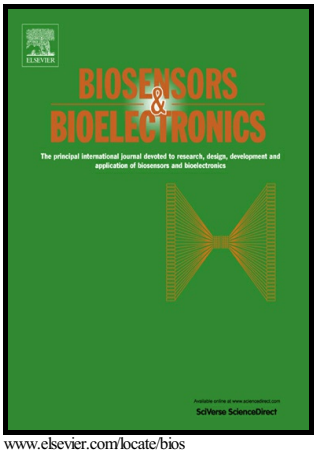
Advances in biosensor development for the screening of antibiotic residues in food products of animal origin – A comprehensive review

Valérie Gaudin



www.elsevier.com/locate/bios

PII: S0956-5663(16)31233-7
DOI: http://dx.doi.org/10.1016/j.bios.2016.12.005
Reference: BIOS9398

To appear in: *Biosensors and Bioelectronic*

Received date: 26 September 2016
Revised date: 22 November 2016
Accepted date: 1 December 2016

Cite this article as: Valérie Gaudin, Advances in biosensor development for the screening of antibiotic residues in food products of animal origin – A comprehensive review, *Biosensors and Bioelectronic* http://dx.doi.org/10.1016/j.bios.2016.12.005

Advances in biosensor development for the screening of antibiotic residues in food products of animal origin – A comprehensive review

Authors: Valérie Gaudin

Corresponding author:

Valérie GAUDIN

ANSES

Laboratoire de Fougères

10 B rue Claude Bourgelat - Javené

CS 40608

35306 FOUGERES Cedex

France

Telephone: 33 2 99 17 27 47

Fax: 33 2 99 94 78 80

E-mail: valerie.gaudin@anses.fr

Journal: Biosensors and bioelectronics

Abstract

Antibiotic residues may be found in food of animal origin, since veterinary drugs are used for preventive and curative purposes to treat animals. The control of veterinary drug residues in food is necessary to ensure consumer safety. Screening methods are the first step in the control of antibiotic residues in food of animal origin. Conventional screening methods are based on different technologies, microbiological methods, immunological methods or physico-chemical methods (e.g. thin-layer chromatography, HPLC, LC-MS/MS). Screening methods should be simple, quick, inexpensive and specific, with low detection limits and high sample throughput. Biosensors can meet some of these requirements. Therefore, the development of biosensors for the screening of antibiotic residues has been increasing since the 1980s.

The present review provides extensive and up-to-date findings on biosensors for the screening of antibiotic residues in food products of animal origin. Biosensors are constituted of a bioreceptor and a transducer. In the detection of antibiotic residues, even though antibodies were the first bioreceptors to be used, new kinds of bioreceptors are being developed more and more (enzymes, aptamers, MIPs); their advantages and drawbacks are discussed in this review. The different categories of transducers (electrochemical, mass-based biosensors, optical and thermal) and their potential applications for the screening of antibiotic residues in food are presented. Moreover, the advantages and drawbacks of the different types of transducers are discussed. Lastly, outlook and the future development of biosensors for the control of antibiotic residues in food are highlighted.

Keywords

Biosensor; nanotechnology; antibiotic residues; screening; food products

1. Introduction

Veterinary drugs and particularly antibiotics are chemicals authorised for use in food and feed products following a pre-marketing approval. Residues of antibiotics may pose a risk to animal and human health. For example, the emergence and spread of antimicrobial resistance could result in serious problems. This antibiotic resistance may spread to other microbial populations and infectious diseases that have become resistant to standard antimicrobial treatments, presenting a threat to human and animal health (Pletinckx et al. 2013; Sapkota et al. 2008). In Europe, specific legislation protects consumers from exposure to potentially harmful residues of veterinary medicines, pesticides and environmental contaminants in food of animal origin (1996). Maximum Residue Limits (MRLs) have been set for veterinary medicines, pesticides and environmental contaminants (European Regulation (EC) No 470/2009). National surveillance and control plans are implemented in each Member State in Europe to monitor residues in food. The first step in control is the screening method. Screening methods can be either qualitative or quantitative. A qualitative method is used to detect the presence of an analyte. The result is absence or presence. A quantitative method is able to identify and quantify the analyte. The result is given as a concentration of analyte. If the screening result is positive, a confirmatory step must be implemented by a physico-chemical method.

Screening methods are defined in Commission Decision EC/2002/657 (2002) as "methods used to detect the presence of an analyte or class of analytes at the level of interest. These methods have the capability for a high sample throughput and are used to sift large numbers of samples for potential noncompliant results. They are specially designed to avoid false compliant results". A screening method is the first method that is applied to sample analyses, the purpose being to establish the presence or absence of antibiotic residues. This procedure should be simple, as fast as possible, and sensitive. Concerning complex matrices, if needed, extraction should be very simple and quick. Lastly, screening methods should have a low cost. The “level of interest” to be screened is usually the regulatory limit (e.g. MRL for authorised substances, or the Minimum Required Performance Limit (MRPL) for banned substances).

Screening methods can be divided into conventional and innovative methods. Conventional methods are the oldest methods that have traditionally been used. Innovative methods are based on new technologies, innovative biorecognition elements or detection elements. Three types of conventional

methods are implemented for the control of antibiotic residues in food of animal origin. Microbiological methods were the first methods implemented for the control of antibiotic residues in food (Bogaerts et al. 1982; Bogaerts and Wolf 1980; Gillet et al. 1972). These methods, based on the sensitivity of bacteria to antibiotics, are simple and inexpensive. Immunological methods have since been developed, based on antibody-antigen recognition. These methods are more specific, due to their principle. Moreover, analytical techniques based on the physico-chemical properties of antibiotic molecules have been developed in parallel (Thin-Layer Chromatography (TLC), High-Performance Liquid Chromatography (HPLC)).

Biosensors are innovative methods in the field of antibiotic screening in food and many other analytical fields. Biosensor instruments consist of two main components: a bioreceptor or biorecognition element, which recognises the target analyte, and a transducer for converting the recognition event into a measurable signal (Velusamy et al. 2010). Technology based on sensors has a very broad scope, in major industries, including pharmaceuticals, health products, food, agriculture, and the environment. In connection with the disadvantages of conventional methods, there is a growing need to develop highly selective and effective biosensors for rapid, simple and inexpensive control of a wide range of molecules in many areas such as the food industry. Biosensors can help meet some of these needs: they offer speed, reliability, a low cost, and good value for money, and can easily be implemented by relatively unskilled personnel.

The use of biosensors in the field of food control began appearing in the literature around 1980 (Best 1987; Evans and Briers 1986; Guilbault and Schmid 1991; Rawson et al. 1989). For the detection of antibiotic residues in food, the first publications date from 1980 to 1990 (Kingdon 1985; Sternesjo et al. 1995; Thompson et al. 1979). Regarding major developments in bioreceptors and transducers during the past ten years (Reverté et al. 2016; Seok Kim et al. 2016; Xia et al. 2016; Zhang and Liu 2016), it is time to present an up-to date-comprehensive review, covering the main recent advances in the design and production of biosensors for antibiotic residue detection in many different types of foodstuffs (milk, meat, eggs, honey, seafood). The present article provides an overview of the different kinds of bioreceptors used to detect veterinary drugs. Even though antibodies were the first bioreceptors to be used, new kinds of bioreceptors are being developed more and more and used for the development of biosensors. The different categories of transducers and their potential applications for the screening of veterinary drugs in food are also presented. The advantages and drawbacks of

the different types of bioreceptors and transducers are discussed in this review. Lastly, outlook and the future development of biosensors for the control of veterinary drugs in food are highlighted.

2. Biosensors

2.1. Bioreceptors

Biosensors can be classified either by type of bioreceptor, or according to the type of transducer (**Figure 1**). Each biosensor element and each step of the method has an influence on the performance of the biosensor.

Insert Figure 1 here

A bioreceptor is an organic molecular species (e.g. an antibody, enzyme, protein, or nucleic acid) or a living biological system (e.g. cells, tissues or whole organisms) using a biochemical recognition mechanism (Vo-Dinh and Cullum 2000). The different types of bioreceptors that can be immobilised on the surface of biosensors are presented in **Figure 2**.

Insert Figure 2 here

In the Scopus database, the keyword "biosensor" was combined with each type of bioreceptor to obtain the number of publications (**Figure 3**).

Insert Figure 3 here

Different kinds of bioreceptors are used to develop biosensors for the screening of veterinary drug residues in food. The advantages and drawbacks of the different kinds of bioreceptors are summarised in **Table 1**.

Insert Table 1 here

Table 1. Advantages and drawbacks of the different kinds of bioreceptors.

			Advantages	Drawbacks
BIORECEPTORS	Antibodies	Monoclonal	Broad specificity Unlimited quantity and reproducibility Strong affinities	High cost Strong affinities
		Polyclonal	Low cost	Specificity is too high Limited quantity and lack of reproducibility
	Enzymes		Usually more accurate Answers faster (shorter diffusion paths) than sensors using cells as bioreceptors	Intrinsic instability Production cost > antibody Variable performance (e.g. pH, temperature, thickness of the enzyme layer on the sensor)
	MIPs		Affinities and specificities equivalent or ↑ / antibodies, thermostability Sensitivity ↑ Reusable Production: cost ↓/antibodies, simple, rapid, reproducible	Risk of release of the template molecule Insolubility Few imprinted cavities actually correspond to the template molecule Not commercialised
	Aptamers		Strong affinities Specificity ↑, sensitivity ↑ Stability (molecule, immobilised surfaces (>antibodies>enzymes)) Reusable Production: cost ↓/antibodies, simple, reproducible, automated	Strong affinities Few are commercialised
	Cells		Several analytes simultaneously Selectivity ↑ Ability to metabolise a wide range of chemical compounds Adaptability (unfavourable conditions) Genetic modifications (e.g. mutations) Economical source of intracellular enzymes Low detection limits Potential high throughput of analysis	Complex selection, culture and maintenance Sometimes selectivity problem (non-specific cellular response (e.g. side reactions catalysed by other enzymes)) Specificity ↓/pure enzymes Slow response times/enzymatic biosensors (substrate and product diffusion across the cell wall)

2.1.1. Antibodies

Antibodies are bioreceptors commonly used in the development of biosensors. Antibodies correspond to a single antigen in a highly specific manner. In biosensors, they are generally immobilised on a substrate, which acts as the detector surface. Antibodies may be polyclonal, monoclonal or recombinant, depending on their selective properties and the way they are synthesised. Polyclonal antibodies are produced using traditional immunisation procedures, namely in rabbits, goats, sheep and pigs.

Immunosensors based on antibodies are often described in combination with piezoelectric transducing elements, whether electrochemical or optical. Antibodies are currently the most commonly used bioreceptors for the development of biosensors in many areas of analysis, particularly for the screening of antibiotic residues. Various antibodies against antibiotics and other veterinary drugs are now commercially available.

2.1.2. Enzymes

Although enzymes are one biorecognition element, they are mainly used to function as markers rather than as biorecognition elements as such. Biosensors based on enzymes are mainly based on two mechanisms for detection. The first mechanism involves the catalytic conversion of an analyte by the enzyme (generally from a non-detectable form to a detectable form). The second mechanism involves the detection of analytes which inhibit or moderate the activity of the enzyme. Enzymatic biosensors use specific enzymes for the capture and catalytic production of the product, which is then directly determined using a transducer (e.g. electrochemical, optical). The most common enzymatic biosensor today is the biosensor for the detection of glucose in blood. Its application for diabetic patients has been the trigger and driver for research into this type of sensor.

