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Review

Food Safety Assessment: Overview of Metrological Issues and Regulatory Aspects in the European Union

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Abstract: The safety of the food we consume has a direct impact on individual and population health and affects the economic growth of the region where food safety is practised and enhanced. The central goal of the European Commission's Food Safety policy is to ensure a high level of protection of human health covering the whole supply chain. In recent years, great attention has been paid to food testing and the application of metrological tools to support food safety. The global food market and national and international food safety regulations have created a huge demand for the measurement traceability and comparability of analytical results that are independent of time or space boundaries. This review provides an overview of the European food safety policy and regulation, with a focus on the measurement-related elements of the European Union (EU) food law. It also highlights how the application of analytical techniques, with particular reference to separation approaches, and metrological tools can ensure the control of certain contaminants that nowadays represent the main challenges for food safety (e.g., mycotoxins, nanoparticles, emerging and process contaminants). METROFOOD-RI-Infrastructure for promoting metrology in food and nutrition is therefore described in this context. This European research infrastructure has been developed and is being implemented in the frame of the European Strategy Forum on Research Infrastructures (ESFRI) to support metrology in food and nutrition and establish a strategy allowing reliable and comparable analytical measurements in food across the entire process line, from primary producers to consumers, and making data findable, accessible, interoperable, and reusable (FAIR).

Keywords: food safety; metrology; regulation; contaminants; mycotoxins; nanomaterials; method validation; proficiency testings; official controls; reference materials

Citation: Sorbo, A.; Pucci, E.; Nobili, C.; Taglieri, I.; Passeri, D.; Zoani, C. Food Safety Assessment: Overview of Metrological Issues and Regulatory Aspects in the European Union. *Separations* **2022**, *9*, 53. https://doi.org/10.3390/separations9020053

Academic Editor: Javier Saurina

Received: 29 December 2021
Accepted: 31 January 2022
Published: 17 February 2022

1. Introduction

Food safety is an important issue that affects all the World's people [1]. Access to nutritionally adequate and safe food was recognized as a right of each individual by the World Declaration on Nutrition, jointly made by the Food and Agriculture Organization of the United Nations and WHO in 1992 [2]. Food safety is also specifically recognized as a fundamental individual right in the United Nations Sustainable Development Goals (UN SDGs), whose goal 2.1 is 'by 2030, to end hunger and ensure access by all people, in particular, of the poor and people in vulnerable situations, including children, to a safe, nutritious environment and sufficient food all year round' [3].

Unsafe food is a risk for the consumers health, at the same time, undermines the socio-economic development of countries, limiting people's ability to buy healthy and safe food. Therefore, safe food saves lives, improves consumer health and contributes to economic growth in countries where there are high food safety standards [4,5]. Food safety refers to all practices that are used to keep our food safe and involves handling, storing, and preparing food to prevent infection and to maintain enough nutrients for us to have a healthy diet. Nowadays, food safety is being tested by the globalization of food supply chains, which have become very long and made up of numerous participants such as producers/farmers, processors, co-packers, distributors, retailers, and consumers in national and international trade. Countries must ensure the safety and quality of their foods that enter international trade but in addition, they must ensure that imported foods comply with national requirements [1].

The flow of information among all the participants in the food supply chain is also crucial for describing the route of foods from the farm (field) to the consumers' tables. To avoid food safety and quality risks, all the involved participants must value some characteristics of the product, like its origin, legal requirements and the respect of the parameters set by the producer's declaration. Important roles are played by the distributors, who are obliged to ensure traceability of a product at any time [6].

