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Critical assessment of recent trends related to screening and confirmatory analytical methods for selected food contaminants and allergens

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ABSTRACT

Food contaminants monitoring is conducted in an intensive manner yet, there are still food safety scandals related to various chemical compounds. This fact highlights the need to review the requirements posed by the current legal framework on analytical methods performance and evaluate its application in published studies. Herein, we present an inventory including more than 470 publications on screening and confirmatory methods, which were used to control hazardous compounds such as pesticides, antibiotics, mycotoxins, aquatic toxins and allergens. Analytical performance characteristics, trends and state of the art, both merits and shortcomings, are critically discussed and summarized in excel tabulations. This repository highlights the ever-increasing use of screening methods and the necessity to confirm their performance by applying confirmatory methods. In conclusion, more effort is needed on validation and benchmarking, especially of newly developed technology such as smartphone-based methods, to avoid false-negative results and ensure that methods fit for purpose.

1. Introduction

Food safety is of critical societal importance. As a result, stakeholders with varying perspectives on food safety issues such as: producers, industry, regulatory bodies and consumers are concerned about the field. Unfortunately, the highly industrialized food production and the food market globalization we are facing today, makes tracing and monitoring food contaminants from farm-to-table a challenging task. Despite strict and pronounced legislation in the western world, food related scandals do still occur, highlighting the necessity of improved and innovative methods. For example, there have been several recent scandals such as fipronil insecticide in eggs (2017, EU) [1], various antibiotic classes in fattening poultry (2013, China) [2], aflatoxins outbreaks in dairy products (2013, Serbia) [3] and cereals (Somalia, 2015) [4], paralytic shellfish poisoning toxins (2012, Tasmania) [5] or undeclared food allergens in various products (2017, UK) (https://www.bbc.com/news/uk-england-46345097, last accessed 25/5/2019). On these occasions, consumer health and the food market financial sustainability were under threat. The exact economic loss cannot always be calculated precisely, e.g. the fipronil case resulted in an undefined countless economic loss [6]. However, the dairy farmers

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Abbreviations

AChE	acetylcholinesterase
ASPs	amnesic shellfish poisoning toxins
BfR	German federal institute for risk assessment
C18	octadecyl silica
DA	domoic acid
DNA	deoxyribonucleic acid
dSPE	dispersive solid phase extraction
DSPs	diarrheic shellfish poisoning toxins
EC	European Commission
EFSA	European food safety authority
ELISA	enzyme linked immunosorbent assay
ESI	electrospray ionization
FL	fluorescence detector
FWHM	full width at half maximum
GC	gas chromatography
GCB	graphitized carbon black
HILIC	hydrophilic interaction liquid chromatography
HRMS	high-resolution mass spectrometry
IMS	ion mobility spectrometry
LC	liquid chromatography
LFIA	lateral flow immunoassay
LLE	liquid-liquid extraction
LOAEL	lowest-observed adverse effect levels
LODs	limits of detection
LRMS	low-resolution mass spectrometry
ME	matrix effect
MIPs	molecularly imprinted polymers
MRLs	maximum residue limits
MRPL	minimum required performance level
MS	mass spectrometry
MS/MS	tandem mass spectrometry
OA	okadaic acid
OTG	on-the-go
PAL	precautionary allergen labelling
PSA	primary−secondary amine
PSPs	paralytic shellfish poisoning toxins
q-TOF	quadrupole-time of flight
QqQ	triple quadrupole
QuEChERS	quick, easy, cheap, effective, rugged and safe
QuPPe	quick polar pesticides method
RP	reversed phase
SERS	substrate enhanced Raman spectroscopy
SFC	supercritical fluid chromatography
SPE	solid phase extraction
SPR	surface plasmon resonance
SRM	selected reaction monitoring
STX	saxitoxin
TPP	triphenylphosphate
UV-Vis	ultraviolet-visible
VITAL	voluntary incidental trace allergen labelling
WHO	world health organization

in Serbia suffered a loss of more than 70 million euros [3] while the Tasmanian case resulted in a loss of 24 million dollars [5]. To provide an overview on the aforementioned food contaminants, their origin, occurrence in food matrices and potential health risks are discussed in the supplementary materials (Fig. S1 and Table S1). All in all, there is an urgent need not only for reliable and precise but also significantly cheaper, portable and faster analytical methods enabling screening followed by confirmatory analysis. In this way, social and financial effects due to contaminated foodstuffs consumption can be tackled easier.

A recent trend in food contaminant analysis is the ever-increased use of sensors as screening tests, which provides several advantages including reduced solvent consumption, simplicity, rapidness, *in-situ* detection and cost-effective analysis [7]. Sensor-based methods utilize (bio)-affinity elements such as antibodies, enzymes or aptamers to selectively interact with an analyte and this interaction can be monitored using typically optical or electrochemical detection systems. Despite their inherent advantages, there is evidence of cases in which screening methods could not achieve limits of detection (LODs)/limits of quantification (LOQs) below the regulated maximum residue limits (MRLs) in food matrices [8]. Another limitation of the reported sensor based studies is that the LODs are not always monitored in real food matrices and thus potential matrix effects (MEs) are not always considered [9]. Also, results from screening tests should be confirmed by a validated confirmatory instrumental analysis method, a practise that is not always followed [10]. This is a regulatory follow-up requirement (Decision 2002/657/EC) for unequivocal identification and quantification indicating that instrumental reference methods are essential to verify the presence of an analyte at the level of interest.

Confirmatory analysis for chemical contaminants generally includes the use of instrumental methods based on chromatographic separation and mass spectrometric detection of the analytes. Liquid or gas chromatography (LC or GC) using various separation systems can been applied, depending on analytes physicochemical properties [11]. Although chromatographic methods might be considered complicated, with long sample preparation protocols and high costs, they can detect hundreds of analytes in a single run and obtain LODs fairly below the regulatory requirements. This is of indisputable importance in food safety for determining whether a method is fit for purpose. Additionally, in contrast to sensors, instrumental methods should provide more accurate results. Considering confirmatory methods validation, it is usually performed in food matrices providing information on performance characteristics such as linearity, precision, trueness and LODs.

In this review, a critical overview of the EU legislation regarding the selected food contaminants is provided as the analytical methods must comply with regulatory requirements to ensure food safety. The European legal framework was thoroughly reviewed since it is uniformly applied in many countries as well as it may be considered one of the strictest globally. This legislation summary helps to identify the analytical challenges that both sensors and confirmatory methods face and also highlights legislative bottlenecks. To present the state of the art on pesticides, antibiotics, mycotoxins, aquatic toxins and allergen analysis, more than 470 studies from 2010 to 2019 were reviewed. The literature search was conducted using a specified algorithm and tabulations of key features of the reviewed methods such as sample preparation and analytical performance characteristics are provided (Fig. 1). Various analytical issues are discussed including sensor capabilities, the emergence of smartphones as analytical detectors and the executive role of confirmatory methods to guarantee the application of the legislation.

2. The EU legislation: an insight

The pivotal role of the EU within the globalized food market requires the establishment and application of strict legislation.