In the analysis of contaminants, enzymatic biosensors for the analysis of herbicides are the most common, with fewer applications reported for antibiotics. An enzyme biosensor was developed to detect penicillin (Kiran and Kale 2002). Penicillinase is produced by transformed bacteria (*Escherichia coli* JM109) that were immobilised on an electrode of a pH meter. This biosensor has not been applied in food matrices, which are more complex.

2.1.3. Cells

A microbial biosensor consists of a transducer in association with viable or non-viable immobilised microbial cells. Cellular biosensors use the response of whole cells for the detection of biologically active agents. A review of the use of microbial cells as biological sensing elements in biosensors was published in 2001 (D'Souza 2001). Currently, different microbial species containing reporter genes which are specifically induced by selected promoters are used in the development of cell biosensors. In the presence of the target analyte, the inducible gene is activated and activates or represses expression of a reporter gene which is responsible for producing a measurable optical signal. Therefore, microbial cellular biosensors based on optical detection are particularly useful in high-throughput screening because they can be used to monitor multiple analytes at the same time. Selecting a suitable bacterial culture is essential, as in conventional microbiological methods, since the specific bacteria used in biosensors have characteristic spectra which may or may not correspond to the spectrum of compounds one wishes to detect.

A review was published on recent advances in the manufacture and application of microbial biosensors based on different types of transducers for detecting a wide range of analytes including glucose, herbicides, and antibiotics (Su et al. 2011). Cellular biosensors have been developed for the detection of antibiotic residues (tetracyclines (Bahl et al. 2005; Virolainen et al. 2008), beta-lactam antibiotics (Ben-Yoav et al. 2009; Ferrini et al. 2008; Kumar et al. 2008; Shapiro and Baneyx 2007; Virolainen et al. 2008), quinolones (Ben-Yoav et al. 2009), chloramphenicol and quinolones (Shapiro and Baneyx 2007)). Most recently, cellular biosensors for the detection of antibiotic residues have allowed for the simultaneous detection of multiple analytes within 30 minutes to three hours.

A receptor that is designed to mimic a bioreceptor is called a biomimetic receptor. MIPs and aptamers are biomimetic receptors. Biomimetic sensors are a promising class of synthetic receptors for the detection of antibiotic residues in particular. Though there are several methods for generating biomimetic receptors, such as genetically engineered molecules and artificial membrane fabrication, the molecular imprinting technique has emerged as an attractive tool for the development of artificial recognition agents.

2.1.4. MIPs

MIPs are produced by forming a polymer around a molecule which can be used as a template. It corresponds to the target molecule of the bioreceptor. Several microcavities are formed within MIPs, of which some are specific binding sites for the template analyte. MIPs can, in principle, be synthesised for any molecule (Bruggemann et al. 2000; Haupt 1999). The recognition site for the target molecule, formed in the cavity of the MIP, is released by removing the imprinting molecule. For ten years, MIPs have been developed for various food contaminants, particularly antibiotics (He et al. 2005; Quesada-Molina et al. 2012; Turiel et al. 2007).

2.1.5. Aptamers

Aptamers are RNA or single-stranded DNA ligands which are selected to recognise different targets from an extensive library of molecules containing randomly generated sequences. The production of aptamers was described for the first time in the early 1990s. The technology for selecting aptamers called SELEX (Systematic Evolution of Ligands by Exponential enrichment) is an integrated technology based on combinatorial chemistry, PCR (Polymerase Chain Reaction), and gene sequencing (Xu et al. 2011). Repeated cycles are performed so that the specific sequence increases exponentially and sequences with low affinity are eliminated. Aptamers are suitable for the recognition of small molecules in addition to high-molecular-weight compounds, and even entire cells. Biosensors using an aptamer as recognition element are called "aptasensors". Food safety applications are very diverse. Some "aptasensors" have been developed for the detection of antibiotic residues in food of animal origin (e.g. aminoglycosides (de-los-Santos-Álvarez et al. 2009), chloramphenicol (Mehta et al. 2011), oxytetracycline (Kim et al. 2009), ampicillin (K.-M. Song et al. 2012a), sulfadimethoxine (K.-M. Song et al. 2012b), dyes (malachite green) (Stead et al. 2010)).

Biomimetic bioreceptors have the advantage of being prepared *in vitro*, thus avoiding work on animals, and of producing tools for the recognition of non-immunogenic molecules. Aptamers and MIPs are more stable than antibodies in sometimes drastic environmental conditions. In addition, analytical costs are reduced because of the long lifetime of the biosensor. The major drawback of MIPs and aptamers is that the commercial development of these bioreceptors is still in its infancy (Baggiani et al. 2013; Van Dorst et al. 2010; Vasapollo et al. 2011). Columns of sample preparation for solid-phase extraction (SPE) are marketed, pre-grafted with MIPs for the detection of antibiotic residues (e.g.

Sigma-Aldrich (France) for chloramphenicol, quinolones), but MIPs alone are not commercially available.

2.1.6. Innovative bioreceptors

Biroeceptors can be the limiting factor in the development of a new biosensor. Therefore, research in this field targets the development of innovative bioreceptors which must be specific or selective, stable, inexpensive to manufacture, and reproducible. Future trends will consist in developing new bioreceptors and improving existing bioreceptors. Some examples of bioreceptors recently developed are given below:

- The structure of an aptamer developed for the recognition of aminoglycoside residues has been modified, so that aptamer-analyte recognition leads to greater conformational changes and thus easier detection (Schoukroun-Barnes et al. 2014). By combining improved electrochemical transduction and modified aptamers, detection limits have been reduced by 100.
- According to a similar principle, an MIP for the detection of metronidazole has been amended to be both the analyte recognition tool and the enzyme for the detection of the electrochemical signal (Gu et al. 2016).
- Affibodies are synthetic binding proteins which have attractive characteristics, compared to conventional antibodies (Justino et al. 2015) (e.g. small size, robustness, stability, high specificity). To date, affibodies have mainly been used in the field of imaging and medical diagnosis (e.g. cancer) and for therapeutic applications, and very recently for the development of biosensors (Baydemir et al. 2016).
- Liposomes coupled to a polydiacetylene (PDA) surface have been designed for the detection of aminoglycosides. The detection mechanism mimics cell membrane interactions between neomycin and phospholipids (Kang et al. 2012).
- Nanozymes combine the development of new bioreceptors and nanotechnology (Sharma et al. 2014; Shin et al. 2015; X. Wang et al. 2016). Nanozymes that mimic the activity of the enzyme are stronger, more stable and less expensive to produce than natural enzymes. To date, nanozymes have been developed mainly for biomedical (e.g. glucose) and environmental (e.g. pesticides (Weerathunge et al. 2014)) applications.

It should be underlined that, irrespective of the kind of bioreceptor, the drawback of commercial supply is that there is no guarantee that these bioreceptors will still be commercially available over a long period, with the same quality and in sufficient quantity. Thus, the methods developed with these bioreceptors could become obsolete.

2.1.7. Immobilisation of bioreceptors on interaction surfaces

The specificity, stability, and detection limits reached by a bioreceptor depend on the bioreceptor's immobilisation on the surface. Most importantly, the bioreceptor must be accessible for interaction and biologically active (undenatured). All of these bioreceptors are immobilised on the surface in various ways (**Table 2**).

Insert Table 2 here

Table 2. The different immobilisation techniques for bioreceptors on surfaces.

	Principle	Advantages	Drawbacks
Adsorption	Van der Waals forces	Simplicity, no denaturation of the bioreceptor	Instability (pH, ionic strength, temperature, solvent)
Inclusion	Physical immobilisation in a polymer matrix (e.g. polyacrylamide)	Preserved enzymatic activity (no chemical links)	Risk of denaturation of bioreceptors May impede the accessibility of the active site of bioreceptor
Entrapment	In solution behind a selective membrane (e.g. dialysis membrane)	Limited biodegradation or contamination	Complex to implement May impede the accessibility of the active site of bioreceptor
Covalent immobilisation	Covalent coupling (pre-activated medium)	High stability Reduced diffusional constraints	Risk of denaturation of bioreceptors Laborious technique
Immobilisation by reticulation	Fabrication of water-insoluble membranes which are adsorbed on a solid surface	Stability (difficult release of the ligand)	Risk of disruption of enzyme kinetics (diffusion problems in the membrane) Risk of denaturation of bioreceptors
Immobilisation by affinity	Affinity between two molecules (e.g. streptavidin / biotin (Kd ~ 10^{-15}M), almost as much as a covalent bond)	Stability More drastic regeneration conditions (as long as the bioreceptor does not lose its activity) Same orientation for all bioreceptors	Potential interference between the modified bioreceptor (e.g. biotinylated) and natural components (e.g. biotin naturally found in certain tissues (e.g. milk, liver, eggs)) Potential interference between the binding molecule (e.g. avidin or streptavidin) and natural components (e.g. eggs)

Dissociation constant: k_d.

2.2. Transducers

Biosensors are classified by their bioreceptor or their transducer type, respectively. The classification below is based on the transducer type. A wide variety of transduction methods have been developed in the past decade.

Insert Figure 4 here

Although there are new types of transducers constantly being developed, optical, electrochemical and mass-based transducers are the most popular and common biosensor methods for the detection of food contaminants and particularly of antibiotic residues (**Figure 4**). Each of these three major classes contains many different subclasses (**Figure 5**) and can be further divided into label and label-free (non-labelled) methods. Labelled methods depend on the detection of a specific label and label-free detection is based on the direct measurement of a phenomenon occurring during biochemical reactions on a transducer surface. Label-free detection is highly attractive because there is no need to produce a labelled conjugate. Thermal biosensors are the fourth class of biosensors but they are less frequently used.

The advantages and disadvantages of the various types of transducers are discussed below.

Insert Figure 5 here

2.2.1. Electrochemical transducers

The basic principle for electrochemical biosensors is that chemical reactions between immobilised biomolecules and target analytes produce or consume ions or electrons, which affects the measurable electrical properties of the solution, such as electric current or potential (Pohanka and Skládal 2008; Thévenot et al. 2001). The biochemical receptor (very often an enzyme, sometimes a membrane or sensitive surface) is immobilised on an electrochemical transduction element (i.e. electrode). Electrochemical sensing technology began in the early 1950s. There are different types of electrochemical biosensors for converting chemical information into a measurable electrical signal (Pohanka and Skládal 2008; Thévenot et al. 2001) (**Table 3**).

Insert Table 3 here

Table 3. Principles, advantages and drawbacks of the different types of electrochemical transducers.

	Principle	Advantages	Drawbacks
Amperometric	Enzyme electrodes (Au, C, Pt) Electrochemical oxidation or reduction of an electroactive species => Measurement of resulting current	Simplicity Automation Miniaturisation Highly sensitive Cost↓ More suitable for mass production than potentiometric transducers	Labelling of the analyte to increase the electrochemical reaction at the working electrode
Potentiometric	Redox or ion-selective electrodes (ISE) or field-effect transistors (FET) Detecting an ion produced by an enzymatic reaction => Measurement of a difference in potential between two electrodes	No labelling Simplicity Easy automation Miniaturisation of instrumentation Cost ↓	Lack of specificity (e.g. other ions in solution) Effect of the ionic strength at high concentrations Possible drift of the signal Less sensitive and slower than amperometric
Conductometric	Pt or Au electrodes Biochemical reactions producing or consuming specific ions => Measurement of the electrical conductivity of a solution at a constant voltage	Simplicity Cost ↓ Biocompatibility with biological samples No reference electrode Miniaturisation possible	Lack of specificity (potential interference of other ions in solution) Less sensitive / amperometric and potentiometric
Impedancemetric or impedimetric	Measurement the variation of resistance and/or interfacial capacitance between the electrode surface and a solution	No labelling Very sensitive Simple, fast Cost ↓	Poor reproducibility => no routine quantitative analysis

Gold: Au; Carbon: C; Platinum: Pt.

