 nM with a limit of detection of 3 pM and 1 pM, respectively. The sensor exhibited good recovery in the range of 99.96–102.22%, thus providing a promising tool for analysis of melamine and urea in cow milk samples. Gold nanoparticles functionalized with cyanuric acid compounds selectively bind to melamine, an adulterant used to enhance the measured proteins content of infant food formulas (Ai et al. 2009).

3.6.5 Pesticide Residues

Various kinds of nanoparticles, such as quantum dots (QDs) and AuNPs, have been used for the development of electrochemical enzyme biosensors. An enzyme biosensor was developed for the amperometric detection of trichlorfon using poly (N-vinyl-2-pyrrolidone) (PVP)-capped CdS QDs (Li et al. 2006). The formation of PVP-QD nanostructures on the electrode surface provided a favorable microenvironment and led to a highly sensitive and stable electrochemical detection of the enzymatically generated thiocholine product. The detection limit was 4.8 × 10–8 M. Another kind of nanoparticles is AuNPs. Their unique property to provide a suitable microenvironment for immobilization of biomolecules retaining their bioactivity is a major advantage for the preparation of biosensors. Moreover, AuNPs facilitate direct electron transfer between immobilized redox proteins and the electrode surface (Pingarron et al. 2008). An electrochemical biosensor based on the colloidal AuNP-modified sol–gel interface was developed for the detection of monocrotophos, carbaryl, and methyl parathion (Du et al. 2008a). The assembled AuNPs on a sol–gel-derived silicate network provided a conductive pathway to electron transfer and favored the interface enzymatic hydrolysis reaction, increasing the sensitivity of the amperometric response. This biosensor presented good stability, retaining 90% of its initial current response after a 30-day storage period. Recently, an efficient biosensor for the detection of monocrotophos was developed by combining the unique properties of AuNPs with those of QDs. This new electrochemical system based on CdTe QD-AuNP electrode was more sensitive than those based on QDs or AuNPs alone (Du et al. 2008b).

Recently, an electrochemical immune sensor was developed for rapid screening of diuron, a substituted phenyl urea herbicide (Sharma et al. 2011). Low-cost ablated electrodes fabricated on polystyrene substrate were modified with Prussian Blue (PB)-AuNP film. The electrodeposition of PBAuNP film enhanced electron transfer in the vicinity of the gold electrode increasing the sensitivity of the system as compared to unmodified gold electrodes. A conductometric immune sensor for the detection of atrazine was also developed using antibodies labeled with nanoparticles (Valera et al. 2008). The authors showed that AuNPs amplify the conductive signal and hence allow the detection of atrazine by means of DC measurements.

Nanoparticles have also been used for the development of efficient optical biosensors (Lin et al. 2006). QDs are candidates to replace conventional fluorescent markers. These semiconductor particles are more photostable than an organic fluorophore. Moreover, QDs exhibit higher fluorescence quantum yields than conventional organic fluorophores, allowing higher sensitivity. Recently, an optical biosensor was developed for the detection of monocrotophos using CdTe as fluorescence probe (Sun et al. 2011). Using positively charged chitosan, CdTe and acetylcholinesterase were assembled onto a quartz surface by a layer-by-layer technique. In the absence of pesticide, acetylcholine was bio-catalytically hydrolyzed inducing the production of choline and acetic acid. The released acid resulted in pH decrease that was sensed by the immobilized pH indicator (CdTe).

The presence of monocrotophos induced a change of the fluorescence intensity that was related to the pesticide concentration. Optical properties of AuNPs have been exploited for the development of localized SPR (LSPR) sensor (Fu et al. 2009). The resonance frequency of the LSPR is highly dependent upon the local environment of the nanoparticle and more specifically upon the binding events that occur to the functionalized NPs. The LSPR was used to develop a biosensor for the detection of paraoxon by immobilizing AChE onto AuNPs layer using a self-assembling technique (Lin et al. 2006). In the presence of pesticides, the enzymatic activity was inhibited causing a change of the light attenuation. The detection limit with optimal conditions was 0.2 ppb. The biosensor retained 94% of its original activity after 6 cycles of inhibition with 500 ppb paraoxon followed by reactivation of AChE with 0.5 mM 2-pyridine aldoxime methiodide. In addition, the sensor retained its activity after 2 months storage in the dry state at 4 °C.