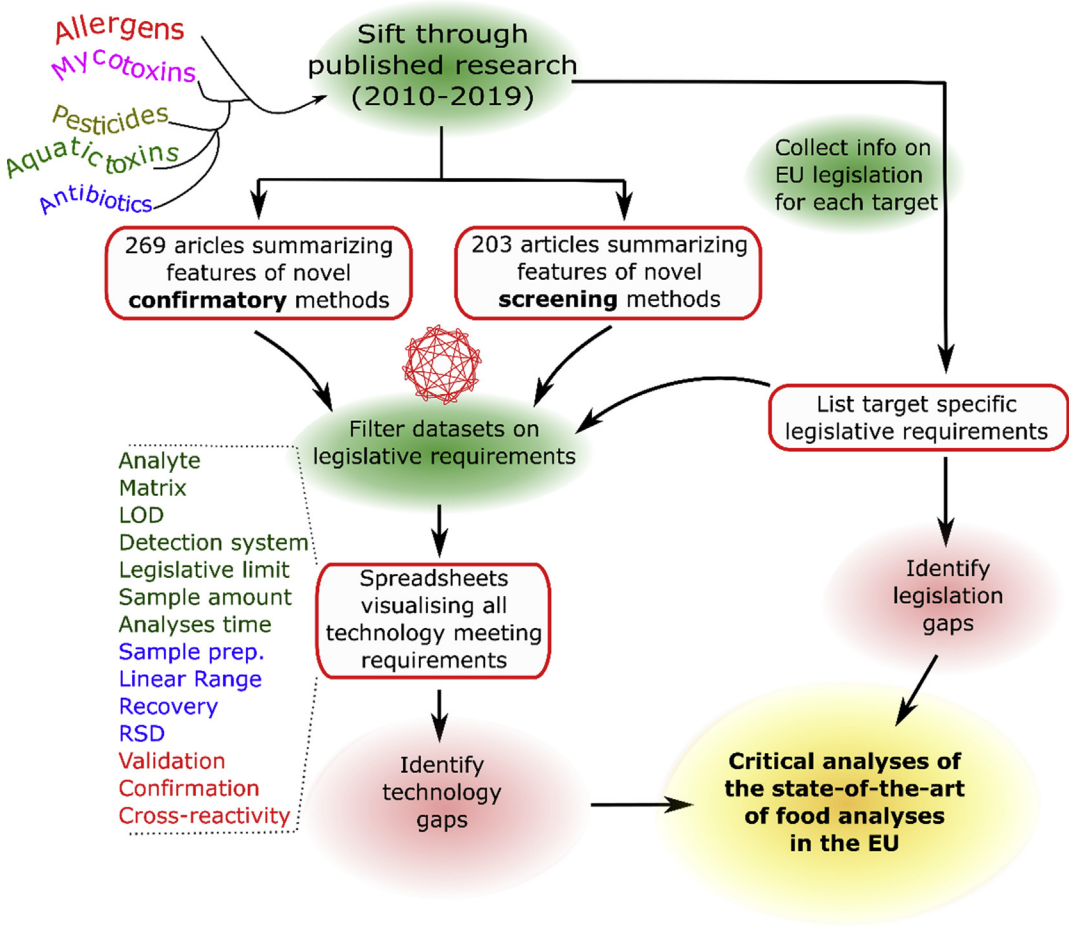

Fig. 1. Workflow utilized in this study: All rectangles represent datasets acquired and all clouds represent major tasks performed in this work. Analytical parameters reported for each method listed in the supplementary spreadsheets are given in colour code (green parameters for confirmatory and screening, blue parameters only for confirmatory, red parameters only for screening methods).

Despite the numerous European Commission (EC) Regulations and Decisions, they are still considered complicated, posing a major challenge to apply the regulated criteria in analytical methods. Herein, we address this intricate situation with the provision of a comprehensive summary emphasising the bottlenecks of the current EU legal framework.

Regarding pesticides, antibiotics, mycotoxins and aquatic toxins, there are different Regulations which include MRLs for numerous analytes in a great number of matrices (Table 1). However, an important difference can be noticed among the studied classes. Impressively, the EC Regulation 396/2005 has set MRLs for more than 1100 pesticides in 315 raw plant- and animal-based food and feed, providing an online database where the user can easily export the regulatory levels in an excel file (http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.selection&language=EN, last accessed 03/04/2019). In cases in which there is no MRL for a pesticide, a default 0.010 mg/kg limit is to be applied. This default MRL is also used for infant food according to Directive 2006/141. Similarly to pesticides, a strict legal framework is prescribed for mycotoxins. It is important to emphasize the EC Regulation 519/2014 which provided additional information on semi-quantitative screening methods validation. In the case of marine biotoxins, there are regulatory limits only for paralytic shellfish poisoning (PSP), diarrheic shellfish poisoning (DSP) and amnesic shellfish poisoning (ASP) toxins in shellfish according to Regulation 853/2004. In fact, the regulatory limits have been set for the most toxic analytes of each toxin group, e.g. saxitoxin (STX) for PSP toxins, okadaic acid (OA) for DSP toxins and domoic acid (DA) for ASP toxins. For the former two there are toxicity equivalent factors, derived from mouse bioassay toxicity data, to calculate the regulatory limit for other structurally similar toxins within those groups. Similarly, the yessotoxin and azaspiracid toxin groups are regulated with yessotoxin and azaspiracid-1 being designated for equivalent factors respectively. Despite this, these compounds have similar toxic effects in humans as the DSP toxin OA. In respect of antibiotic legislation, the EC defined MRL for permitted antibiotics setting in which matrices should be determined and found. These regulations, guidelines and performance criteria are under the framework of Directive 96/23/EC and 2002/657/EC. MRLs have been established for as beta-lactams, sulphonamides, fluoroquinolones or aminoglycosides in milk, meat or fish matrices. In case of prohibited antibiotics such as chloramphenicol, a minimum required performance level (MRPL) is defined. According to Decision 2002/657/EC MRPL is the *"minimum content of an analyte in a sample, which to be detected and confirmed. It is intended to harmonise the analytical performance of methods for substances for which no permitted limited has been established"*.

Another important, firmly regulated is food sampling as it assures that the analytical result is representative for the tested commodity. Clear definitions are provided to define critical points such as "analytical sample" or "laboratory sample" alongside practical instructions on how to obtain a representative sample.

Table 1
The EU legislative framework for pesticides, antibiotics, mycotoxins and aquatic toxins at a glance.

Key points	Food contaminants			
	Pesticides	Antibiotics	Mycotoxins	Aquatic Toxins
MRLs	Reg. 396/2005	Reg. 37/2010	Reg. 1881/2006	Reg. 853/2004
Sampling	Dir. 2002/63/EC	Dir. 96/23/EC	Reg. 401/2006	Reg. 854/2004
Validation	Decision 2002/657/EC			
Supplementary validation guidelines	SANTE/11813/2017	EURLs 20/1/2010	SANTE/12089/2016	Reg. 2074/2005

Noticeably, the regulations are amended frequently, highlighting the dynamic nature of EU food safety legislation. For example, the Regulation 519/2014 amended the sampling procedure (Regulation 401/2006) for some mycotoxins (T-2, HT-2 and citrinin) to clarify problems related with cereals sampling. Also, during 01/2019 there were five amending regulations adjusting some pesticides MRLs to keep in line with the latest toxicological data (http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN, last accessed 19/06/2019).

Undoubtedly, the legislation is directly linked to the analytical capabilities and the quality assurance of the provided results. Therefore, the Decision 2002/657/EC provides the general validation guidelines which are applicable to any type of analyte and classifies analytical methods to "screening" and "confirmatory" (see paragraph 3). In this context, there are several performance characteristics [12] such as detection capability (CCβ, the smallest content of the substance that may be detected, identified and/or quantified in a sample with an error probability of β), recovery and precision that must be included during the in-house validation and vary for screening and confirmatory methods and also their quantification capability. Validation is a critical procedure as it provides the necessary evidence that a method can perform within the legislative requirements. Nevertheless, a full method validation is a laborious and challenging task and therefore additional guidelines tailored to a specific group of analytes have been released by European Union Reference Laboratories (EURL) [13] and the Directorate-General for Health and Food Safety (DG SANTE) [14]. Additionally, there are specific guidelines for qualitative [15] and semi-quantitative screening methods (Regulation 519/2014) validation.