The most common electrochemical devices are potentiometric pH sensors. The first article on the development of an electrochemical biosensor for the detection of antibiotic residues (amphotericin B and nystatin) was published in 1979 (Thompson et al. 1979). Since then, many articles have been published concerning the production of electrochemical biosensors, among the various types presented. The examples provided in **Table 4** illustrate some applications of biosensors for the detection of antibiotic residues.

Insert Table 4 here

Table 4. Examples of electrochemical biosensors for the screening of antibiotic residues.

	Analyte	Matrix	Bioreceptor	Interaction surface	Enzyme or membrane composition	Assay time (min)	Reference
Amperometric	SULF	Milk	Antibody	SPCE	HRP	30	(Conzuelo et al. 2012)
	TCYC	/	Gene induction by a promoter	Platinum electrode	Enzyme expression (e.g. β-galactosidase)	/	(W. Song et al. 2012)
	BL	Milk	PBP	SPCE	HRP	30	(Conzuelo et al. 2013)
	CEPH, SULF, TCYC	Milk	Antibody + PBP	Magnetic beads	HRP	5	(Conzuelo et al. 2014)
Potentiometric	QNL, TTC	Milk	Whole cells *E. coli*	Galvanic cell	/	120	(Pellegrini et al. 2004)
	Erythromycin	Milk, honey	MIP	Au + NP Au electrodes	/	/	(Lian et al. 2012)
	Penicillin G	Milk	Penicillinase	Platinum electrode	Polytyramine film	1-2	(Ismail and Adeloju 2010)
Impedancemetric and conductometric	Penicillin G	Milk	Antibody	Gold electrode	SAM	20-25	(Thavarungkul et al. 2007)
	CAP	Shrimp	Antibody	Gold nanoparticles	SATUM	30	(Chullasat et al. 2011)
	Neomycin	Milk	Antibody	SWNT	Filter paper	10	(Wu et al. 2012)
	Ampicillin, kanamycin A	Milk	Aptamer	Electrode	PEDOT	2-3	(Daprà et al. 2013)

Beta-lactams (BL); Cephalosporins (CEPH); Sulphonamides (SULF); Tetracyclines (TCYC); Quinolones (QNL); Chloramphenicol (CAP); Penicillin-Binding Protein (PBP); Horseradish peroxidase (HRP); Escherichia coli (E. coli); Screen Printed Carbon Electrodes (SPCE); Molecularly Imprinted Polymer (MIP); Gold nanoparticles (NP Au); Self-Assembled Monolayer (SAM); Self-Assembled Thiourea Monolayer (SATUM); Single-Wall Carbon Nanotube (SWNT); Polymer of 3,4-ethylenedioxythiophene (PEDOT).

2.2.2. Mass-sensitive transducers

A mass-sensitive detector responds to the mass of solute passing through it per unit time. Mass-sensitive biosensors are also called gravimetric biosensors. Mechanical transduction methods are mainly based on the generation and detection of mechanical or acoustic waves (**Figure 6**). The most common mass-sensitive devices use piezoelectric crystals, quartz crystal microbalances (QCM), and surface acoustic waves (SAW). Piezoelectricity is the electric charge which accumulates in certain solid materials (notably crystals, ceramics and some organic materials such as bone, DNA and various proteins) in response to pressure (mass change to the area). Acoustic wave transducers are classified according to the mode of wave propagation through or on the surface of the piezoelectric material. Detailed principles for the different types of acoustic-based biosensors and the advantages and drawbacks of the different systems are presented and discussed in a recent review (Durmuş et al. 2014). Quartz Crystal Microbalance or QCM is by far the most popular mass-sensitive biosensor (Vo-Dinh and Cullum 2000). It is a reference tool for the detection of biomolecules without labelling (Janshoff et al. 2000). Mechanical wave transducers are called cantilevers. A cantilever is a beam anchored at one end only. The change in mass at the end of the beam is detected by an optical phenomenon (oscillation amplitude) (Lin and Datar 2006). Cantilever biosensors are ultra-sensitive electromechanical sensors used for the label-free detection of a large number of biological entities.

Insert Figure 6 here

Over the last fifteen years, thanks to advances in miniaturisation, biosensors based on microcantilevers (MCLs) have become a sensitive tool for chemical and biological detection.

Three main types of mass-sensitive transducers are most commonly used for the detection of antibiotic residues. Their principles, advantages and drawbacks are summarised in **Table 5**. Overall, these biosensors are fast and inexpensive and do not require labelling.

Insert Table 5 here

Table 5. Principles, advantages and drawbacks of different types of mass-sensitive transducers.

	Principle	Advantages	Drawbacks
Piezoelectric Quartz Crystal Microbalance (QCM)	Disturbance of propagation of an acoustic wave	No labelling Stable materials, chemically inert, mechanical and ageing characteristics Detection of small mass changes (small molecules) Selective surface films Rapid (real-time measurements) and simple	Lack of sensitivity and specificity Sensitivity to external disturbances
Piezoelectric Surface Acoustic Wave (SAW)		Simple and inexpensive fabrication Multiple analytes simultaneously (microchips)	
Cantilever	Converts a chemical signal into a mechanical movement	No labelling Simple Fast Low detection limits Simple and inexpensive fabrication Multiple analytes simultaneously (microchips) Simple sample preparation	

A review of various types of analytes measurable by QCM biosensors was published (Skládal 2003). Piezoelectric biosensors allow for the quick and easy determination of small molecules such as drugs, hormones and pesticides. However, there are very few reports in the literature regarding the use of piezoelectric biosensors for detecting residues of antibiotics and other food contaminants. Several QCM biosensors have been developed for the screening of chloramphenicol (CAP). The first biosensor was developed for the detection of CAP, but only in solutions, not in food matrices (Adanyi et al. 2006). Later on, another team also worked on a QCM biosensor for the detection of chloramphenicol residues in various matrices (milk, meat, eggs, honey) (Karaseva and Ermolaeva 2012). The announced detection levels of 5 and 10 µg/kg were much higher than the MRPL for CAP (0.3 µg/kg). In addition, another team developed a QCM biosensor, based on an MIP as biorecognition element for the detection of CAP in pig muscle, milk, honey and shrimp (Ebarvia et al. 2015). The biosensor was able to detect CAP in honey and in shrimp at concentrations below the MRPL.
Surface acoustic wave (SAW) biosensors are available on the market (e.g. SamX®, NanoTemper Technologies GmbH (Germany)). SAW biosensors can be used to detect low-molecular-weight analytes, such as antibiotic residues. Screening methods for antibiotic residues based on SAW biosensors have been developed for instance for penicillin in milk (Gruhl and Länge 2014) and for flumequine in water (Ktari et al. 2015). Cantilever biosensors are increasingly being used for the high-throughput screening of new active principles (Xu and Mutharasan 2009). Some recent applications for the detection of antibiotic residues were found in the literature (oxytetracycline in solution (Hou et al. 2013), kanamycin in solution (Bai et al. 2014a),vancomycin in serum (Bai et al. 2014b)).
Despite their potential, mass-sensitive biosensors are not commonly used for the screening of residues of veterinary drugs. However, the development of microchips (or "microarrays") could amplify their use in the field of bioanalysis in particular. Microchips have been developed to combine a few to hundreds of spots on a single surface or chip, thereby undertaking several immunoassays in parallel. In general, a chip comprises a network of several biosensors, which can be individually controlled. Several mass-sensitive biosensors of the same type can thus be combined in the form of microchips, thanks to advances in miniaturisation. This is called multiplexing technology, enabling the simultaneous detection of multiple analytes in a single analysis. This technology also enables dramatically increased sample throughput and reduced analysis time and costs. In addition, multiplex methods provide broad selectivity. Most often, multiplex biosensors require low sample preparation.

However, non-specific interactions between the target analytes and other analytes or matrix components have to be studied.

2.2.3. Optical transducers

Optical sensors are based on the change in optical properties when specific analytes bind to molecular receptors. The output signal that is measured is light. Optical-based detection offers a large number of subclasses based on different optical principles described below (**Figure 7**).

Insert Figure 7 here

Classical fluorescence and Time Resolved FluoroImmunoAssay (TR-FIA)

Different methods have been developed since 1990 using classical fluorescence for the detection of antibiotic residues (aminoglycosides in milk (Chu et al. 2008), in milk and tap water (Ton et al. 2012), sulfadimethoxine in milk (K.-M. Song et al. 2012b)). Other screening methods for veterinary drug residues (antibiotics, coccidiostats) were developed through a technology called time-resolved fluoroimmunoassay (TR-FIA) between 2006 and 2015 (Bacigalupo et al. 2008; Cháfer-Pericás et al. 2011; Chafer-Pericas et al. 2010; Hagren et al. 2006; Le et al. 2015; Shen et al. 2006; Zhang et al. 2013; Zhou et al. 2014). These methods could detect a single antibiotic (e.g. chloramphenicol) or a group of antibiotics (e.g. fluoroquinolones). Biosensors based on fluorescence detection are compatible with multiplexing technology. A multiplex biosensor based on fluorescence was developed by Chen *et al.* for the detection of eight antibiotics in chicken and porcine muscle and liver (Chen et al. 2009). A microarray of different spots was printed on a modified glass chip. The test lasted three hours to screen and quantify the eight antibiotics in six samples, which was slightly lower sample throughput compared to conventional ELISA techniques.

Flow cytometric immunoassay (FCIA)

The first articles demonstrating the potential use of flow cytometry to detect interactions between antibody and antigen date back to the 1980s. This technology uses small fluorescent microspheres. Each set of beads can be coupled to a different bioreceptor. Several different biomolecular interactions in a single microplate well can be measured simultaneously. Flow cytometry falls into the category of multiplexed technologies in suspension (or "suspension array technology"), since the

interaction between the beads grafted with antibodies, for example, and analytes occurs in suspension and not on a chip surface.

Immunoassay applications coupled with detection by flow cytometry (FCIA) have been published using commercial flow cytometers. For example, the Belgian National Reference Laboratory has developed a screening method for 64 antibiotics from ten different families in porcine muscle and in milk, based on flow cytometry (Suárez-Pantaleón et al. 2-5 June, 2014). As a result of this research project, kits called BeadyPlex® have been marketed since 2015 by the company Unisensor (Belgium), in partnership with a manufacturer of flow cytometers.

The second application concerns the Multi-Analyte Profiling system (xMAP®) (Luminex, Texas, United States). This open system enables the development of methods. Several applications of flow cytometry using this system for the detection of antibiotic residues were found in the literature. The first application for the detection of sulphonamides in milk was published in 2008 (de Keizer et al. 2008). The second application concerned, at first, the screening of three veterinary drugs, including chloramphenicol, then the extension of the screening method to five antibiotics in milk, and lastly the simultaneous screening of seven pesticides and veterinary drugs in water and in milk (N. Liu et al. 2013). The latter method is rapid (less than two hours) and the detection limit announced for chloramphenicol (0.05 µg/L) is less than the MRPL (0.3 µg/L).