Food contamination has been reported as a major public health concern associated with the food market, and it has a negative impact on the food quality and food safety [1]. Council Regulation (EEC) No 315/93 (last consolidated version, 2009) defines a contaminant as 'any substance not intentionally added to food which is present in such food as a result of the production (including operations carried out in crop husbandry, animal husbandry and veterinary medicine), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food, or as a result of environmental contamination' and excluding extraneous matter, such as, for example, insect fragments, animal hair, and so forth. Food contaminants belong to three main categories, that is, biological, chemical, and physical, and can occur at different steps of the food supply chain, and from micro-organisms, fungi or toxins or chemicals-environmental pollutants or pesticides (environmental contamination), from industrial cleaning processes (such as, disinfection, cleaning, and sterilization), from food preparation processes (process contaminants-produced during food processing, contact materials contamination or cross-contamination), during storage or by food contact materials.

In addition, there is a group of contaminants known as 'contaminants of emerging concern' (CEC), which are chemicals that are currently unregulated (not subject to routine monitoring and/or an emissions control regime), but which may be under examination for future regulation [7]. New industrial processes, agricultural practices, environmental pollution and climate change are increasing the presence of emerging contaminants and mixtures of them in food. Among the most important groups of emerging food contaminants are perchlorate, organophosphoric flame retardants (OPFR), polybrominated flame retardants (PBFR), perfluoroalche substances (PFASS), microplastics (MP), nanomaterials (NM) and certain toxins (cyanogenic glucosides and pyrrolizidine alkaloids) [8–10]. The global market increases the spread of food-borne diseases and contributes to the development and spread of new diseases. Food-borne diseases are of various types and to date are a significant cause of morbidity and mortality worldwide. Every year in Europe, more than 23 million people fall ill from eating contaminated food, resulting in 5000 deaths and more than 400,000 disability-adjusted life years. *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli.* are among the most common bacteria that cause foodborne illness. Foodborne parasitic diseases such as those caused by *Taenia solium* and *Echinococcus* spp. are also threats to public health. The main viruses that caused foodborne diseases are Norovirus or hepatitis A virus.

Chemical sources of foodborne illness include natural compounds (mycotoxins and marine toxins), environmental contaminants and contaminants derived from agriculture and industrial practices (toxic elements such as lead, cadmium, arsenic, and mercury) and

naturally occurring chemicals in plants, food additives, vitamins, essential oils, pesticides, and veterinary drug residues. Antimicrobial resistance is another food safety issue. Resistance in food-borne zoonotic bacteria such as *Salmonella* spp. and *Campylobacter* spp. is linked to the use of antimicrobial agents in feed and foodborne diseases caused by these resistant bacteria are well documented in humans. The effects of these diseases on the individual depend on their health, nutritional status, age and virulence of the pathogen. The food policy of the European Union (EU) is based on high food safety standards that protect the health of consumers and foster the smooth operation of the European single market. In 2000, EU food policy was reformed with the measure known as the White Paper on Food Safety (COM 99/719 final) and the Farm to Fork approach was defined [11]. This ensures high safety standards throughout the whole food supply chain, from primary production to the consumer. Food safety impacts the agrifood sector also with reference to its ability to deliver food security, thus food safety and food security are closely inter-related concepts, that in turn represents complementing elements of sustainability [12,13]. As stated by the Food and Agriculture Organization of the United Nations (FAO), there is no food security without food safety [14]. To this end, 'One Health' is the concept that the health of humans, animals, and the environment are interconnected and the 'One Health' approach consists of multidisciplinary teams (academics, producers, consumers, and government agencies) working together to achieve food security for the global population, preserve natural resources, and improve health through safeguarding food safety [15]. As suggested by the 'One Health' approach, in order to model and analyze agrifood systems in terms of quality and safety, there is a need to use an integrated, multidisciplinary and interoperable approach [16].

Nowadays, great attention has been given to the relationships between metrology, agriculture, and food sciences. Metrology is 'the science of measurement, embracing both experimental and theoretical determinations at any level of uncertainty in any field of science and technology' [17]. In order to ensure that the food we eat is safe, it is necessary that the content of contaminants is consistent with the limits imposed by the law and that the measurements of these contaminants are accurate. To verify these requirements, it is necessary to apply metrological concepts to food analyses to provide sensitive, accurate and standardized analytical methods and to harmonize their application in analytical laboratories [18]. This can be considered essential to ensure food quality and safety in the 'farm to fork' model, for consumer protection and for certification of origin of food products [16].