Carbon nanotubes (CNTs) consist of cylindrical graphene sheets with diameter in nanometer diameters. They present unique mechanical, physical, and chemical properties. CNTs include both single-walled and multi-walled structures. Since their discovery, CNTs have been used in nanoelectronics, biomedical engineering, biosensing, and bioanalysis. Recently, CNTs have been used for the development of biosensors based on the inhibition of AChE activity (Du et al. 2007; Oliveira and Mascaro 2011; Firdoz et al. 2010). An amperometric biosensor based on layer-by-layer assembly of single-walled CNT-poly(diallyldimethylammonium chloride) and AChE was developed for the analysis of carbaryl (Firdoz et al. 2010). The biosensor showed good sensitivity and stability toward the monitoring of pesticides in water. The detection limit was 4.9 × 10–15 M. In some cases, the authors developed efficient biosensors for the detection of pesticides by associating the properties of CNTs with those of nanoparticles (Du et al. 2010).

A simple and selective aptamer-based colorimetric assay for the detection of omethoate has been developed by Wang et al. (2016). The principle of the assay is that single-stranded DNA (ssDNA)-wrapped gold nanoparticles (AuNPs) are resistant to salt-induced aggregation. By employing an "artificial antibody" organophosphorus pesticide-binding aptamer (OBA) as the recognition element, aptamer-wrapped AuNPs (Au-apta) show high selectivity toward omethoate, resulting in the disconnection of aptamers from AuNPs and the aggregation of AuNPs. As there is a significant color change from the interparticle plasmon coupling during the aggregation of AuNPs, the established assay showed good linearity between 0.1 and 10 μmol/L, with a low detection limit of 0.1 μmol/L.

A novel nanohybrid composite with good electrochemical responses was developed by Xu et al. (2017), and it was prepared by the esterification reaction of hydroxyl-terminated polybutadiene (HTPB) with MWCNT-COOH, followed by atom transfer radical polymerization of 4-acryloyloxybutyl(ethyl) ferrocene carboxylates with different spacers. The nanohybrid composites were characterized by FTIR, TGA, Raman, XRD, XPS, SEM, and TEM techniques. Cyclic voltammetry (CV) determination showed that a longer spacer between the side ferrocene groups and main chains endowed the electrochemically modified electrodes with active electron response, obvious redox current, and reversible electrochemical properties

because of the faster electron transfer rates. The modified electrode sensor with a longer spacer was used to detect melamine and trichlorfon residues by CV and differential pulse voltammetry (DPV) techniques. The sensor had a good linear relationship over a wide concentration range, a maximal recovery of ca. 112.4% and a low detection limit of about 1.5×10^{-7} and 3.5×10^{-8} mol L^{-1}, respectively.

Turan et al. (2016) have used an innovative approach for the fabrication of a biosensor utilizing a conducting polymer and silver nanowires. To obtain immobilization platform for butyrylcholinesterase (BChE), a graphite electrode was modified with the poly(5,6-bis(octyloxy)-4,7-di(thieno[3][3,2-b]thiophen-2-yl)benzo[c][1,2,5]oxoadiazole) (PTTBO) which has a hydrophobic alkyl chain as the pendant group providing hydrophobic nature to the matrix. Since biomolecules contain both hydrophobic and hydrophilic parts in their structure, alkyl chains interact with the proteins which provide an enhanced stability. Biosensor performance was improved through the deposition of silver nanowires on the polymer-coated surfaces which enhances the charge transfer rate. This enabled the development of rapid, highly sensitive, and stable amperometric sensors for the quantitative determination of organophosphorus pesticide, paraoxon. Fabricated biosensor showed two linear ranges between 0.5–8 μM and 10–120 μM with a low detection limit of 0.212 μM when butyrylthiocholine iodide is used as the substrate.