Surface Plasmon Resonance (SPR)

Biosensors based on Surface Plasmon Resonance (SPR) are optical sensors using special electromagnetic waves to detect the interactions that occur at the surface. Mass changes on the surface of the sensor chip which occur during the association or dissociation of biomolecular complexes cause a shift in the position of the resonance angle. The sensorgram allows for the changes in resonance angle as a result of the binding of molecules on the chip to be monitored in real time. This technique was introduced in the 1990s.

The high cost of investment in SPR biosensors such as Biacore® systems (GE Healthcare, Sweden) was a hindrance to wider application in food control laboratories. Another less expensive biosensor based on SPR was marketed (Spreeta™, Texas Instruments, USA). However, this system proved to be less robust and had only one channel available to measure interactions, instead of two to eight depending on the different Biacore systems (Biomolecular Interaction Analysis or BIA technology).

Then a portable biosensor, SPReeta® SPR3 Kit, including three channels in parallel, was developed and evaluated for milk analysis (Fernández et al. 2011). Milk samples were analysed after simple sample preparation (centrifugation and dilution of milk).

Many methods were developed between 1995 and 2008 for the detection of antibiotic residues using Biacore® systems (Baxter et al. 2001; Caldow et al. 2005; Crooks et al. 2003; Dumont et al. 2006; Gaudin et al. 2001; Gaudin et al. 2007; Huet et al. 2009; McCarney et al. 2003; Sternesjo et al. 1995). The Biacore® system with eight channels allows for the simultaneous detection of eight different analytes or analyte families.

Sometimes non-commercial intra-laboratory-developed SPR systems have been applied to the screening of antibiotic residues. For example, a multi-antibiotic screening method (fluoroquinolones, sulphonamides and chloramphenicol) was developed in milk. The interaction of antibiotics and graft polyclonal antibodies is detected by a non-commercial SPR optical sensor with six channels (Fernández et al. 2010).

The BIA/MS combination

SPR biosensors may be used in combination with mass spectrometry (MS). This combination of instrumentation allows for the detection and quantitation of molecules of interest by SPR and, in addition, their molecular characterisation by MS analysis. The BIA system is used to separate analytes from complex samples. Mass spectrometry is used to identify and quantify the analyte. The first articles about the combination of biosensors with mass spectrometry were published in 1997 (Krone 1997; Nedelkov et al. 2000; Sonksen et al. 1998). The technique of matrix-assisted laser desorption/ionisation (MALDI) coupled with mass spectrometry (MALDI-MS) is a flexible technique which can also be used in combination with bioanalytical methods such as SPR biosensors. This combination increases the specificity of the method, because MS allows for the differentiation of molecules that are difficult to distinguish by the simple use of an antibody. This combination of techniques could result in the development of rapid, automated and robust methods. To our knowledge, no application for the detection of antibiotic residues in foods has been published to date using these combined technologies. The main drawback is the cost of different hardware investments.

Localised Surface Plasmon Resonance (LSPR)

Localised Surface Plasmon Resonance (LSPR) is generated by noble metal nanostructures, when classical SPR is generated by continuous planar films of metal (*eg.* gold). The physical theory of LSPR was well described by Petryayeva *et al.*, illustrated by applications of LSPR to biological and chemical sensing (Petryayeva and Krull 2011). Localised SPR means that the optical sensing is "highly localized around the nanoparticle" (Olaru et al. 2015). The advantages of LSPR compared to classical SPR are simpler and more compact (portable) optical systems, less sensitive to the changes of composition of the medium (refractive index); LSPR allows to develop more specific and sensitive methods (Chuang et al. 2015; Lin et al. 2016). Moreover, LSPR is compatible with multiplexing technology.

Some applications of LSPR either for the detection of antibiotic substances in pharmaceutical products (Chavada et al. 2017; Miranda-Andrades et al. 2017), for therapeutic drug monitoring in human serum samples (Cappi et al. 2015; Chavada et al. 2017; McKeating et al. 2016) or for the screening of antibiotic residues in food matrices (Anand et al. 2015; Frasconi et al. 2010; Ozhikandathil et al. 2012) have been published the recent past years.

Moreover, the LSPR could be combined to classical ELISA tests, which will be so called plasmonic ELISA (Satija et al. 2016; Tokel et al. 2014). One of the main advantages of pELISA is to offer tests with a reading with the naked eye. This track is explored to develop easy to use, low cost and sensitive Point of Care (POC) tools (Tokel et al. 2014). The application of pELISA to the detection of a small molecule (eg. methyltestosterone) by the naked eye is promising and predictive of a potential application to cost-effective and sensitive detection of antibiotic residues (Peng et al. 2014).

Surface Plasmon Resonance imaging (SPRi)

The Flexchip Biacore® system (GE Healthcare, Uppsala, Sweden) was the first commercially available SPRi platform. The IBIS SPRi system (IBIS Technology, Netherlands) is the system most frequently cited in the literature for the screening of antibiotic residues (Rebe Raz et al. 2008; Rebe Raz et al. 2009). This IBIS SPRi platform can analyse a maximum of 56 multiplexed assays.

The main advantage of combining SPRi and microarrays is that each microarray site is a single detection area. Krishnawoorthy *et al.* presented an application of the SPRi microarray format for the detection of five different molecules and the kinetic analysis of antigen/antibody interactions (Krishnamoorthy et al. 2010). Of these five molecules, two antibiotics, neomycin and gentamicin, have

been tested. In conclusion, this method could be used for the screening of these antibiotics or other antibiotics.

Diffractive Optics Technology (DOT)

Diffractive Optics Technology (DOT) combines the multiplex immunoassay format with real-time measurements of protein interactions (Borisenko et al. 2006). A photodiode measures the intensity of the diffraction order, which is correlated with the analyte concentration.

The dotLab® mX system (Axela Biosensors, Canada) is a flexible trading system that allows for the development of methods for protein biomarkers and new diagnostic tests (Houle 2009). This system could be tailored to the screening of low-molecular-weight compounds such as antibiotics. At this time, nothing has been found in the literature on the screening of antibiotic residues with this system.

Chemiluminescence ImmunoAssay (CLIA)

The bioreceptor (or analyte) is covalently labelled directly with a chemiluminescent compound (e.g. luminol). Triggering the luminescent marker, the light-emitting reaction produces a signal with a given intensity (photons/sec.). Measuring the light intensity is relatively simple, requiring only a photomultiplier or photodiode, and associated electronics for converting and recording the signals. Most of the tests are heterogeneous and require separation of unbound label. These tests are simpler to develop, but a bit more complicated to achieve. On the contrary, a homogeneous assay requires that the reaction of light emission has been affected in any way by the interaction between analyte and bioreceptor.

A review was published on the applications of chemiluminescence and bioluminescence in different areas related to contaminants (e.g. bacterial contamination and inorganic environmental contaminants (heavy metals)) (Roda and Guardigli 2012).

Two types of chemiluminescent biosensors have been identified:

- Intra-laboratory chemiluminescent biosensors:

CLIA offers several applications in clinical chemistry, environmental analysis, and food analysis. Advances in the field of biosensors based on chemiluminescence detection coupled with immunoassays are presented and discussed in a literature review (Zhao et al. 2009). These advances have been made for example in the development of new luminescent markers and the improvement of

existing markers by signal enhancers, as well as in the field of interaction surfaces. Examples of the intra-laboratory development of immunoassays based on chemiluminescence for food contaminants have been found in the literature (Guo and Gai 2011; Knecht et al. 2004; Thongchai et al. 2010; Yu et al. 2014).

- Commercial chemiluminescent biosensors:

Only two commercial chemiluminescence biosensors were identified for the screening of antibiotic residues.

- The Microarray Chip Reader System 3 (MCR 3), developed at the University of Munich in Germany, is marketed by R-Biopharm AG (Darmstadt, Germany) and used for the analysis of milk (Kloth et al. 2009) and honey (Wutz et al. 2011).
- The Evidence Investigator® system (Randox, UK) is a semi-automated system based on biochips, designed for forensic and veterinary applications (O'mahony *et al.* 2013). Evaluations of several kits have been published for the screening of antibiotic residues in honey (Gaudin et al. 2014a, b; O'Mahony et al. 2011) and in muscle and aquaculture products (Gaudin et al. 2016).

Luminescent bacteria

Bioluminescence is a form of luminescence, or emission of "cold light". The variation of luminescence can be caused by the enzyme luciferase, encoded by the lux gene in response to the presence of the target analyte in a dose-dependent relationship. The expression of the lux gene in microorganisms can be either controlled constitutively or inducible. Bacterial strains are constructed using bioluminescence genes (lux) as reporters of transcriptional responses. Light production increases in the presence of specific substances. Conversely, there are naturally bioluminescent bacteria such as *Vibrio fischeri*. In this case, light production decreases in the presence of a contaminant that inhibits bacterial growth. Examples of biosensors based on the use of luminescent bacteria developed for the screening of different antibiotics have been found in the literature (Valtonen et al. 2002; Virolainen et al. 2008).

In conclusion, the different types of optical transducers show advantages and disadvantages, in terms of both practicality and performance (**Table 6**).

Insert Table 6 here

Table 6. Advantages and drawbacks of different types of optical transducers.

Fluorescence	TR-FIA	FCIA	SPR	SPRi	DOT	CLIA	Bioluminescence
Selectivity Sensitivity	Increased sensitivity / single fluorescence No step to increase the signal Easy sample preparation Stability of conjugates Rapid (1:30-3:30)	Simultaneous measurement of several characteristics per cell or particle Rapid	No labelling Real-time study of interactions Simple to use Rapid Low detection limits	No labelling Real-time imaging Combining multiple immunoassays on a chip Simultaneous measurement of hundreds of interactions High sample throughput	No labelling Real-time measurements Flexibility Speed (15 to 45 minutes) Multiplex Rapid	CCD cameras Rapid No background noise Simple Reduced sample preparation Multiplex Reusable biochip (r-Biopharm)	Large number of samples Cheap Rapid Lyophilised bacteria
Labelling required No real-time measurement	Labelling required Complex instrumentation / classic fluorescence Quite expensive instruments and reagents	Labelling required	Cost ↑ of investment	Cost ↑ of investment	To date, no application for small molecules	Labelling required No real-time measurement Cost ↑of investment (CCD) and kits Closed commercial systems (no intra-laboratory development) Disposable biochip (Randox))	Not specific (unless modified bacterium) Production of genetically modified bacteria (expertise)

Time-resolved fluoroimmunoassay (TR-FIA); Flow cytometric immunoassay (FCIA); surface plasmon resonance (SPR); SPR imaging (SPRi); diffractive optics technology (DOT); Chemiluminescence immunoassay (CLIA); charge-coupled devices (CCD).

For some of these techniques, the labelling of the analyte or bioreceptor is necessary. This additional step of conjugation is complex and requires special experience. Moreover, conjugation may alter the recognition site between the analyte and the bioreceptor. Techniques without labelling should be preferred, provided that other features of the method (e.g. cost, performance) also meet our expectations.

Furthermore, multiplexing technology is applied to many of these optical biosensors, which is a major advantage for simultaneously detecting several antibiotics or families of antibiotics in food. Saving time and reducing the analysis workload are two major benefits of multiplex assays, compared to individual tests. A review was published about recent developments in multiplexed technologies, ranging from conventional (e.g. strips) to innovative techniques, based on different principles of optical detection (e.g. flow cytometry, chemiluminescence) (Rebe Raz and Haasnoot 2011). This review includes a synthetic diagram of the different technologies (on chips and in suspension). Their performance has been assessed in terms of detection limits and analysis times, based on the molecular weight of the analytes. The limits of detection and analysis times are correlated with the technology (planar or suspension) and type of application (pathogenic bacteria, small or large molecules). Regarding antibiotics which are low-molecular-weight analytes, the diagram shows that the detection limits obtained with multiplex techniques are generally of the order of ppb (µg/kg), thus consistent with the regulatory limits. In addition, methods based on chemiluminescence and SPR can be fast (a few minutes). These observations confirm our conclusions about the potential of multiplexed optical biosensors.