Although the EU legal framework has been, in general terms, well established, there are still many challenges towards achieving sustainable and safe food production. In this context, European Food Safety Authority (EFSA) acts proactively and provides scientific opinions that enable shaping the upcoming legislation by EC. In the case of pesticides, EFSA releases yearly reports, provides scientific opinions on controversial issues and also practical tools for the prediction of dietary pesticide intake [16]. Worthy to notice is the absence of EU MRLs for processed food which was faced by the German Federal Institute for Risk Assessment (BfR) by providing an online spreadsheet where the user can calculate processing factors applied to obtain the MRL for a processed food (https://www.bfr.bund.de/cm/349/bfr-compilation-of-processing-factors.xlsx, last accessed 08/04/2019). In the most recent EFSA report concerning antibiotics [17], honey was reported with the highest frequency of non-compliant samples for antibacterial substances despite this no MRLs have been established for this matrix. However, in the EU, veterinary medicinal products containing antibiotics are restricted in beekeeping which explains the absence of MRLs in honey since antibiotics use is totally prohibited (Regulation 37/2010). In terms of mycotoxin metabolites, these emerging contaminants are of public health concern, since they can transform into the free mycotoxin during digestion. The so called "conjugated mycotoxins" have been frequently detected in feed and food [18] and EFSA highlighted the need for more information related to metabolite structures, toxicity and methods able to detect them [19]. Regarding marine toxins, opinions on the risk related to tetrodotoxin, palytoxin, brevetoxin, cyclic imines and ciguatoxin consumption have been published (see supplementary materials). Nevertheless, EU Regulation for cyanotoxins in freshwater is less developed. For microcystin-LR (MC-LR), a provisional limit of 1 μg/L has been advised by the World Health Organization (WHO) [20]. This advice has been adopted by various countries including Brazil, Czech Republic, France, Spain, Uruguay and South Africa [21]. Importantly, there is no EU regulation in place and no advice is currently available by EFSA or the WHO due to lack of data.

Concerning allergens, the EC has legislated the 'allergen-labelling-directive' (Directive 2003/89/EC) which stipulates the requirement for the labelling of food products which intentionally contain 14 allergens (milk, eggs, peanuts, tree-nuts, fish, shellfish, soy, wheat celery, mustard, sesame, sulphur dioxide/sulphites, lupine and molluscs). The EU applies a zero-tolerance approach to this amendment, meaning that if a food manufacturer uses any of these ingredients in their product, regardless of the amount, it is mandated that it is explicitly stated on the packaging [22]. Therefore, any food containing one of the 14 legislated allergens, which does not contain a label, is in direct breach of this amendment and liable to legal action (Regulation 1169/2011). A further amendment came into effect in 2014 which specified the requirement for labelling of even non-packaged foods containing the 14 legislated allergens. Despite this regulatory framework safeguarding individuals from exposure to foods definitely containing the target allergens; the EU currently does not provide guidance for labelling of foods which may contain unintentionally incurred allergens through cross-contamination [23]. Many food manufacturers aim to prevent risk of allergic attack by including voluntary precautionary allergen labelling (PAL) statements on their packaging. These are most often 'May contain X' labels, but the language of the statements differs from product to product and from country to country, making PAL statements inconsistent and often confusing for consumers. The key issue with PAL statements is that they are not defined by clinically derived threshold levels and as a result their use is often more to protect the food manufacturer, rather than the consumer. By developing thresholds based on lowest-observed adverse effect levels (LOAEL) it will be possible to protect consumers by only applying PAL statements for foods containing allergens at/above these thresholds [24]. The Allergen Bureau of Australia and New Zealand is at the forefront of regulatory allergen labelling having already established the Voluntary Incidental Trace Allergen Labelling (VITAL) program [25] VITAL aims to limit the over-use of PALs by implementing a safety-assessment based approach focusing on using LOAELs to establish action levels for when a PAL statement should be triggered. VITAL levels protect 95% of the allergic population from severe reactions, by using LOAEL based reference doses, defined as milligrams of total protein from an allergenic food that only the most sensitive allergic individual would experience a negative reaction from Ref. [26]. Although VITAL is currently a voluntary program, and is only applied in Australia and New Zealand, more countries, including countries within the EU, are adopting this approach.

3. Critical literature search

Legislation drives the performance requirements that both screening and confirmatory methods have to achieve. It is important to find if these legislative requirements are reflected in the published literature and highlight trends and major gaps. To this end, a critical literature search was conducted on articles published between 2010 and 2019. An inventory regarding the detection of pesticides, antibiotics, mycotoxins, aquatic toxins and allergens in various food matrices was developed. This inventory is structured in excel file spreadsheets permitting at a glance comprising information about key features of a method such as performance characteristics (see supplementary materials). The inventory building was based on research papers found on the Scopus database using a general keyword structure consisting of three elements: (i) the analyte type, (ii) the detection method and (iii) the most common food matrices in each case. The exact keywords alongside with a further explanation of the search criteria are described in the supplementary material.

To begin with, more than 470 articles were reviewed providing a wealth of knowledge about the current status in food contaminants detection. Interestingly, the reviewed papers were scattered among 49 different countries indicating the importance of food contaminants detection globally (Fig. 2a). Almost the 70% of the published papers originated from 10 countries, with China publishing the most papers (24.2%) followed by the USA (10.2%) and Spain (9.6%). However, it is more important to focus on the per million capita publications rate, which is equal to the number of publications per country divided to their population in millions. Interestingly, the first 5 countries are European indicating their leading role in food safety field (Fig. 2b). On the contrary, the USA and China published fairly lower per million capita publications rate compared to the leading EU countries showing that they were less involved in the field. Finally, the developed repository offers the opportunity to extract useful information on sample preparation, screening and confirmatory methods which are presented in the following paragraphs.

3.1. Sample preparation

Undoubtedly, sample preparation is one of the most crucial steps to achieve low LODs and a selective analyte detection. Nevertheless, the diverse physicochemical properties of analytes, as well as differences in food matrices and chemical composition prove that sample preparation is rather a challenging task. Another important issue is the duration of a sample preparation protocol since highly affects the method throughput.

Regarding sensors, the sample preparation featured high-throughput as these methods aim to sift large numbers of samples for potential noncompliant results. Thus, simplified sample preparation protocols were developed including sample homogenization, incubation in a buffer (during this incubation some protocols heat or move the sample to increase extractability) and finally filtration to remove any solid particulate interfering matrix components. Buffers were selected to minimize the risk of denaturation of biomolecules, for example antibodies or enzymes, which are usually used as the recognition part in sensor-based methods. Worthy to notice is that numerous examples of commercial screening methods related to pesticides, mycotoxins and aquatic toxins have been recently published in Ref. [7] providing information about assays duration as well as their LODs. Another interesting example, related to allergen, is the Nima sensor which can alert if a food in a restaurant contains gluten in an amount over 20 ppm (in less than 3 min), susceptible to elicit an allergic reaction [27]. Nevertheless, there were cases where the convenience and simplicity of sample preparation for screening methods may also be considered as a bottleneck as matrix components co-isolation may affect the method detectability. Another problem was that recognition elements usually feature certain intolerance against organic solvents which are mostly used for analytes extraction or matrix removal. This is a significant advantage of instrumental methods as the detection is not based on (bio)-molecular interaction but on differences on physicochemical characteristics. In terms of allergens extraction, it is important to consider that different food processing procedures can affect the allergen content and extractability (e.g. baked, salted etc). On the other hand, the same changes induced by the processing or sample preparation will not represent an insurmountable problem for MS methods [28].