Zhang et al. (2013) have developed novel nanobiosensing principles for organophosphorus pesticides. Thiocholine generation by AChE catalysis leads to the aggregation of AuNPs, resulting in the recovery of fluorescence resonance energy transfer (FRET) between AuNPs and NaYF4: Yb, upconversion NPs (Long et al. 2015). Immobilization of AChE in fenugreek hydrogel-agarose matrix with AuNPs results in high enzyme retention efficiency of 92% and a significantly prolonged half-life of the AChE (55 days) (Kestwal et al. 2015). Apart from AChE, pesticides can also inhibit other enzyme activity such as trypsin and tyrosinase (Yan et al. 2015). Trypsin easily hydrolyzes protamine covered on the surface of AuNPs, leading to fluorescence quenching of QDs.

Electrochemical and photochemical properties of pesticides such as omethoate, malathion, lindane, carbofuran, carbaryl, etc. are being used for the development of nanobiosensors (Yang et al. 2016). Nanobiosensors based on copper oxide nanowires-CNTs, AgNPs decorated polyaniline-nanocrystalline zeolite organic-inorganic hybrid material, cobalt oxide (CoO)-reduced GOx, zirconia-ordered macroporous polyaniline, and other nanosystems, have already been reported to improve the sensitivity of the nanosensors (Huo et al. 2014; Kaur et al. 2015, Wang et al. 2014, 2015; Wu et al. 2014). In addition to electrochemical methods, a few NP-enhanced surface-enhanced Raman spectroscopy (SERS) methods have been developed, but these methods have limitations in terms of low affinity. Such problems can be overcome by optimizing metal NPs, for example, the type, molecular linker, surface coverage, and laser excitation wavelength of NPs (Kubackova et al. 2015).

Immunoassay-based nanobiosensing systems are most widely being used in the detection of pesticides (Belkhamssa et al. 2016; Sun et al. 2015; Xiao et al. 2016). The application of nanometal organic framework and other materials can greatly

reduce the LOD (Deep et al. 2015). Pesticides are known to hinder certain photo-physical as well as photo-chemical functions of nanomaterial, through specific recognition of pesticides by antibodies immobilized on nanomaterial surfaces may lead to discovery of many excellent phenomena, for example, pentachlorophenol obstructs electrochemiluminescence of Au nanoclusters/graphene hybrid (Luo et al. 2014), acetamiprid decreases enhanced photocurrent produced by electron donor of quercetin in Co-doped ZnO diluted magnetic semiconductor, thiram quenches blue luminescence of Cu^{2+} decorated NaYF4:Yb/Tm up conversion NPs fixed on filter paper (monitored by the smartphone camera through a self-written Android program) (Mei et al. 2016).

3.6.6 Microbial Safety and Quality

Rapid detection of foodborne pathogens is a key step in the control of food-related diseases. Conventional methods for the detection of food pathogens, although typically sensitive, often require multiple time-consuming steps such as extraction, isolation, enrichment, counting, etc., prior to measurement, resulting in testing times which can be days (Paul et al. 2013). There is an urgent necessity to develop rapid and sensitive detection methods. To overcome these limitations, several examples of innovative integration of microbial biosensors with recent nanotechnologies have been proposed in the past decade. For instance, microfluidic systems showed many advantages by minimizing the sample and reagent volumes required, shortening analysis time with high resolution and repeatability, and demonstrating multiple assays on a chip in a high-throughput manner (Kim et al. 2014). In addition, it was demonstrated that microfluidic systems cannot only provide microorganisms with an ideal cell culture microenvironment that is close to in vivo (Shaw and Kado 1986) but also enable high portability and more rapid analysis compared to conventional methods (Joyner and Lindow 2000). The nano-fabrication showed a remarkable potential for microbial biosensors with the following features (Fujimoto et al. 2006):

1. Enhanced optical and electrochemical measurements
2. Improved immobilization and automated culture environments
3. High portability and more practical applications

Nano-based sensing approaches include the use of nanoparticles (NPs) and nanostructures to enhance sensitivity and selectivity, design new detection schemes, improve sample preparation, and increase portability (Bülbül et al. 2015). Recently, nanotechnology allowed for the design of nanosensors for identification of foodborne pathogens or toxins.