The major drawback of multiplexing is that the risk of observing interference in the detection of different analytes increases with the number of multiplexed assays. The optimisation of such methods is therefore crucial and labour-intensive to limit interferences. That is why this type of system must be automated to reduce the workload during the development and optimisation stages (Marquette et al. 2012).

2.2.4. Thermal transducers

Thermal biosensors make it possible to determine the concentration of a substrate by the energy change (generation or absorption) associated with a biochemical reaction (e.g. enzyme). The released or absorbed energy is proportional to the number of molecules produced by the biochemical reaction.

The temperature change is measured by microcalorimetry. In these biosensors, transducers are thermocouples, resistance thermometers or thermopiles (series of several thermocouples in combination). The most commonly used thermal biosensors are enzymatic biosensors. Such biosensors can be developed for the simultaneous detection of multiple analytes (multiplex). Indeed, a column may be divided into several distinct regions; each region is immobilised with a specific enzyme for the detection of a specific analyte. A combined thermal biosensor immunoassay is called a "thermometric ELISA" (TELISA).

Applications of thermal biosensors vary, from clinical analyses (e.g. glucose, cholesterol) to the monitoring of industrial processes (e.g. penicillin V production by fermentation) (Rank et al. 1992), by way of environmental analyses (e.g. heavy metals, pesticides) (Ramanathan and Danielsson 2001). A thermal biosensor called HEATSENS® (NitBiosensing (Nanoimmunotech), Spain) is marketed for various applications, including the detection of analytes in real time, in complex matrices. This portable biosensor is being used as part of a project to trace antibiotic residues in live animals (Spanish project called INNOSABOR).

Table 7 shows the advantages and disadvantages of thermal biosensors.

Insert Table 7 here

Table 7. Advantages and drawbacks of different types of thermal transducers.

Transducer	Advantages	Drawbacks
Isothermal Titration Micro Calorimetry	No labelling Stability Multiplex Easy miniaturisation => sensitivity ↗ No immobilisation of compounds Rapid Reproducible Possible automation Continuous measurements Not sensitive to light In solution No molecular-weight limitation No electrochemical or optical interferences (e.g. coloured , turbid solutions) Compatible with organic solvents	Difficult development of the cell sensor Difficult to implement High cost Possible fouling Pre-treatment of some samples

Whatever the type of transducer, nanotechnology is increasingly being used to improve the performance of biosensors.

2.3. Nanotechnologies

Nanotechnology is a field that is growing very rapidly and attracting many multidisciplinary teams. In other areas such as the detection of toxins, nanotechnologies that offer prospects for development include nanomaterials, magnetic beads and microfluidics (Reverté et al. 2016). It appears that for the detection of antibiotic residues in food, the same paths can be followed for the development of more efficient biosensors. The development of nanotechnology, regardless of contaminants, will in the coming years be the basis for the miniaturisation of biosensors. This miniaturisation will make it possible to develop the multiplexing and portability of biosensors (McGrath et al. 2012).
Regarding the progress of microfluidics and nanofluidics, screening methods for antibiotic residues will, as before, take advantage of advances in the biomedical field, which is always at the forefront of new technologies. The following applications in biomedicine can be highlighted, among other promising development prospects:

- A review by Derkus *et al.* has consolidated the various devices that enable the miniaturisation of biosensor systems: micro- and nanopatterning, microfluidics, and Micro-Electro-Mechanical Systems (MEMS) (Derkus 2016). Bio-MEMS technology is the development of biomedical (or biological) MEMS, i.e. microfabrication techniques (e.g. microelectrodes, microneedles). The many recent developments in MEMS technology will help improve the miniaturisation and portability of biosensors in all fields of application. For example, an optical biosensor, associated with MEMS technology, has been developed for the detection of a small molecule (a drug) and a large molecule (an antibody). This system is potentially applicable to the measurement of contaminants in environmental or medical home diagnostics (Kehl et al. 2016). This technology is also applicable to other types of biosensors (i.e. electrochemical, mass-sensitive (Lulec et al. 2016) or thermal).
- Lab-on-a-chip (LOC), Lab-in-a-tube (LIT) and Micro Total Analysis Systems (μTAS) technologies:

Micro Total Analysis Systems (μTAS) are devices that automate and include all necessary steps for a chemical analysis of a sample (e.g. sampling, sample transport, chemical reactions, detection). These

three systems can work across a chip, reducing the cost and duration of analysis. For example, a method based on LIT technology has been developed on the COBAS Liat® system (Roche Molecular Diagnostics, USA) for the detection of the influenza virus in sera from patients (Smith et al. 2012). Kovarick *et al.* presented a bibliographical review which shows examples of biosensors developed with μTAS technology (Kovarik et al. 2013). The developed methods are fast, automated and produce methods with low detection limits.

Table 8 summarises current and future trends in the field of nanomaterials, for the development of new and improved biosensors, especially for the detection of antibiotic residues. The different types of nanomaterials generally help improve the signal, thus lowering biosensor detection limits.

Insert Table 8 here

Table 8. Different types of nanomaterials, principles and advantages, through their recent applications to the screening of antibiotic residues.

	Constituents	Principle/advantages	Analytes	References
Nanoparticles	Metals (e.g. Au, Ag, Pt), Metal oxides (e.g. iron), silica, fatty acids	Increases the interaction surface Facilitates the transfer of load => active area of the electrode ↑	CAP, fluoroquinolones, enrofloxacin, streptomycin, sulfamerazine, tetracyclines	(Bougrini et al. 2016; Cháfer-Pericás et al. 2013; Emrani et al. 2016; Fernández et al. 2012; Kim et al. 2013; Yuan et al. 2008)
Nanorods or nanowires	Metals (e.g. Au, ZnO, CuO) or semi-conductor materials (e.g. silicone)	Absorption of light ↑ Excellent scattering properties	Gentamicin, penicillin, ofloxacin	(Ibupoto et al. 2011; Noor and Krull 2014; Zang et al. 2013; Zhu et al. 2011)
Quantum Dots (QD)	Semi-conductor materials (e.g. zinc sulphide, cadmium telluride)	Semiconductor nanostructure Optical properties (e.g. quantic yield ↑, fluorescence spectrum) QD commercialised	CAP, malachite green, multi-antibiotics, nitrofurans, sulphonamides and quinolones	(Esteve-Turrillas and Abad-Fuentes 2013; Feng et al. 2015; Jiang et al. 2015; Le et al. 2016; Liu et al. 2015; Y. Miao et al. 2016; Taokaenchan et al. 2015; Taranova et al. 2015)
Carbon nano-materials	Carbon nanotubes (single wall or multiple walls)	Surface ↑ ➔quantity of bioreceptors ↑ Electrochemical signals ↑	Kanamycin, sulphonamides, tetracyclines, ofloxacin, QCA	(Cesarino et al. 2013; Guo et al. 2015; He et al. 2015; Z. Wang et al. 2016; Xu et al. 2013; Yang et al. 2013; Zhou et al. 2012)
	Graphene, graphene oxide (GO)	Electric conductivity ↑ Fluorescence quencher	Aminoglycosides, kanamycin, penicillin	(Pumera 2011; Wei et al. 2012; Wu et al. 2014; Zhang et al. 2015)
Magnetic NP	Inorganic magnetic core (e.g. Au, multi-metals)	Separation of target molecules from other molecules through the magnetic field Electric conductivity ↑	CAP, streptomycin	(B. Liu et al. 2013; Y.-B. Miao et al. 2016; Yan et al. 2015)

Gold nanoparticles (NP Au); Silver (Ag); Platinum (Pt); Zinc Oxide (ZnO); Copper Oxide (CuO); Chloramphenicol (CAP); detection limit (LOD); quinoxaline-2- carboxylic acid (QCA).

3. Summary and conclusions

The four main classes of transducers are used to develop methods with or without labelling. Labelled methods require conjugation to the bioreceptor or to a molecule that enables detection. On the contrary, methods without labelling are based on the direct measurement of a phenomenon produced by biochemical reactions on a transducer surface. Methods without labelling avoid the long and complex preparation of the conjugate. They therefore offer a great advantage over the others, especially when a laboratory wants to develop an internal method and when conjugates are not commercially available. This is why SPR technology, for example, was strongly developed in the 1990s for the detection of antibiotic residues, while less expensive electrochemical techniques have been somewhat forgotten until now. This conclusion is also in favour of the development of mass-sensitive biosensors for the screening of antibiotic residues.

The "ideal" biosensor for the screening of antibiotic residues in food of animal origin should be inexpensive, fast, easy to use, and specific, with detection limits in line with the regulatory limits, and having high sample throughput (low sample preparation). **Table 9** shows the characteristics/performance of different types of transducers to develop screening methods fit for purpose. Biosensors represent the future of screening methods for antibiotic residues in food of animal origin.

Insert Table 9 here

Table 9. Expectations for an effective method of screening and compliance of each type of transducer.

Transducer	Economical	Rapid	Low LOD	Specificity	Sample preparation	Multiplex	High throughput	Portability
Potentiometric	++	++	++	++	++	++	++	++
Amperometric	++	++	++	++	++	++	++	++
Piezoelectric	++	++	++	+	+	++	++	++
SPR	-	++	++	++	++	+	++	++
Chimiluminescence	+	++	++	++	++	++	++	+
Bioluminescence	++	+	++	+	+	+	++	++
FCIA	+	++	++	++	+	++	++	-
Thermal	+	+	+	+	+	+	+	+

Surface Plasmon Resonance (SPR); Flow cytometric immunoassay (FCIA); Limit of detection (LOD); -: does not meet the expected criteria; +: partially meets the expected criteria; ++: completely meets the expected criteria.

4. Future perspectives

Biological screening methods have undergone major changes in the last 40 years. The principles and performance of these methods, including conventional microbiological and immunological methods and biosensors, are different.

In 1986, the future of biological screening methods for veterinary drug residues was ELISA for rapid, sensitive, specific and automated screening (Clark and Crosby 1986). Many technological advances have since occurred mainly in the areas of biology, chemistry, physics and electronics. However, the "ideal" method has not yet been developed. Therefore, research needs to continue into the development of more efficient and more economical biosensors (offering sensitivity, specificity, speed and portability (miniaturisation)). New advances in biosensors related to technology should strengthen the role of biosensors in food safety for the detection of various contaminants (e.g. environmental pollutants, pathogens), especially for the screening of antibiotic residues in food.

Three main factors have been identified that need to be worked on to develop more efficient biosensors: biorecognition elements, transducers and nanotechnology. Progress made in relation to each of these factors independently is crucial for developing new biosensors. In addition, it is the combination of simultaneous progress in these three areas that will lead to the future development of cheaper and more efficient biosensors.

Many of these developments began in the early 2000s and are growing steadily. The bibliography clearly shows that work for the improvement of these three factors represents different volumes.

The development of new tools such as transducers and bioreceptors improves the intensity of the signal to be detected and/or improves signal detection (**Figure 8**). Therefore, biosensor detection limits are lowered and can better meet the expectations of users. Efforts must also be made to develop biosensors with more automation, which could reduce analysis times, improve sample throughput, and reduce cost per analysis.