Focusing on confirmatory instrumental methods, liquid-liquid extraction (LLE) followed by purification based on a dispersive solid phase extraction (dSPE) are the most common analytical approaches. In detail, Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) extraction is mostly used for pesticides and mycotoxins detection but also for antibiotics and aquatic toxins. In QuEChERS, acetonitrile is used as the extractant as it can extract a wide range of polarities. In terms of sample preparation duration, QuEChERS is longer in comparison to simple protocols followed by the aforementioned screening methods. However, it has to be noted that even rapid screening methods were coupled to QuEChERS extraction indicating the high effectiveness of this method. In the case of highly polar pesticides such as glyphosate [29], the so called Quick Polar Pesticides Method (QuPPe) is used, which includes acidified methanol as the extractant followed by octadecyl silica (C18) dSPE or solid phase extraction (SPE) to eliminate any non-polar interfering compounds. It has to be underlined that the use of internal standards (IS) is of outmost importance to compensate errors during the long experimental protocols and retain high recovery rates, for example triphenylphosphate (TPP) is an IS widely used in pesticide residues analysis. Despite using isotopically labelled ISs is more effective due to the similar physicochemical properties to the analytes which enables MEs compensation [30], their high cost and limited commercial availability pose an obstacle to their widespread application in food contaminants analysis.

In contrast to low-molecular weight contaminants, allergens are proteinic macromolecules and thus different sample preparation is needed. Allergens are extracted using various buffers at slightly basic conditions, often containing SDS to denaturate proteins. The linear proteins are then reduced and alkylated to ensure absence of sulphur bridges and thus optimum enzymatic digestion into peptides [31]. Filter aided sample preparation (FASP) is often used to perform the reduction and alkylation steps followed by a clean-up of the sample removing all SDS prior to digestion and MS analyses [32]. The most commonly used enzyme for allergenic protein digestion is trypsin, an endopeptidase which cleaves peptide bonds in proteins at the *C*-terminal to lysine and arginine, generating peptides amenable to MS analysis [31]. Additionally, a combination of endoproteinase LysC and trypsin can be applied [33]. Pepsin is sometimes used for digesting peanut allergen, although it has been recognised that major peanut allergens Ara h 2 and 6 are resistant to pepsin digestion [34]. In some cases, however, other enzymes targeting other amino acids are preferable if the peptide digestion using trypsin renders sub-optimal peptide sizes. Finally, the peptide mixture is eluded in acidified acetonitrile. These universal sample preparation methods, used routinely in proteomics, can aid to obtain a robust confirmatory analyses method for allergen detection.

3.2. Screening methods

According to Commission Decision 2002/657/EC *"screening methods are used to detect the presence of a substance or class of*

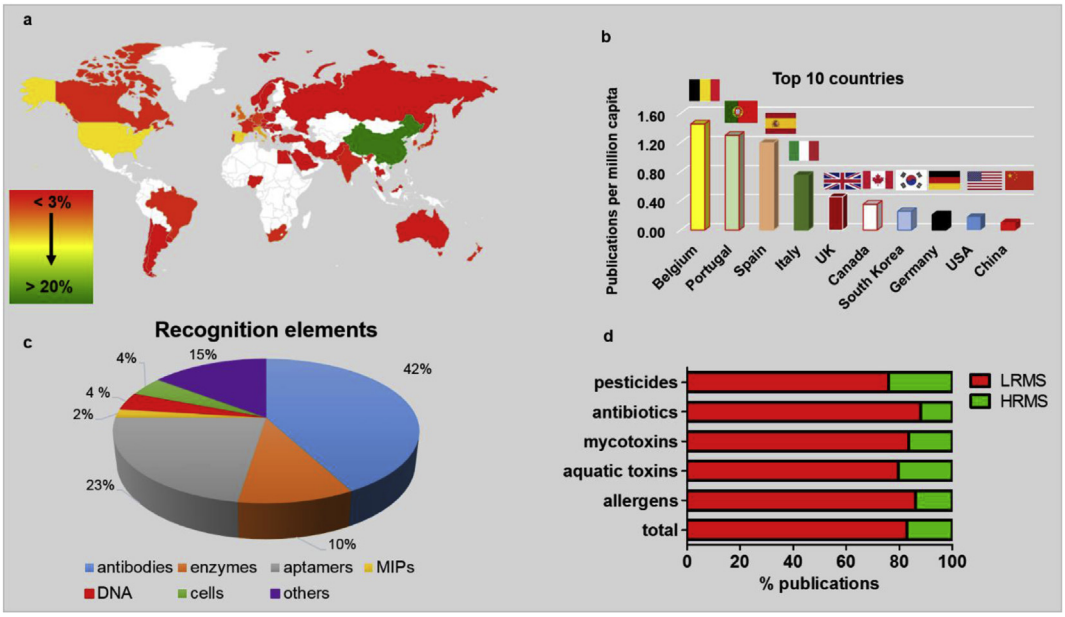

Fig. 2. a) The cumulative number of papers (n = 472) on both screening and confirmatory methods per country from 2010 to 2019. A red (<3% of the total) to green (>20% of the total) colour scale was used to depict the percentage increase of publications while no data were found for white regions. b) Food safety publications per million capita of the Top 10 countries. c) Clustering of the studied screening methods (n = 203) based on their recognition elements. d) An overview of the MS detectors used in the studied confirmatory methods (n = 269). Low resolution mass spectrometry (LRMS) corresponds to single quadrupole (q), triple quadrupole (QqQ) and ion trap (IT) analysers while high resolution mass spectrometry (HRMS) to time-of-flight (TOF), Q-TOF, orbitrap and Q-orbitrap analysers.

substances at the level of interest". This can be achieved by selective recognition elements that bind with an analyte and their interaction is detected by either optical, electrochemical or mechanical transducers. Obviously, recognition elements are of upmost importance for a selective and robust screening method. It was found that more than 40% of the studied articles on sensors used antibodies as the recognition element (Fig. 2c). Immuno-recognition screening methods, including enzyme linked immunosorbent assay (ELISA) and lateral flow immunoassay (LFIA) have found wide application in food safety. ELISA is based on the specific interaction between an enzyme labelled analyte specific antibody and its antigen. Owing to the labelling of the antibody with an enzyme, upon the addition of a substrate a measurable colour change is initiated. It has to be noted that as allergens are high molecular proteins, their detection is based on sandwich format assays. Therefore, in a sandwich ELISA the measured response is directly proportional to the amount of allergen present within the sample. Although immuno-recognition tests are facile, they have a limited scope in terms of the analytes and matrices. An ever-increasing application of aptasensors was noticed (23% of the studies). Aptamers are short single-stranded, synthetic oligonucleotides that can fold in characteristic shapes capable of binding with high specificity to target molecules [35]. Nevertheless, stability of aptamers in food matrices is still under investigation. Enzymes were found in the third place (10% of the studies), with acetylcholinesterase (AChE) and laccase being extensively used as bioreceptors. Nevertheless, enzymes commonly show problems related to instability (affected by pH, temperature, solvent), risk of denaturation and non-specific recognition due to matrix components. In contrast to the rest recognition elements, DNA-probes, cells and molecularly imprinted polymers (MIPs) were less well used while quite a diverse group of screening methods was noticed (15% of the publications). In this group, label-free sensing was applied resulting in direct analyte detection without a recognition element use. Striking examples of that are direct analysis in real time mass spectrometry (DART-MS) and substrate enhanced Raman spectroscopy (SERS), which both do not require any sample preparation. Overall, Table 2 presents a summary of screening methods characteristics and performance whilst an additional great number of reviewed papers can be found in the supplementary material in excel spreadsheet formats.