The poly(dimethylsiloxane) (PDMS) immune-sensing chips have been developed by Dong et al. (2006) with reinforced, supported, fluid bilayer membranes (r-SBMs) and specific antibodies to the toxin for the detection of with S*taphylococcus* enterotoxin B. Rivas et al. (2006) developed universal G-liposomal nanovesicles based on immune-magnetic bead sandwich assay to detect *E. coli* O157: H7, *Salmonella* sp.,

and *L. monocytogenes* in food. Other pathogenic microorganisms were detected with a specific type of immunosorbent assay using universal protein G-liposomal nanovesicles (Chen and Durst 2006). Furthermore, nanoparticles have been used as nano-sieves to filter out bacteria. On the other hand, detection of bacterial toxins using nanoparticle technology was recently reported (Zhu et al. 2014). Yang et al. (2009) reported a capacitive immune sensor for the detection of *Salmonella* spp. which was fabricated by immobilizing an Au nanoparticle monolayer onto a glassy carbon electrode and then the Salmonella monoclonal antibodies through physical adsorption. It was found that the Au nanoparticles can effectively improve the sensitivity and stability of the immune sensors, which can detect the *Salmonella* spp. concentrations in the range of $1.0 \times 10^2 - 1.0 \times 10^5$ cfu·mL^{-1} with the detection limit of 1.0×10^2 cfu·mL^{-1}. In addition to Au nanoparticles, metal-oxide nanoparticles which possess high surface area and thermally stable, chemically inert, nontoxic inorganic oxide have been also used in the development of bacterial biosensors. Huang et al. (2010) used Fe_3O_4 nanoparticles to immobilize monoclonal antibodies in the construction of electrochemical impedimetric immune sensors for the rapid detection of *Campylobacter jejuni*. The Fe_3O_4 nanoparticle-based immune sensor showed good performance with respect to simplicity of use, fast response, wide linear range, acceptable reproducibility, and long stability. In addition to nanoparticles, nanowires have been attracted much scientific interest in analytical chemistry, especially in biosensing technologies. This is due to their unique semiconductive properties associated with the nanostructures, and they are believed to be ultrasensitive in performing single-molecule sensing. Wang et al. (2009) developed a TiO_2 nanowire bundle microelectrode-based impedimetric immune sensor for rapid and sensitive detection of *L. monocytogenes*. TiO_2 nanowire bundle was connected to gold microelectrodes using mask welding, and then monoclonal antibodies were immobilized on the surface of a TiO_2 nanowire bundle to specifically capture bacteria. Impedance changes caused by the nanowire-antibody-bacteria complex were measured and correlated to the bacterial number. Since the TiO2 nanowires can be highly oriented on substrates or form free-standing membranes, the fabricated electrode showed a large specific surface area, good biocompatibility, good chemical and photochemical stabilities, and negligible protein denaturation. This nanowire bundle-based immune sensor also exhibited a good performance that can detect as low as 10^2 cfu·mL^{-1} of *L. monocytogenes* in 1 h without significant interference from other foodborne pathogens. Ali et al. (2014) have developed a sensitive colorimetric method for the detection of *E.coli* O157:H7 using conjugated gold nanoparticles anti-*E. coli* O157:H7. The key point of gold nanoparticle-based visual detection assay is to control dispersion and aggregation of colloidal nanoparticles by targets of interest *E. coli* O157:H7. The existence of the target molecules can be translated into optical signals and monitored by the naked eye resulting in a dramatic color change from red to blue (Table 3.1).

Table 3.1 Nanobiosensors for detection of microbial quality of food products

Nanomaterials	Microorganisms	Electrode	Detection range	References
Au nanoparticles (NPs)	Sulfate-reducing bacteria	Foam Ni electrode	2.1×10^1 – 2.1×10^7	Wan et al. (2010)
Fe3O4 NPs	*C. jejuni*	GCE	10^{-3} – 10^{-7}	Huang et al. (2010)
AU NPs	*Salmonella* spp.	GCE	10^2 – 10^7	Yang et al. (2009)
Magnetic nanoparticles	*E. coli* O157:H7	IDAM	Pure culture (10^4 – 10^7)	Varshney and Li (2007)
Magnetic nanoparticles	*E. coli*	Pt. plate electrode	10–10^4	Maalouf et al. (2008)