Insert Figure 8

Work is also being done for the development of new transducers. For example, advances in chemical luminescence biosensors consist in increasing the ability to collect light, working on light detection systems (e.g. photomultiplier tubes, charge-coupled device (CCD) cameras) and working on luminescent markers and signal amplification (Roda et al. 2016).

However, it appears that existing transduction methods have already benefited from all current knowledge and opportunities. In addition, current transducers already have developed potential, but this can be improved with alternative tools, such as bioreceptors and nanotechnology.

This improvement relates to the development of new types of bioreceptors and the improvement of bioreceptors for which there is already technology. The development of a third generation of amperometric enzymatic biosensors is also promising. There is direct electron transfer between enzyme and electrode. Unlike previous generations, there is no need for a mediator for transfer (Das et al. 2016). This third generation of biosensors allows for the development of more selective and sensitive methods. One of the enzymes that can be used in the third generation of biosensors is horseradish peroxidase (HRP), used most often in enzymatic biosensors for the detection of antibiotic residues. This type of biosensor can potentially be developed for antibiotic residues. However, for the moment, these biosensors have problems of enzyme stability, reproducibility and high cost of manufacture.

The most significant breakthrough in terms of the volume of publications and performance improvement has been nanotechnology. Nanotechnology is moving towards the miniaturisation of systems and therefore portability and cost reduction. It also helps in reducing microfluidic circuits for example, to reduce analysis times. In addition, by increasing interaction surfaces, nanomaterials can contribute to reducing detection limits.

Nanotechnology would also enable these methods to be used for self-monitoring, such as dairy self-monitoring, for which sample throughput must be very high (e.g. many thousands of samples per day). In the area of biomedical analysis, new biosensors are being developed for home testing. The test is easy to perform; reading and analysis of results are on the patient's smartphone (Cho et al. 2015; Giavazzi et al. 2014; Vashist et al. 2015; Zangheri et al. 2015). This type of test points to a possible application for the screening of antibiotic residues in the field, such as at the tanker on milk collection, at the slaughterhouse or on the farm. The identified needs are the same: inexpensive methods, extremely rapid (a few minutes, using dipsticks for example), no sample preparation, the simplest possible handling (whether for a patient, tanker driver or farmer), and with as few steps as possible. This type of biosensor would essentially improve the detection range and detection limits of tests at the tanker or on the farm. Currently, the tests used at the tanker are dipsticks that give a result within minutes and are specific for one or two families of antibiotics only (beta-lactam antibiotics in general

and/or tetracyclines). In addition, the use of smartphones as reading tools does not require the development and production of a specific dedicated reading device.

Acknowledgments

This work of literature review was conducted as part of the phD thesis in biology I successfully defended in the year 2016. I wish to thank in this context my supervisor, Dr. Michel Laurentie, Anses Fougeres, who gave me his advice, experience and kindness during this work. I also thank the analysts I work with daily Annie Rault and Celine Hédou, which allowed me to work calmly on writing my thesis. Thanks also to the head of the Antibiotic Biocide Residue Resistance (AB2R) unit, Christophe Soumet, Anses Fougères.

References

Commission Decision 2002/657/EC implementing Council Directive 96/23/EC concerning the performance of analytical methods and interpretation of results, 2002. Off. J. Eur. Commun., L221, 1-32.1996. pp. 10-32.

2002. pp. 8-36, Off J Eur Comm.

Adanyi, N., Varadi, M., Kim, N., Szendro, I., 2006. Curr. Appl. Phys. Engin. Aspects of Nanomaterials and Technologies 6(2), 279-286.

Anand, M.S., Satyendra, K.M., Banshi, D.G., 2015. Materials Research Express 2(3), 035007.

Bacigalupo, M.A., Meroni, G., Secundo, F., Lelli, R., 2008. Talanta 77(1), 126-130.

Baggiani, C., Anfossi, L., Giovannoli, C., 2013. Mol. Imprint. 1, 41-54.

Bahl, M.I., Hansen, L.H., Sørensen, S.J., 2005. FEMS Microbiol. Lett. 253(2), 201-205.

Bai, X., Hou, H., Zhang, B., Tang, J., 2014a. Biosens. Bioelectron. 56(0), 112-116.

Bai, X., Lu, B., Chen, X., Zhang, B., Tang, J., 2014b. Biosens. Bioelectron. 62(0), 145-150.

Baxter, G.A., Ferguson, J.P., O'Connor, M.C., Elliott, C.T., 2001. J. Agric. Food Chem. 49(7), 3204-3207.

Baydemir, G., Bettazzi, F., Palchetti, I., Voccia, D., 2016. Talanta 151, 141-147.

Ben-Yoav, H., Elad, T., Shlomovits, O., Belkin, S., Shacham-Diamand, Y., 2009. Biosens. Bioelectron. 24, 1969–1973.

Best, D., 1987. Prepared Foods 56(11), 182-186.

Bogaerts, R., Degroodt, J.M., de Vos, D., 1982. Ann. Pharm. Fr. 40(1), 37-41.

Bogaerts, R., Wolf, F., 1980. Fleischwirtschaft 60, 672-674.

Borisenko, V., Hu, W., Tam, P., Chen, I., Houle, J.-F., Ausserer, W., 2006. Clin. Chem. 52(11), 2168-2170.

Bougrini, M., Florea, A., Cristea, C., Sandulescu, R., Vocanson, F., Errachid, A., Bouchikhi, B., El Bari, N., Jaffrezic-Renault, N., 2016. Food control 59, 424-429.

Bruggemann, O., Haupt, K., L., Y., Yilmaz, E., Mosbach, K., 2000. J. Chromatogr. A 889(1-2), 15-24.

Caldow, M., Stead, S.L., Day, J., Sharman, M., Situ, C., Elliott, C., 2005. J. Agric. Food Chem. 53(19), 7367-7370.

Cappi, G., Spiga, F.M., Moncada, Y., Ferretti, A., Beyeler, M., Bianchessi, M., Decosterd, L., Buclin, T., Guiducci, C., 2015. Anal. Chem. 87(10), 5278-5285.

Cesarino, I., Cesarino, V., Lanza, M.R.V., 2013. Sens. Actuators B 188, 1293-1299.

Cháfer-Pericás, C., Balaguer, Á., Maquieira, Á., Puchades, R., 2013. Anal. Biochem. 432(1), 31-37.

Cháfer-Pericás, C., Maquieira, Á., Puchades, R., Miralles, J., Moreno, A., 2011. Food control 22, 993-999.

Chafer-Pericas, C., Maquieira, A., Puchades, R., Miralles, J., Moreno, A., Pastor-Navarro, N., Espinos, F., 2010. Anal. Chim. Acta 662, 177–185.

Chavada, V.D., Bhatt, N.M., Sanyal, M., Shrivastav, P.S., 2017. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 170, 97-103.

Chen, A., Wang, G., Cao, Q., Wang, Y., Zhang, Z., Sun, Y., Wang, H., Xu, C., Zhou, Q., Han, P., Liu, M., Yang, Y., Xing, W., Mitchelson, K.R., Cheng, J., 2009. J. Forensic Sci. 54(4), 953-960.

Cho, S., Park, T.S., Nahapetian, T.G., Yoon, J.-Y., 2015. Biosens. Bioelectron. 74, 601-611.

Chu, X., Wu, L., Liu, X., Li, N., Li, D., 2008. Anal. Biochem. 376, 144-150.

Chuang, P.-C., Liao, P.-C., Chen, Y.-F., 2015. pp. 93400T-93400T-93404.

Chullasat, K., Kanatharana, P., Limbut, W., Numnuam, A., Thavarungkul, P., 2011. Biosens. Bioelectron. 26(11), 4571-4578.

Clark, C.M., Crosby, N.T., 1986. Trends Anal. Chem. 5(5), 118-120.

Conzuelo, F., Gamella, M., Campuzano, S., G. Pinacho, D., Reviejo, A.J., Marco, M.P., Pingarrón, J.M., 2012. Biosens. Bioelectron. 36(1), 81-88.

Conzuelo, F., Gamella, M., Campuzano, S., Martínez-Ruiz, P., Esteban-Torres, M., de las Rivas, B., Reviejo, A.J., Muñoz, R., Pingarrón, J.M., 2013. Anal. Chem. 85(6), 3246-3254.

Conzuelo, F., Ruiz-Valdepeñas Montiel, V., Campuzano, S., Gamella, M., Torrente-Rodríguez, R.M., Reviejo, A.J., Pingarrón, J.M., 2014. Anal. Chim. Acta 820(0), 32-38.

Crooks, S.R.H., McCarney, B., Traynor, I.M., Thompson, C.S., Floyd, S., Elliott, C.T., 2003. Anal. Chim. Acta 483(1-2), 181-186.

D'Souza, S.F., 2001. Biosens. Bioelectron. 16(6), 337-353.

Daprà, J., Lauridsen, L.H., Nielsen, A.T., Rozlosnik, N., 2013. Biosens. Bioelectron. 43, 315-320.

Das, P., Das, M., Chinnadayyala, S.R., Singha, I.M., Goswami, P., 2016. Biosens. Bioelectron. 79, 386-397.

de-los-Santos-Álvarez, N., Lobo-Castañón, M.J., Miranda-Ordieres, A.J., Tuñón-Blanco, P., 2009. Biosens. Bioelectron. 24(8), 2547-2553.

de Keizer, W., Bienenmann-Ploum, M.E., Bergwerff, A.A., Haasnoot, W., 2008. Anal. Chim. Acta 620(1-2), 142-149.

Derkus, B., 2016. Biosens. Bioelectron. 79, 901-913.

Dumont, V., Huet, A.-C., Traynor, I., Elliott, C., Delahaut, P., 2006. Anal. Chim. Acta 567(2), 179-183.

Durmuş, N.G., Lin, R., Kozberg, M., Dermici, D., Khademhosseini, A., Demirci, U., 2014. In: Li, D. (Ed.), Encyclopedia of Microfluidics and Nanofluidics, pp. 1-15. Springer US.

Ebarvia, B.S., Ubando, I.E., Sevilla Iii, F.B., 2015. Talanta 144, 1260-1265.

Emrani, A.S., Danesh, N.M., Lavaee, P., Ramezani, M., Abnous, K., Taghdisi, S.M., 2016. Food Chem. 190, 115-121.

Esteve-Turrillas, F.A., Abad-Fuentes, A., 2013. Biosens. Bioelectron. 41(0), 12-29.

Evans, G.P., Briers, M.G., 1986. Biosens. 2, 287-300.

Feng, X., Gan, N., Zhang, H., Yan, Q., Li, T., Cao, Y., Hu, F., Yu, H., Jiang, Q., 2015. Biosens. Bioelectron. 74, 587-593.

Fernández, F., Hegnerová, K., Piliarik, M., Sanchez-Baeza, F., Homola, J., Marco, M.P., 2010. Biosens. Bioelectron. 26(4), 1231-1238.

Fernández, F., Pinacho, D.G., Sánchez-Baeza, F., Marco, M.P., 2011. J. Agric. Food Chem. 59(9), 5036-5043.

Fernández, F., Sánchez-Baeza, F., Marco, M.P., 2012. Biosens. Bioelectron. 34(1), 151-158.

Ferrini, A.M., Mannoni, V., Carpico, G., Pellegrini, G.E., 2008. J. Agric. Food Chem. 56, 784-788.