Worthy to notice is that smartphones have emerged as an attractive analytical platform enabling a new era in food testing in which individuals without any expertise may be able to test their food. Although a smartphone is not able to detect any food contaminant without using auxiliary parts, it features multiple useful characteristics such as an independent power source, computing power, camera with a flash-light (in other words an optical system with a constant light source), online web access and wireless data communication. Considering that smartphones number in the market is greater than the human population (https://www.independent.co.uk/life-style/gadgets-and-tech/news/there-are-officially-more-mobile-devices-than-people-in-the-world-9780518.html, last accessed 18/06/2019), smartphone-based analytical methods have the potential to revolutionize food testing. Despite developing various smartphone-based methods [36], it was common to transform a smartphone to a lab device. In fact, the real challenge is to retain a fully functional smartphone and couple it to a bio-affinity test. In this context, portable assays such as LFIA and dipsticks have a great potential as they can be applied *in-situ* and the test result can be detected using an optical smartphone read-out. Moreover, paper-based methods can be combined to a smartphone read out. Paper is an attractive material for the development of on-site screening sensors as it combines cost-effectiveness, simplicity, is available even in remote regions and biomolecules can be adsorbed/immobilized on it. A successful example of combining an AChE paper sensor with smartphone-based detection was published by C. Sicard et al. [37], where malathion and paraoxon (organophosphate pesticides) were detected in water samples and the results were evaluated by a smartphone application. This is a very promising approach, but certain drawbacks related to sample preparation, especially in the case of complex food matrices, and sensitivity have to be considered.

Table 2
Examples of pesticide and antibiotic residues, mycotoxins, aquatic toxins and allergens detection in various food matrices using novel screening methods. More publications can be found in the supplementary material in excel spreadsheet form.

Group	analyte	matrix	recognition	detection principle	LOQ	EU legislative limit	validation in food matrix	Instrumental confirmatory method	Ref
Pesticides	paraquat	potato	immunosensor	EC	0.003 mg/kg	0.02 mg/kg	yes	LC-MS	[38]
	acetamiprid	vegetables	aptasensor	fluorescence	0.006 mg/kg	<3 mg/kg, depending the matrix	yes	LC-MS	[39]
	azinphos-methyl and carbaryl	apple	label free	SERS	15 mg/kg	in mg/kg: 0.05 for azinphos methyl, 0.01 for carbaryl	yes	no	[40]
	parathion	cabbage washing solutions	AChE	SPR	in mg/L: 0.003 (aquatic sol), 15 (paper strip)	0.05 mg/L	yes	LC-MS	[41]
Antibiotics	Tetracycline	honey	aptasensor	colorimetric	0.3 μg/kg	n.a	yes	no, comparison to ELISA	[42]
	Tylosin, tetracycline, gentamicin, streptomycin, and chloramphenicol	milk	multiplex immunosensor	optical	in mg/L: 0.001 tylosin, 0.005 tetracycline, 0.012 gentamicin, 0.060 streptomycin, and 0.075 chloramphenicol	in mg/L: 0.05 tylosin, 0.1 tetracycline, 0.1 gentamicin, 0.2 streptomycin, and 0.0003 chloramphenicol	yes	no	[43]
	Sarafloxacin, desfuroylceftiofur cysteine disulfide, thiamphenicol, streptomycin, tilmicosin, doxycycline;	honey	immunosensor	chemiluminescence	in mg/kg: 0.45 sarafloxacin, 0.03 desfuroylceftiofur cysteine disulphide, 0.018 thiamphenicol, 0.09 streptomycin, 0.03 tilmicosin, 0.09 doxycycline	n.a	yes	LC-MS	[44]
	Ampicillin	milk	inkjet printed aptasensor	EC	0.03 mg/L	0.004 mg/L	yes	no	[45]
Mycotoxins	fumonisin B1 + fumonisin B2	maize	LFIA	chemiluminescence	7.5 μg/L	40 μg/kg	yes	LC-MS	[46]
	patulin	solution	immunosensor	SPR	0.045 ng/mL	n.a	n.a	n.a	[47]
	T-2 toxin	corn, rice, soybean	MIPs	EC	0.45 ng/g	n.a	yes	no	[48]
	aflatoxin-B1	peanut, maize, wheat, pearl rice, aromatic rice and red rice	aptasensor	visual	0.06 ng/mL	n.a	yes	no	[49]
Aquatic toxins	Azaspiracids (several)	shellfish	ELISA	optical	33 μg/kg	160 μg AZA-eq/kg shellfish meat	no	LC-MS	[50]
	MC-LR	freshwater and drinking water	LFIA	optical	<3 μg/L	1 μg/L	no	no, comparison to ELISA	[51]
	tetrodotoxin	Pufferfish extract	immunosensor	Planar waveguide	1200 μg/kg fish	44 μg tetrodotoxin eq./kg fish	yes	LC-MS	[52]
	STX	freshwater and shellfish	anti-STX incorporated lipid films on graphene nanosheets	EC	0.9 μg/L (in buffer)	800 μg STX eq/kg shellfish meat	yes	no, comparison to ELISA	[53]
Allergens[a]	Ovalbumin (egg)	Wines	antibody	SPR	0.09–0.6 mg/L	0.75 mg/kg	yes	LC-MS	[54]
	Ara h 6 (peanut)	Cookies & chocolate	sandwich ELISA	EC	0.81 ng/mL	5 mg/kg	yes	n.a	[55]
	Gluten (wheat) & Ara h 1	Biscuits, flour, chocolate and peanut butter	microfluidic ELISA	optical	Gluten: 14 ng/mL, Ara h 1: 45 ng/mL	gluten:20 mg/kg, peanut: 5 mg/kg	yes	n.a, comparison to commercial ELISA	[56]
	B-conglutin (lupin)	Cereal products	lateral flow aptasensor	optical	24 fM	n.a	no	n.a	[57]

[a] Threshold which can trigger a voluntary precautionary allergen statement (mg/Kg) based on VITAL (mg/kg = total allergenic food/total food).

3.3. Confirmatory methods

Recent technological advances have permitted the wide application of powerful instrumental methods for the detection of food contaminants. According to Commission Decision 2002/657/EC:

> "*Confirmatory methods for organic residues or contaminants shall provide information on the chemical structure of the analyte. Consequently, methods based only on chromatographic analysis without the use of spectrometric detection are not suitable on their own for use as confirmatory methods*".

In other words, chromatographic separation is not enough to confirm a screening result (compliance of the analyte retention time with a standard) and confirmatory methods require a mass spectrometric detector. However, conventional detectors such as fluorescence (FL) or ultraviolet-visible (UV-Vis) detectors may also be used, under certain conditions, for confirmation; for example in the case of FL detector "*only for molecules that exhibit native fluorescence and to molecules that exhibit fluorescence after either transformation or derivatisation*". Thus, even laboratories without high-end instrumentation are able to confirm the performance of screening methods for certain analytes. A summary on the reviewed confirmatory methods, including analytical performance characteristics and sample preparation is provided in Table 3.