Adopted from Bülbül et al. (2015)

3.6.7 Packaging

The use of nanomaterials in food packaging is already a reality. Nanotechnology can be used in plastic food packaging to make it stronger, lighter, or perform better. Antimicrobials such as nanoparticles of silver or titanium dioxide can be used in packaging to prevent spoilage of foods. Another addition is the introduction of nanoparticles of clay into packaging to block oxygen, carbon dioxide, and moisture from reaching the food and also aids in preventing spoilage. Chemical giant Bayer produces a transparent plastic film called Durethan which contains nanoparticles of clay. Durethan is an engineering plastic based on polyamide 6 and polyamide 66; these particles offer an excellent combination of properties which include high strength and toughness, abrasion resistance, chemical resistance, and resistance to cracking. Durethan is used in various industries and applications, including packaging film for the medical field and food packaging. The nanoparticles are spread throughout the plastic and are able to block oxygen, carbon dioxide, and moisture from reaching fresh meats or other foods. The advantage of using nanoclay is it also makes the plastic lighter, stronger, and more heat-resistant. Durethan film material with nanoparticles combines the advantages of polyamide 6 and ethylene vinyl alcohol (EVOH) to produce an inexpensive but still very airtight packaging material. The embedded nanoparticles prevent gases from penetrating the film and also keeping moisture from escaping. An example is bottles made with nanocomposites which minimize the leakage of carbon dioxide out of the bottle; by minimizing the leakage of CO_2 in the bottle, this will cause an increase in the shelf life of a carbonated beverage without having to use heavier glass bottles or more expensive cans. Another example is food service bins made out of silver nanoparticles embedded in the plastics. The silver nanoparticles kill bacteria from any food previously stored in the bins, which will minimize harmful bacteria.

Generally, nanobiosensors are placed in food packaging to control internal and external conditions of food (Ramachandraiah et al. 2015). From a microbiological point of view, the main objective of nanosensors is to reduce pathogen detection time

from days to hours or even minutes (Fuertes et al. 2016). These nanomaterials are used in the detection of molecules, gases, and microorganisms and detection by surface-enhanced Raman spectroscopy (SERS) (Duncan 2011); nanosensors in raw bacon packaging for detecting oxygen (Mills 2005); electronic tongue for inclusion in food packaging consisting of an array of nanosensors extremely sensitive to gases released by spoiled food, giving a clear and visible sign if the food is fresh or not (Bowles and Lu 2014); use of fluorescent nanoparticles to detect pathogens and toxins in food (Burris and Stewart 2012), for example, detection of pathogenic bacteria in food (*S. typhimurium*, *Shigella flexneri*, and *E. coli* O157:H7), based on functionalized quantum dots coupled with immunomagnetic separation in milk and apple juice (Burris and Stewart 2012); nanosensors to detect temperature changes (Iliadis and Ali 2011; Lee et al. 2011), where food companies like Kraft Foods are incorporating nanosensors that detect the profile of a food consumer (likes and dislikes), allergies, and nutritional deficiencies (Meetoo 2011); nanosensors for the detection of organophosphate pesticide residues in food (Liu et al. 2008), nanosensors to detect humidity or temperature changes due to moisture (Zhang et al. 2010), sensor for detecting *E. coli* in a food sample, by measuring and detecting scattering of light by cellular mitochondria (Horner et al. 2006); biosensor for instantly detecting Salmonella in foods (Fu et al. 2008) and sensor to detect CO_2 as a direct indicator of the quality of the food (Puligundla et al. 2012); and biosensor for the detection of the pathogen-food, *Bacillus cereus* (Pal et al. 2007).

Scientists at Kraft, as well as at Rutgers University, are working on nanoparticle film concentration and another packaging with embedded sensors that will detect food pathogens. Called "electronic tongue" technology, the sensors can detect substances in parts per trillion and would trigger a color change in the packaging to alert the consumer if a food has become contaminated or if it has begun to spoil (Anonymous 2004).