Frasconi, M., Tel-Vered, R., Riskin, M., Willner, I., 2010. Anal. Chem. 82(6), 2512-2519.

Gaudin, V., Fontaine, J., Maris, P., 2001. Anal. Chim. Acta 436, 191-198.

Gaudin, V., Hédou, C., Sanders, P., 2007. J. AOAC Int. 90(6), 1706-1715.

Gaudin, V., Hedou, C., Soumet, C., Verdon, E., 2014a. Food Agric. Immunol. 26(4), 477-495.

Gaudin, V., Hedou, C., Soumet, C., Verdon, E., 2014b. Food Addit. & Contam.: Part A 31(10), 1699-1711.

Gaudin, V., Hedou, C., Soumet, C., Verdon, E., 2016. Food Addit. & Contam.: Part A 33(3), 403-419.

Giavazzi, F., Salina, M., Ceccarello, E., Ilacqua, A., Damin, F., Sola, L., Chiari, M., Chini, B., Cerbino, R., Bellini, T., Buscaglia, M., 2014. Biosens. Bioelectron. 58, 395-402.

Gillet, A., Vanderhaegue, H., Bogaerts, R., Boudru, I., Brouckaert, A., Coucke, G., Dony, G., Drion, P., Dumont, P., Haemers, A., Pijck, J., Van Kerchove, C., 1972. J. Pharm. Belg. 27(4), 381-401.

Gruhl, F.J., Länge, K., 2014. Food Analytical Methods 7(2), 430-437.

Gu, Y., Yan, X., Li, C., Zheng, B., Li, Y., Liu, W., Zhang, Z., Yang, M., 2016. Biosens. Bioelectron. 77, 393-399.

Guilbault, G.G., Schmid, R.D., 1991. Biotechnol. Appl. Biochem. 14, 133-145.

Guo, W., Sun, N., Qin, X., Pei, M., Wang, L., 2015. Biosens. Bioelectron. 74, 691-697.

Guo, Z., Gai, P., 2011. Anal. Chim. Acta 688(2), 197-202.

Hagren, V., Peippo, P., Tuomola, M., Lovgren, T., 2006. Anal. Chim. Acta 557(1-2), 164-168.

Haupt, K.M., K., 1999. Biochem. Soc. Trans. 27(2), 344-350.

He, Y., Lu, J., Liu, M., Du, J., 2005, 2005. Analyst 130(7), 1032-1037.

He, Z., Zang, S., Liu, Y., He, Y., Lei, H., 2015. Biosens. Bioelectron. 73, 85-92.

Hou, H., Bai, X., Xing, C., Gu, N., Zhang, B., Tang, J., 2013. Anal. Chem. 85(4), 2010-2014.

Houle, J.-F., 2009. Comb. Chem. High Throughput Screening 12(8), 801-811.

Huet, A.-C., Charlier, C., Weigel, S., Benrejeb, S., Delahaut, P., 2009. Food Addit. & Contam.: Part A 26(10), 1341–1347.

Ibupoto, Z.H., Ali, S.M.U., Khun, K., Chey, C.O., Nur, O., Willander, M., 2011. Biosens. 1(4), 153.

Ismail, F., Adeloju, S.B., 2010. Sensors 10(4), 2851.

Janshoff, A., Galla, H.J., Seinem, C., 2000. Angewandte Chemie - International Edition 39(22), 4004-4032.

Jiang, W., Beloglazova, N.V., Wang, Z., Jiang, H., Wen, K., de Saeger, S., Luo, P., Wu, Y., Shen, J., 2015. Biosens. Bioelectron. 66(0), 124-128.

Justino, C.I.L., Duarte, A.C., Rocha-Santos, T.A.P., 2015. TrAC Trends in Analytical Chemistry 65, 73-82.

Kang, D.H., Jung, H.-S., Ahn, N., Lee, J., Seo, S., Suh, K.-Y., Kim, J., Kim, K., 2012. Chem. Commun. (Cambridge, U. K.) 48(43), 5313-5315.

Karaseva, N.A., Ermolaeva, T.N., 2012. Talanta 93(0), 44-48.

Kehl, F., Etlinger, G., Gartmann, T.E., Tscharner, N.S.R.U., Heub, S., Follonier, S., 2016. Sens. Actuators B 226, 135-143.

Kim, S., Ko, J., Lim, H.B., 2013. Anal. Chim. Acta 771(0), 37-41.

Kim, Y.S., Niazi, J.H., Gu, M.B., 2009. Anal. Chim. Acta 634(2), 250-254.

Kingdon, C.F.M., 1985. Appl. Microbiol. Biotechnol. 22(3), 165-168.

Kiran, B.R., Kale, K.U., 2002. Indian J.Pharm. Sci. 64(3), 205-208.

Kloth, K., Rye-Johnsen, M., Didier, A., Dietrich , R., Märtlbauer , E., Niessner, R., Seidel, M., 2009. Analyst 134(7), 1433-1439.

Knecht, B.G., Srasser, A., Dietrich, R., Martlbauer, E., Niessner, R., Weller, M.G., 2004. Anal. Chem. 76(3), 646-654.

Kovarik, M.L., Ornoff, D.M., Melvin, A.T., Dobes, N.C., Wang, Y., Dickinson, A.J., Gach, P.C., Shah, P.K., Allbritton, N.L., 2013. Anal. Chem. 85(2), 451-472.

Krishnamoorthy, G., van den Berg, A., Schasfoort, R.B.M., 2010. Sens. Actuators B 148(2), 511-521.

Krone, J.R., 1997. Anal. Biochem. 244, 124-132.

Ktari, N., Fourati, N., Zerrouki, C., Ruan, M., Nassoko, D., Seydou, M., Yaakoubi, N., Chehimi, M.M., Kalfat, R., 2015. Procedia Eng. 120, 998-1002.

Kumar, S., Kundu, S., Pakshirajan, K., Dasu, V.V., 2008. Appl. Biochem. Biotechnol. 151(2-3), 653-664.

Le, T., Yu, H., Niu, X., 2015. Food Chem. 175, 85-91.

Le, T., Zhu, L., Yu, H., 2016. Food Chem. 199, 70-74.

Lian, W., Liu, S., Yu, J., Xing, X., Li, J., Cui, M., Huang, J., 2012. Biosens. Bioelectron. 38, 163-169.

Lin, D.Z., Chuang, P.C., Liao, P.C., Chen, J.P., Chen, Y.F., 2016. Biosens. Bioelectron. 81, 221-228.

Lin, H., Datar, R.H., 2006. Review Series: Bench to Bedside 27 19(1).

Liu, B., Tang, D., Zhang, B., Que, X., Yang, H., Chen, G., 2013. Biosens. Bioelectron. 41(0), 551-556.

Liu, N., Gao, Z., Ma, H., Su, P., Ma, X., Li, X., Ou, G., 2013. Biosens. Bioelectron. 41(0), 710-716.

Liu, Y., Yan, K., Okoth, O.K., Zhang, J., 2015. Biosens. Bioelectron. 74, 1016-1021.

Lulec, S.Z., Adiyan, U., Yaralioglu, G.G., Leblebici, Y., Urey, H., 2016. Sens. Actuators A 237, 147-154.

Marquette, C.A., Corgier, B.P., Blum, L.J., 2012. Bioanalysis 4(8), 927-936.

McCarney, B., Traynor, I.M., Fodey, T.L., Crooks, S.R.H., Elliott, C.T., 2003. Analytica Chimica Acta - 4th International Symposium on Hormone and Veterinary Residue Analysis. 483(1-2), 165-169.

McGrath, T.F., Elliott, C.T., Fodey, T.L., 2012. Anal. Bioanal. Chem. 403(1), 75-92.

McKeating, K.S., Couture, M., Dinel, M.-P., Garneau-Tsodikova, S., Masson, J.-F., 2016. Analyst 141(17), 5120-5126.

Mehta, J., Van Dorst, B., Rouah-Martin, E., Herrebout, W., Scippo, M.-L., Blust, R., Robbens, J., 2011. J. Biotechnol. 155(4), 361-369.

Miao, Y.-B., Gan, N., Ren, H.-X., Li, T., Cao, Y., Hu, F., Chen, Y., 2016. Talanta 147, 296-301.

Miao, Y., Gan, N., Li, T., Cao, Y., Hu, F., Chen, Y., 2016. Sens. Actuators B 222, 1066-1072.

Miranda-Andrades, J.R., Pérez-Gramatges, A., Pandoli, O., Romani, E.C., Aucélio, R.Q., da Silva, A.R., 2017. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 172, 126-134.

Nedelkov, D., Rasooly, A., Nelson, R.W., 2000. Int. J.Food Microbiol. 60(1), 1-13.

Noor, M.O., Krull, U.J., 2014. Anal. Chim. Acta 825, 1-25.

O'Mahony, J., Moloney, M., McConnell, R.I., Benchikh, E.O., Lowry, P., Furey, A., Danaher, M., 2011. Biosens. Bioelectron. 26(10), 4076-4081.

Olaru, A., Bala, C., Jaffrezic-Renault, N., Aboul-Enein, H.Y., 2015. Crit. Rev. Anal. Chem. 45(2), 97-105.

Ozhikandathil, J., Badilescu, S., Packirisamy, M., 2012. pp. 84120W-84120W-84128.

Pellegrini, G., Carpico, G., Petz, M., 2004. Anal. Chim. Acta 520(1-2), 13-18.

Peng, C., Duan, X., Gabriel Wafala Khambaa, Xiea, Z., 2014. Anal. Methods 6, 9616-9621.

Perumal, V., Hashim, U., 2014. J.Appl. Biomed. 12(1), 1-15.

Petryayeva, E., Krull, U.J., 2011. Anal. Chim. Acta 706(1), 8-24.

Pletinckx, L.J., Verhegghe, M., Crombé, F., Dewulf, J., De Bleecker, Y., Rasschaert, G., Butaye, P., Goddeeris, B.M., De Man, I., 2013. Prev. Vet.Med. 109(3–4), 293-303.

Pohanka, M., Skládal, P., 2008. J.Appl. Biomed. 6(2), 57-64.

Pumera, M., 2011. Mater. Today 14(7–8), 308-315.

Quesada-Molina, C., Claude, B., García-Campaña, A.M., del Olmo-Iruela, M., Morin, P., 2012. Food Chem. 135(2), 775-779.

Ramanathan, K., Danielsson, B., 2001. Biosens. Bioelectron. 16(6), 417-423.

Rank, M., Danielsson, B., Gram, J., 1992. Biosens. Bioelectron. 7(9), 631-635.

Rawson, D.M., Willmer, A.J., Turner, A.P.P., 1989. Biosens. 4(5), 299-311.

Rebe Raz, S., Bremer, M.G.E.G., Giesbers, M., Norde, W., 2008. Biosens. Bioelectron. 24(4), 552-557.

Rebe Raz, S., Bremer, M.G.E.G., Haasnoot, W., Norde, W., 2009. Anal. Chem. 81(18), 7743-7749.

Rebe Raz, S., Haasnoot, W., 2011. Trends Anal. Chem. 30(9), 1526-1537.

Reverté, L., Prieto-Simón, B., Campàs, M., 2016. Anal. Chim. Acta 908, 8-21.

Roda, A., Guardigli, M., 2012. Anal. Bioanal. Chem. 402(1), 69-76.

Roda, A., Mirasoli, M., Michelini, E., Di Fusco, M., Zangheri, M., Cevenini, L., Roda, B., Simoni, P., 2016. Biosens. Bioelectron. 76, 164-179.