Liquid chromatography tandem mass spectrometry (LC-MS/MS) and gas chromatography tandem mass spectrometry (GC-MS/MS) were commonly used enabling wide linear ranges and LODs down to the μg kg^{-1} level or even less. The extended use of this instrumentation reflects also the decrease of its market price enabling more laboratories to use it. In detail, EURL developed a LC-MS/MS method for lipophilic marine biotoxins (okadaic acid, dinophysistoxin, pectenotoxin, azaspiracid toxin and yessotoxins and their analogues) in molluscs [58]. The method uses MeOH extraction (2×) and centrifugation followed by 0.45 μm or 0.2 μm syringe filtration. It showed recovery rates between 70 and 140% and interlaboratory reproducibility with a relative standard deviation (RSD) of <30% depending on the toxin. In the case of veterinary drug residues, Dasenaki et al. [59] developed and validated an LC-MS/MS method for 115 residues in milk powder, butter, fish tissue and egg matrices. The method included a solid−liquid extraction step with 0.1% formic acid in aqueous solution of EDTA 0.1% (w/v)−acetonitrile −methanol (1:1:1, v/v) with additional ultrasonic-assisted extraction. Also, this study illustrates the laborious and time-consuming sample preparation that is needed to remove lipids (crude extracts were frozen for 12 h at −23°C followed by hexane clean-up for fat removal). Worthy to notice is also a GC-MS/MS study, where 203 pesticide residues were detected in less than 13 min in fruit and vegetable samples showing high throughput [60]. The method was fully validated and obtained an LOQ of 2 μg kg^{-1}. GC-MS/MS has been used also as an alternative in mycotoxins analysis as it requires analytes derivatisation after their extraction from food matrices. For example, A.F Mahmoud et al. developed and validated a GC-MS/MS method for trichothecenes detection in chicken liver achieving good performance characteristics [61]. In conclusion, although long sample preparation protocols were commonly used, the performance of chromatographic systems coupled to QqQ detector was great providing results for hundreds of analytes per run. Importantly, the reader can find more reviewed methods in our inventory.

ME is also an issue of paramount importance both in LC- and GC-based methods. In the LC case, co-extracted matrix compounds are also ionized by electrospray ionization (ESI) source [62] resulting in ion suppression (decreased ion formation) or ion enhancement (increased ion formation). ME do occur also in GC-based methods, however, they have a totally different nature. Further information on ME of chromatographic methods can be found in Ref. [63]. Another significant finding was that only the 7% of the studied papers related to aquatic toxins detection reported the use of matrix matched calibration curves for analyte quantification. Matrix matched calibration curves are of indispensable importance to accurately detect analytes in a food matrix as ME are compensated. Recently, nanoflow LC-HRMS (nano-LC-HRMS) has been proposed as an alternative in order to reduce ME problems [64]. In this approach, nano-C18 column is used, resulting in reduced dead volumes and increased ionization efficiency. The impressively low LODs (ng kg^{-1} level) obtained, made high dilution factors feasible, thus minimizing the MEs. Finally, another promising alternative to reduce ME is ion mobility spectrometry (IMS) which can be integrated to LC and GC systems providing improved selectivity, lower LODs and additional information to mass spectra and retention time due to an additional electrophoretic separation [65].

Regardless of the separation mechanism, targeted approaches are the common analytical choice for food contaminant detection. In fact, more than the 80% of the reviewed studies applied LRMS methods (Fig. 2d). In this case, a specified list of analytes is investigated using a QqQ detector operating in a selected reaction monitoring mode (SRM). However, an increased number of analytes means that more necessary ion transitions have to be recorded which is a common case in multi-residue analysis where more than 300 compounds may be included in a single method. In addition, according to the latest SANTE guidelines [66], at least two product ions are necessary for a compound identification while the ion ratio from sample extracts should be within ±30% of calibration standards from the same sequence. Therefore, this requirement highlights a major drawback of SRM mode as the more analytes that are included in the method, the more necessary ion transitions there are that have to be measured. So, there is an increased chance of common or overlapped transitions affecting the method LODs [67]. To counter this problem, HRMS targeted methods have been proposed as an alternative. In this concept, time-of-flight (TOF), orbitrap and hybrid mass analysers such as Q-TOF and Q-orbitrap are used as mass detectors providing accurate mass measurement (<5 ppm), high resolution (more than 20 000 full width at half maximum (FWHM)), structural elucidation and full MS scan capabilities (usually for the range 100−1000 Da). Although HRMS detectors resolve SRM-related problems, there is still controversy on their quantification capabilities and narrower linearity range compared to QqQ. Comparison of QqQ with QTOF confirmed in the most cases the assumption of lower LODs when using QqQ [68]. On the other hand, another study showed that better HRMS selectivity and LODs can be achieved with a resolution of 50000 FWHM [69]. Identification requirements have been also addressed for HRMS, where it is necessary to monitor two ions with mass accuracy of less than 5 ppm; the analyte peaks from precursor and/or product ion(s) in the extracted ion chromatograms must fully overlap [66]. Finally, it is important to clarify that chromatographic methods coupled to HRMS may also be used for food contaminants screening due to their high throughput and excellent selectivity (see paragraph 4.3.2). In this case, chromatographic methods are validated following the performance criteria of screening methods (a false compliant rate of <5% at the level of interest).

4. Emerging analytical trends and issues

The developed inventory provided extensive information about sample preparation approaches and the analytical performance of screening and confirmatory methods for food contaminant detection. In addition to these fruitful data, it is of paramount importance to distinguish novel emerging trends. Therefore, the following

Table 3
A selection of interesting publications regarding residues of pesticides and antibiotics, mycotoxins, aquatic toxins and allergens detection in various food matrices using confirmatory methods. More publications can be found in the supplementary material in excel spreadsheet form.