The intelligent packaging (IP) incorporating nanosensors will have great benefits for the food industry. This NM in the form of tiny chips invisible to the human eye is embedded in food or in containers, for use as electronic bar code, which allows for the monitoring of food in all its phases (production, processing, distribution, and consumption) (Fuertes et al., 2016). Communication between NMs is a promising technology that ensures the development of new devices capable of performing basic and simple tasks at nanolevel (computing, data storage, detection, and triggering). The nanosensors have a limited field of measurement; therefore, the development of the wireless nanosensor networks (WNSNs) is essential for the IP industry. developing nanosensors.

One major drawback is the limited energy that can be stored in a nanosensor speck in contrast to the energy required by the device to communicate. Recently, novel collecting energy mechanisms have been proposed to replenish energy stored in nanodevices. With these mechanisms, WNSNs can overcome the bottleneck and even have infinite life (perpetual WNSNs). For now, the limitations of size and power of nanodevices limit the applicability of wireless communication.

One of the most recent alternatives is based on the use of graphene, a nanomaterial of one atom thickness, which was first obtained experimentally in

2004 (Geim and Novoselov 2007). Graphene enables wireless communication between nanosystems, because of its ability to support surface plasmon polariton (SPP) in the terahertz frequency range (Cabellos-Aparicio et al. 2015). The main difference between classical plasmonic antennas and graphene-based plasmonic antennas is that SPP waves in graphene are observed at frequencies in the terahertz band, for example, two orders of magnitude below SPP waves observed in gold and other noble materials (Jornet and Akyildiz 2014). The SPP waves require less energy making the communication between NMs feasible (Akyildiz et al. 2014).

3.7 Challenges

The main focus of nanosensor researchers from the comparative evaluation of nanosensors and conventional based techniques to designing of commercially viable sensors for its field application. Robust comparisons against traditional technologies would also help address a related challenge, i.e., the substantial inertia involved in encouraging professional analysts to replace older technologies with new methods, a process that is surprisingly difficult even when the new methods promise significant benefits.

Despite what could be regarded as a slow adoption of nanosensor technology into the commercial space, nano-sensing is still a growing field with many exciting possibilities for both the food industry and regulatory authorities. Undoubtedly, many challenges need to be resolved for the effective commercialization of this know-how. However, continued research and development and especially a renewed focus on validation against more established detection methods will help solidify nano-sensing potential role in making the world's food supply healthier, safer, and – possibly – more delicious.

Furthermore, with the development of lab-on-a-chip technique, the integration of analyte onto a microfluidic chip to develop a biotic microelectromechanical system would supply a new research aspect in the field of biosensors because such systems only require minimal amounts of sample and provide good sensitivity in the detection of analytes. Current methods of target immobilization on transducer have limitations which affect cell viability as well as cell function. Physical adsorption suffers from poor stability. A major disadvantage of immobilization is the additional diffusion resistance caused by the entrapment material, which would result in a loss of sensitivity. As the world becomes seriously concerned about the effect of food on public health and the safety against biowar, the aforementioned prospects will be a breakthrough in targets immobilization and identification in biosensor field. However, there are still several challenges to overcome, which limit the progress of technology transfer and commercialization, mainly related to the difficulties in the integration of all the components into a single portable platform. Yet, there is still a long road ahead for this emerging technology to be fully adapted to a filed application.

3.8 Conclusion

Dairy food safety problems frequently are compromised due to antibiotic residues, aflatoxin M1, pesticides, heavy metals, adulterants, microbial foodborne pathogens, etc. These classes of milk and milk product contaminations could not be detected efficiently by conventional methods due to the fact they require longer time for the confirmation. These dairy products cannot be stored for the longer period of time because there may be chances change of chemical nature of the products. Therefore, dairy industries are under tremendous pressure to meet the consumer requirement with quality and safety with in one working day. Therefore, the need of the hour is to development of sensors with the use of nanomaterial in link with specific biorecognition molecules. By the application of nanobiosensor with the use of nanoparticles, various food contaminants including microbial pathogens can be identified accurately. Therefore nanosensors have been widely used in the dairy food quality and safety evaluation. Despite what could be regarded as a slow adoption of nanosensor technology into the commercial space, nano-sensing is still a growing field with many exciting possibilities for both the food industry and regulatory authorities.

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