Sapkota, A., Sapkota, A.R., Kucharski, M., Burke, J., McKenzie, S., Walker, P., Lawrence, R., 2008, 2008. Environ. Int. 34(8), 1215-1226.

Satija, J., Punjabi, N., Mishra, D., Mukherji, S., 2016. RSC Advances 6(88), 85440-85456.

Schoukroun-Barnes, L.R., Wagan, S., White, R.J., 2014. Anal. Chem. 86(2), 1131-1137.

Seok Kim, Y., Ahmad Raston, N.H., Bock Gu, M., 2016. Biosens. Bioelectron. 76, 2-19.

Shapiro, E., Baneyx, F., 2007. J. Biotechnol. 132(4), 487-493.

Sharma, T.K., Ramanathan, R., Weerathunge, P., Mohammadtaheri, M., Daima, H.K., Shukla, R., Bansal, V., 2014. Chem. Commun. (Cambridge, U. K.) 50(100), 15856-15859.

Shen, J., Zhang, Z., Yao, Y., Shi, W., Liu, Y., Zhang, S., 2006. Anal. Chim. Acta 575, 262-266.

Shin, H.Y., Park, T.J., Kim, M.I., 2015. J. Nanomater. 2015, 11.

Skládal, P., 2003. J. Braz. Chem. Soc. 14, 491-502.

Smith, E.J., Xi, W., Makarov, D., Monch, I., Harazim, S., Bolanos Quinones, V.A., Schmidt, C.K., Mei, Y., Sanchez, S., Schmidt, O.G., 2012. Lab Chip 12(11), 1917-1931.

Song, K.-M., Jeong, E., Jeon, W., Cho, M., Ban, C., 2012a. Anal. Bioanal. Chem. 402(6), 2153-2161.

Song, K.-M., Jeong, E., Jeon, W., Jo, H., Ban, C., 2012b. Biosens. Bioelectron. 33(1), 113-119.

Song, W., Pasco, N., Gooneratne, R., Weld, R.J., 2012. Biosens. Bioelectron. 35(1), 69-74.

Sonksen, C.P., Nordhoff, E., Jansson, O., Malmqvist, M., Roepstorff, P., 1998. Anal. Chem. 70, 2731-2736.

Stead, S.L., Ashwin, H., Johnston, B.H., Dallas, A., Kazakov, S.A., Tarbin, J.A., Sharman, M., Kay, J., Keely, B.J., 2010. Anal. Chem. 82(7), 2652-2660.

Sternesjo, A., Mellgren, C., Bjorck, L., 1995. Anal. Biochem. 226, 175-181.

Su, L., Jia, W., Hou, C., Lei, Y., 2011. Biosens. Bioelectron. 26(5), 1788-1799.

Suárez-Pantaleón, C., Colombo, M., Huet, A.-C., Chabottaux, V., Delahaut, P., Granier, B., 2-5 June, 2014. Seventh International Symposium on Hormone and Veterinary Drug Residue Analysis, De Bijloke Ghent, Belgium.

Taokaenchan, N., Tangkuaram, T., Pookmanee, P., Phaisansuthichol, S., Kuimalee, S., Satienperakul, S., 2015. Biosens. Bioelectron. 66, 231-237.

Taranova, N.A., Berlina, A.N., Zherdev, A.V., Dzantiev, B.B., 2015. Biosens. Bioelectron. 63, 255-261.

Thavarungkul, P., Dawan, S., Kanatharana, P., Asawatreratanakul, P., 2007. Biosens. Bioelectron. 23(5), 688-694.

Thévenot, D.R., Toth, K., Durst, R.A., Wilson, G.S., 2001. Biosens. Bioelectron. 16(1–2), 121-131.

Thompson, M., Worsflod, P.J., Holuk, J.M., Stubley, E.A., 1979. Anal. Chim. Acta 104(2), 195-203.

Thongchai, W., Liawruangath, B., Liawruangrath, S., Greenway, G.M., 2010. Talanta 82(2), 560-566.

Tokel, O., Inci, F., Demirci, U., 2014. Chem. Rev. (Washington, DC, U. S.) 114(11), 5728-5752.

Ton, X.A., Acha, V., Haupt, K., Tse Sum Bui, B., 2012. Biosens. Bioelectron. 36(1), 22-28.

Turiel, E., Martin-Esteban, A., Tadeo, J.L., 2007. J. Chromatogr. A 1172(2), 97-104.

Valtonen, S.J., Kurittu, J.S., Karp, M.T., 2002. J.Biomol. Screen. 7(2), 127-134.

Van Dorst, B., Mehta, J., Bekaert, K., Rouah-Martin, E., De Coen, W., Dubruel, P., Blust, R., Robbens, J., 2010. Biosens. Bioelectron. 26(4), 1178-1194.

Vasapollo, G., DelSole, R., Mergola, L., Lazzoi, M.R., Scardino, A., Scorrano, S., Mele, G., 2011. Int. J.Mol. Sci. 12(9), 5908-5945.

Vashist, S.K., van Oordt, T., Schneider, E.M., Zengerle, R., von Stetten, F., Luong, J.H.T., 2015. Biosens. Bioelectron. 67, 248-255.

Velusamy, V., Arshak, K., Korostynska, O., Oliwa, K., Adley, C., 2010. Biotechnol. Adv. 28(2), 232-254.

Virolainen, N.E., Pikkemaat, M.G., Elferink, J.W.A., Karp, M.T., 2008. J. Agric. Food Chem. 56(23), 11065-11070.

Vo-Dinh, T., Cullum, B., 2000. Fresenius. J. Anal. Chem. 366(6-7), 540-551.

Wang, X., Hu, Y., Wei, H., 2016. Inorg. Chem. Front. 3(1), 41-60.

Wang, Z., Yu, J., Gui, R., Jin, H., Xia, Y., 2016. Biosens. Bioelectron. 79, 136-149.

Weerathunge, P., Ramanathan, R., Shukla, R., Sharma, T.K., Bansal, V., 2014. Anal. Chem. 86(24), 11937-11941.

Wei, Q., Zhao, Y., Du, B., Wu, D., Li, H., Yang, M., 2012. Food Chem. 134(3), 1601-1606.

Wu, X., Kuang, H., Hao, C., Xing, C., Wang, L., Xu, C., 2012. Biosens. Bioelectron. 33(1), 309-312.

Wu, Y., Tang, L., Huang, L., Han, Z., Wang, J., Pan, H., 2014. Mater. Sci. Eng., C 39(0), 92-99.

Wutz, K., Niessner, R., Seidel, M., 2011. Microchim. Acta 173(1-2), 1-9.

Xia, Y., Si, J., Li, Z., 2016. Biosens. Bioelectron. 77, 774-789.

Xu, D.-M., Wu, M., Zou, Y., Zhang, Q., Wu, C.-C., Zhou, Y., Liu, X.-J., 2011. Chin. J. Anal. Chem. 39(6), 925-933.

Xu, S., Mutharasan, R., 2009. Expert Opin. Drug Discovery 4(12), 1237-1251.

Xu, Y., Ding, J., Chen, H., Zhao, Q., Hou, J., Yan, J., Wang, H., Ding, L., Ren, N., 2013. Food Chem. 140(1–2), 83-90.

Yan, Z., Gan, N., Wang, D., Cao, Y., Chen, M., Li, T., Chen, Y., 2015. Biosens. Bioelectron. 74, 718-724.

Yang, Y., Fang, G., Liu, G., Pan, M., Wang, X., Kong, L., He, X., Wang, S., 2013. Biosens. Bioelectron. 47, 475-481.

Yu, X., He, Y., Jiang, J., Cui, H., 2014. Anal. Chim. Acta 812(0), 236-242.

Yuan, J., Oliver, R., Aguilar, M.-I., Wu, Y., 2008. Anal. Chem. 80(21), 8329-8333.

Zang, S., Liu, Y., Lin, M., Kang, J., Sun, Y., Lei, H., 2013. Electrochim. Acta 90(0), 246-253.

Zangheri, M., Cevenini, L., Anfossi, L., Baggiani, C., Simoni, P., Di Nardo, F., Roda, A., 2015. Biosens. Bioelectron. 64, 63-68.

Zhang, D., Liu, Q., 2016. Biosens. Bioelectron. 75, 273-284.

Zhang, Y., Zuo, P., Ye, B.-C., 2015. Biosens. Bioelectron. 68(0), 14-19.

Zhang, Z., Liu, J.-f., Feng, T.-t., Yao, Y., Gao, L.-h., Jiang, G.-b., 2013. Environ. Sci. Technol. 47(1), 454-462.

Zhao, L., Sun, L., Chu, X., 2009. Trends Anal. Chem. 28(4), 404-415.

Zhou, B., Zhang, J., Fan, J., Zhu, L., Zhang, Y., Jin, J., Huang, B., 2014. Eur. Food Res. Technol. 240(3), 619-625.

Zhou, L., Li, D.-J., Gai, L., Wang, J.-P., Li, Y.-B., 2012. Sens. Actuators B 162(1), 201-208.

Zhu, Y., Qu, C., Kuang, H., Xu, L., Liu, L., Hua, Y., Wang, L., Xu, C., 2011. Biosens. Bioelectron. 26(11), 4387-4392.

Figure captions

Figure captions

Figure 1. The different types of biosensors. Biosensors can be classified either by type of bioreceptor, or according to the type of transducer.

Figure 2. The different types of bioreceptors immobilised on the surfaces of biosensors *(Perumal and Hashim 2014).* Five major types of bioreceptors are used to develop biosensors, especially for the detection of antibiotic residues in food of animal origin. This figure was extracted from the article of Perumal and Hashim 2014.

Figure 3. Evolution of the annual number of articles (Scopus) concerning bioreceptors from 2000 to 2015. This graph represents the evolution of the number of articles published from 2000 to 2015 on the different kinds of bioreceptors. The number of annual articles is represented in the y-axis. Years are represented in the x-axis. The combination “biosensor and enzym*” is clearly the most frequently found combination, followed by “biosensor and antibod*”.

Figure 4. Evolution of the annual number of articles (Scopus) concerning biosensors from 2000 to 2015. This graph represents the evolution of the number of articles published from 2000 to 2015 on the different kinds of biosensors. The number of annual articles is represented in the y-axis. Years are represented in the x-axis. The electrochemical biosensors are clearly the most frequently found biosensors, followed by optical biosensors.

Figure 5. Different classes and sub-classes of biosensors, in relation to the type of transducer. The four categories of transducers (optical, electrochemical, mass-based and thermal transducers) can be divided into several sub-classes.

Figure 6. Classification of mass-sensitive biosensors. Mechanical transduction methods are mainly based on the generation and detection of mechanical or acoustic waves. Mass-sensitive biosensors can be divided into several subclasses.

Figure 7. Principles of measurement of the different types of optical transducers. Optical transducers can be divided into a large number of subclasses based on different optical principles.

Figure 8. Combination of three factors for improving the performance of biosensors: current trends. Future developments in the field of biosensors in general and especially for the screening of antibiotic residues are based on several tools (microfluidic, nanomaterials, transducers, bioreceptors). These tools could result in the system miniaturisation and in the improvement of the performance characteristics of the biosensors.

Highlights:

- Biosensors represent the future of screening methods for antibiotic residues.
- Optical biosensors despite of their cost are attractive screening tools.
- Inexpensive and sensitive electrochemical biosensors are very promising tools.
- Nanotechnologies result to portable and inexpensive systems for self-monitoring.