Group	analytes	matrix	sample preparation	analytical performance characteristics				instrumental reference method	ref
				linear range	R %	RSD %	LOQ (mg/kg)		
Pesticides	64 residues	tomato, baby food, jam, orange, olive oil	unbuffered QuEChERS and AOAC 2007.01 (for fatty matrices)	0.002−200 μg/kg	n.a	<10	<0.00003 (at least 100 times lower than MRLs)	nanflow LC-Q Exactive Orbitrap MS	[64]
	7 residues	olive oil and olives	QuEPPe (MeOH as the extractant)	1−1000 μg/kg (olive), 10 −10 000 μg/kg (olive oil)	60−120	<15	<0.015	HILIC-MS/MS	[68]
	1396 residues	lettuce and pear	QuEChERS (AOAC 2007.01)	untargeted screening				LC-TOF MS, LC-MS/MS	[70]
	243 residues	cardamom	ethyl acetate, MeOH, QuEChERS, modified QuEChERS	0.002−0.05 μg/kg	70−120	<20	<0.03	GC-MS/MS	[71]
Antibiotics	7 macrolids	milk	QuECHERS + sodium sulfate, sodium chloride, and potassium carbonate	0.78−18.75 ng/mL	74−104	<12	0.003	LC-MS/MS	[72]
	164 residues	chicken, porcine and bovine meat	QuEChERS extraction followed by SPE or dSPE	n.a	70−120	<30	ranging at ng/kg level	LC-Orbit trap MS	[73]
	88 residues	milk	ultrasonic extraction, centrifugation and Turboflow online SPE	1-200μg/kg	63.1−117.4	<18	0.0006−0.006	LC-MS/MS	[74]
	12 penicillins	bovine, porcine and chicken muscle	SPE (Bond Elut C18, ENV + Isolute, Oasis HLB, Oasis MAX)	0.5−200μg/kg	50−101	<12	0.0003−0.0075	LC-MS/MS	[75]
Mycotoxins	patulin	fruits and fruit products	QuEChERS + SPE	n.a	92−109%.	<10%	0.001−0.0025	UHPLC-MS/MS	[76]
	8 mycotoxins	maize and rice	MeOH/H2O/CHCl3/NaCl + ultrasound-assisted	n.a	93.8−109%	<9.8%	0.00003−0.003	LC-MS/MS	[77]
	Fusarium masked mycotoxins	wheat and oats	ACN + Mycosep column	untargeted screening				LC−Orbitrap MS	[79]
	58 compounds	dairy products	QuEChERS + dSPE	0.001−100 μg/kg	86.6−113.7%	<6.2%	0.00003−0.003	UHPLC/ESI Q-Orbitrap	[78]
Aquatic toxins	tetrodotoxin and analogues	Puffer fish	acetic acid additioned ethanol-water (7:3) extraction, active charcoal cleanup, filtration.	na	70	na	depending analogμe	HILIC-MS	[80]
	14 DSP analogues	mussels	QuEChERS + C18 clean-up	25−350 μg/kg	75−102	<20	0.075	UPLC = Orbitrap MS	[81]
	11 DSPs	shellfish	75% MeOH extraction, turbulent flow chromatography	2.5−200 μg/kg	80−114	<15	0.0005−0.004	LC-MS/MS	[82]
	Microcystins	freshwater and algae extracts	MeOH extraction	untargeted screening				LC-Orbitrap	[83]
Allergens	12 allergens	Cookies	Protein extraction: ammonium bicarbonate + SDS (pH 8.2). Precipitation: methanol/chloroform. Enzymatic digestion: DTT-IAA-Trypsin-Stopped with acid	1−150 mg/kg	20−26	<20	4	LC-MS/MS	[84]
	5 allergens	Milk	Deffated Protein extraction: urea, Trizma base and OGS. Enzymatic digestion: DTT-IAA-Trypsin-Stopped with acid	10−1000	60−119	<20	30	LC-MS/MS	[85]
	Mustard allergen Sin a 1	7 sauces	Protein extraction: ammonium bicarbonate (pH 8.0), lyphilized and resuspended in PBS Enzymatic digestion: DTT-IAA-Trypsin-Stopped with acid	0-8 ug	/	<14	0.75	LC-MS/MS	[86]
	4 allergens	4 matrices	Protein Extraction: Tris-HCl (pH 9.2) with 2 M urea. Enzymatic digestion: DTT-IAA-Trypsin-Stopped with acid	Milk: 0.1−20 mg/kg tree nut/ peanut: 0.5−100 mg/kg egg: 1 −200 mg/kg	/	<45	Milk: 1.5 mg/kg Peanut, hazelnut, pistachio and cashew: 7.5 mg/kg Egg: 6 mg/kg Soy, almond, walnut and pecan: 15 mg/kg	UHPLC-MS/MS	[87]

paragraphs are devoted to emerging trends and issues regarding sample preparation, screening and confirmatory methods.

4.1. Sample preparation

4.1.1. Increased use of d-SPE clean-up

Matrix clean-up is a decisive step during sample preparation permitting selective analyte detection. Traditionally, SPE clean-up has been used for both analyte pre-concentration as well as sufficient elimination of matrix compounds. However, SPE is only suitable for compounds with similar physicochemical properties, and so is not applicable when using multi-residue methods. Additionally, it requires multiple steps (column conditioning, washing, analytes elution) which increases the analysis time. Consequently, dSPE emerged as an alternative, offering analytical convenience, simplicity and matrix elimination. In dSPE, a sorbent is directly added into the analytical solution followed by dispersion favouring the contact between the sorbent and analytes/matrix components [88]. When the dispersion process is completed, the sorbent is separated by a mechanical process, for example filtration or centrifugation. Although primary–secondary amine (PSA) was commonly used as a sorbent to remove co-extracted matrix components such as organic acids (for example in QuEChERS extraction), there was also a great variety of sorbents e.g. C18 (functions as a reverse-phase system), graphitized carbon black (GCB) (eliminates chlorophyll, carotenoids), zirconia-based (removes fats, waxes) that can be applied independently or in combination. In any case, potential losses of target analytes should be controlled when using dSPE sorbents (quantitative recoveries of the targeted analytes) and ISs and matrix matched calibration curves have to be used to retain high recovery rates. Alternatively, magnetic SPE (MSPE) utilized nanocomposite sorbents which adsorbed matrix compounds due to their large specific surface areas (diameter of 8–25 nm) [89]. MSPE is drawing more and more attention and a recently published review is highly recommended for a deeper understanding of this promising approach [90]. Recently, turbulent flow extraction was used for DSP toxins [82] and antibiotics [74] detection in shellfish and milk, providing simultaneous size exclusion and chromatographic adsorption. This approach can be useful for samples containing low molecular weight analytes and interferences with high molecular weight.

4.2. Screening methods

4.2.1. Problems in validation and benchmarking

The review of more than 200 articles for the five studied groups provided insight on screening methods validation and benchmarking towards confirmatory instrumental methods. Firstly, there were cases that LODs were calculated in buffers and then recovery studies were performed in matrices at a higher concentration level [53,91]. The assumption that the MEs are not strong enough has to be proven experimentally. On the other hand, some sensors have achieved LODs about 2 orders of magnitude lower than the MRL [92]. Another significant finding was the absence of confirmatory analysis using instrumental methods to verify the suspected results obtained by screening methods (see Table 2 and supplementary materials). Benchmarking towards instrumental methods is a regulatory follow-up requirement for analytes unequivocal identification and quantification. However, there were studies that compared their results to well-established screening methods such as commercial ELISA tests. This can be considered as a step in the right direction as a screening method has always a false compliance rate (the regulatory requirement is a false compliant rate of <5% at the level of interest). Important to notice is the lack of certified reference materials (especially in the case of allergens [93]) as well as the organization of interlaboratory studies applying sensor-based methods, probably due to high cost. A striking example of interlaboratory study among 7 laboratories using an SPR sensor for PSP toxins detection was published by H.J Van den Top et al. [94] presenting how an optical sensor can provide reliable and robust results (Horwitz Ratio<1) among laboratories.

Smartphones have emerged as novel analytical platforms that have the potential to radically change food testing. With respect to the degree of quantification, smartphone-based methods can be classified as (i) qualitative, just providing a binary (yes/no) response above or below a cut-off level and/or as (ii) semi-quantitative, including a numerical readout and a calibration curve provided by a smartphone. The result of such a screening method is either "negative" (sample is compliant versus a regulatory limit) or "suspect" (sample must be sent to a lab for confirmatory analysis providing unambiguous identification and quantification). The most important performance characteristic for such a screening method is the false compliance rate or β error which must be (equal or) lower than 5%. In any case, smartphone-based methods have to be developed as any other screening test and thus their validation is of indispensable importance. The minimum validation requirements, as these are reflected in the EU regulation and EU reference laboratories (see "2. The EU legislation: an insight"), must be met to move out of the proof of concept realm. Additionally, benchmarking against a well-established screening test, as well as a confirming positive screening results by an instrumental methods is fundamental to proving that these novel methods are operating at an acceptable analytical level as well as being affordable.

4.2.2. Optical and electrochemical detection in a smartphone

Smartphone-based biosensing is an emerging trend requiring further investigation especially in terms of signal processing. Smartphones have been used to record colour changes or fluctuations of a colour intensity, making them fantastic optical biosensors. Photographs or videos can be exploited to record a colorimetric response related to biomolecular interactions, for instance an enzyme that catalyses a substrate and produces a coloured product. Smartphone flashlight and the screen are commonly available light sources and smartphone built-in cameras are widely supported image sensors on a smartphone. Spectral composition, intensity, and polarisation of light are the three elements that optical biosensors aim to quantify [95]. After passing through the Bayer filter arrays and being measured by complementary metal-oxide-semiconductor transistor (CMOS) on a smartphone camera, light in the visible range, will be transferred into red-green-blue (RGB) colour space. Despite there being studies that analyse colour in the RGB colour space directly [96], it is more common to transfer the colour from the device-oriented RGB colour space to human perceptual colour spaces such as CIE XYZ, LUV, and LAB interpreting one or more colour channels. There were also cases exploiting spatial information of the final image to achieve novel applications such as barcode recognition [97].

In contrast to optical smartphone-based detection, which can be limited by the resolution and focus of the smartphone camera as well as by ambient lighting conditions [98], electrochemical detection has the advantage of being mostly independent of the smartphone's capabilities. In relation to an electrochemical measurement, a smartphone can offer power, two-way data transmission, stimulus generation and signal quantification. Additionally, there are three different ways to integrate a peripheral module to a smartphone: i) internally installed as a hardware, ii) wired and iii) wireless. The case of internal integration [99] is not convenient because different interfaces are not compatible across different smartphones while the electrochemical module integration must be allowed by the smartphone manufacturer. In the case

of wired interfaces, the USB 2.0 interfaces, where a master-slave protocol is used, have been commonly used. In this case the mobile must have the USB On-The-Go (OTG) protocol built into it and enabled by the firmware. This module allows switching between master or slave depending on what is connected at its USB port, but still it is not available in all the smartphones, limiting compatibility. It has to be underlined that the available power from these interfaces is more than enough for electrochemical measurements [100]. In terms of wireless connection, Bluetooth is compatible with all types of smartphones [101]. Commercial potentiostats have also embraced Bluetooth technology as a universal method to connect to a smartphone for portable use. In this way, platforms that use Bluetooth are similar to standalone biosensors and only exploit smartphones as a readout tool. Finally, it should be noticed that currently the only advance smartphone technology brings for electrochemical-based detection is data treatment, since electrochemical signal generation and detection is done with a potentiostat and there has been, to the best of our knowledge, little to no effort to create a potentiostat using a smartphone. However, PalmSens developed a miniaturized potentiostat (called EmStat) in a USB-dongle, which is already commercially available. This being said, automated data treatment using a smartphone interface to create a user friendly device is an equally important development towards the development of point of harvest electrochemical sensors with commercial potential.

4.3. Confirmatory methods

4.3.1. Alternative LC separation mechanisms

Considering LC applications, there is an upcoming trend of using different separation mechanisms instead of the classical reversed phase (RP) systems for the separation of polar analytes. Although C18 or octyl (C8) columns can efficiently separate non-polar compounds, polar analytes separation can be a rather challenging task. Therefore, hydrophilic interaction liquid chromatography (HILIC) and supercritical fluid chromatography (SFC) have been proposed as alternatives. In HILIC a polar stationary phase retains polar analytes that are eluted by a mobile phase consisting of a mixture of acetonitrile (usually) and water, and thus this is the opposite mechanism of RP [102]. In fact, the complementary nature of HILIC and RP mechanisms was successfully exploited using the two separations in parallel within the same system for the simultaneous detection of both polar and non-polar marine toxins [103]. Regarding SFC, it is capable to separate compounds with a wide range of polarities e.g. $-4.6 < \log Pow < 7.05$ [104] within the same run. In SFC, carbon dioxide is used as the mobile phase featuring several advantages, but most interestingly the adjustable elution power due to carbon dioxide miscibility with more polar modifiers such as methanol and ethanol highlighting the versatility of this approach [105]. Nevertheless, it should be noted that SFC is rarely used for routine control.

4.3.2. Non-targeted screening of food contaminants using HRMS

HRMS capabilities have been also utilized for qualitative screening using in-house accurate mass databases and MS^2 spectral libraries. To obtain these data, both QTOF [106] and Q-orbitrap [107] methods have been developed. In these non-targeted approaches, the MS/MS data is collected using data-dependent acquisition (DDA) or data-independent acquisition (DIA) approaches. According to a recent review from our group, "in DDA, a limited number of ions with the highest abundance detected in the full MS scan are isolated and fragmented in a product ion scan experiment" while "DIA involves sequential isolation of windows across a mass range for MS/MS …" and "… allows the use of fragment ions for quantification" [11]. The robustness of this concept was reflected in an inter-laboratory study for 250 pesticides in spinach, carrot and orange matrices, in which semi-automated data handling was achieved using the ToxID software [108]. Similarly, an accurate mass database was constructed including around 1400 compounds and this was compared with a common LC-MS/MS method [70]. This LC-TOFMS method was able to detect about 80% (105 out of 130 pesticides) of the compounds detected with the LC-MS/MS and additionally another 34 "unknown" compounds were detected.

4.3.3. Allergens MS-based detection

Allergens MS-based detection remains a challenging process owing to the need to know the protein sequences of the proteins in the matrix and the need to quantify target peptides unique to the allergen [109]. Moreover, the use of stable isotope internal standards using (for example) C^{13} modified proteins can be rather expensive for routine analyses [110]. However, even for this bottleneck some options exist such as parallel reaction monitoring (PRM) [111]. This method correlates ion counts of peptides with a known concentration (for example trypsin peptides) to marker peptide ion counts to obtain the absolute concentration. Such methods are attractive since the driving force behind the development of MS methods for food allergen detection the ability to multiplex regulated allergens. However, the cost of the instrument and the need for further development of the method for food allergens currently prevent MS from overtaking the well-established immunochemical/DNA methods of detection.

5. Conclusions

Overall, a critical review reflecting the intense research performed in the contaminant detection field in the past decade is presented. Our study provides insight on the EU legal framework and the current status for screening and instrumental methods. Despite these in depth legislative directives, there are still many challenges to face. This fact also underlines the constant need for revaluation of the available regulations in line with recent advances in methods development. EFSA has a pivotal role in undertaking risk assessment and providing opinion which will shape the upcoming legal framework. The application of the legal requirements is partially reflected in the reviewed methods, showing that there is still space for improvement.

Although screening methods were more frequently applied, usually insufficient method validation and the absence of benchmarking towards instrumental methods was noticed. It is also important to notice the emergence of smartphone-based methods for the detection of food contaminants. Smartphones can revolutionize the current food testing concept, by engaging farmers or consumers in their own food safety analysis. This will be feasible only when using a simple sample preparation protocol in addition to result evaluation by a smartphone application. In this context, the users will need only to follow some simple instructions and receive a fast answer directly to their phone. Additionally, the smartphone online connectivity may be used as a quality assurance feature. Thus, in case of a contaminated sample the user will notify an expert group which will be responsible for confirmatory analysis.

Regarding instrumental methods, chromatographic separation coupled to various MS detectors remained the strongest weapon to detect contaminants in food matrices. Considering the decreasing cost of such instrumentation confirmatory analysis plays a key role in food chain sustainability. However, the long and complicated sample preparation remains a challenge that has to be faced in the future. Also, increasing focus on green chemistry, e.g. replacing of acetonitrile as solvent in LC based separations, is considered a

major challenge. In fact, the use of SFC-based separations can be a step towards this direction since carbon dioxide is used as the mobile phase and only low amount of modifiers are used resulting in reduced solvent consumption. In respect of detection tools, there is a trend towards both targeted and untargeted HRMS methods which can detect a much wider range of compounds. All in all, more effort has to be paid on the development of screening methods either aimed to reduce the number of samples being analysed by instrumental methods or the use of non-destructive methods of analysis enhanced. Nonetheless, validation and benchmarking issues have to be considered carefully to ensure methods do not provide false-negative result and are fit for purpose.

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Appendix A. Supplementary data

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