This review aims at examining main metrological issues and regulatory aspects in food safety assessment along the value chain with particular focus on the EU area, highlighting how metrology, with its main tools (i.e., method validation, proficiency testing schemes, and reference materials), can support the agrifood systems in ensuring food quality, safety, and traceability. After a brief overview of the effects of the COVID-19 outbreak on food safety, which represented an additional challenge in the food sector, the EU regulatory framework is described. Contaminants are then briefly described focusing on contaminants of emerging concern, nanomaterials, mycotoxins, process contaminants, with the relevant analytical techniques. Metrology for food safety is addressed, illustrating method validation, proficiency testings, official controls, and reference materials. Finally, the opportunities offered by the Research Infrastructure METROFOOD-RI-Infrastructure for promoting metrology in food and nutrition (ESFRI Roadmap, domain Health and Food) in support of food safety are presented.

2. COVID-19 and Food Safety

The COVID-19 pandemic involved and is still involving all the agrifood systems and all dimensions of food security at a global level, jeopardizing the availability of food resources, as well as limiting the access to food markets and the possibilities of finding nutritious and quality foods. It represents an exceptional and unprecedented challenge for food safety authorities as regards both routine food inspection activities and food

control activities along the food chain through food sampling and analysis practices, also because many of the public sector food testing laboratories have been reassigned to trials on clinical samples of COVID-19 [19]. To support the food supply chain, the WHO has developed two main guidance documents: the first one addresses the food companies, and the other one the authorities responsible for national food safety systems [19,20]. In parallel, various other guides have been developed and updated during the pandemic period in light of new knowledge at local or international level from governments and/or various food associations, helping the food sector to face the crisis [21]. The disruptions that have occurred as a result of the COVID-19 have affected all parts of the food supply chain, including farmers, processors, distributors, retailers (the most affected step), the hotel-restaurant-cafè/catering (HORECA) sector, and consumers [22]. One of the main issues concerning food safety and COVID-19 is the possibility of transmission through contaminated food. In this regard, both international organisations and the scientific community highlight that it is very unlikely that the transmission of SARS-Cov-2 can be carried out via contaminated food or contaminated packaging [23]. On the other hand, here is a possibility of transmission of the virus in food by touching a contaminated surface, an object or the hand of an infected person. Therefore, observing hygiene advice such as frequent hand washing, separation of raw materials from cooked raw materials, cleaning of food contact surfaces and not using raw food, can play a preventive role in the transmission of the virus through food [24]. These lifestyle changes and the increased focus on hand washing adopted, may also have contributed to the large one-year decrease in reported cases of food disease [25,26]. Overall, the COVID-19 pandemic has highlighted the importance of a solid and resilient food system, able to ensure citizens have a sufficient supply of food at affordable prices. As specified by the 'farm to fork' strategy [27], it is necessary to guarantee the security of food supply, nutrition, and public health, making sure that everyone has access to nutritious and sustainable foods in sufficient quantities, ensuring high safety and quality standards, plant and animal health and welfare, while meeting nutritional needs and food preferences. In order to avoid any contamination and to ensure food quality in food production, distribution, sale, handling, storage, and preparation, the adoption of preventive hygiene requirements such as good manufacturing practice (GMP) and good hygiene practice (GHP) remain effective, also to avoid cross-contamination especially for food of animal origin [24,28,29]. It is essential to follow good practices throughout the food chain 'from field to fork'. Concerning consumer health, it is still important to strengthen environmental safety objectives as regards sustainable land use, the conservation of microbial fauna and biodiversity, sustainable land management, environmental contamination, the control of contaminants in environmental matrices and the risk of transfer from the primary production agroecosystem along the food chain. In this regard, the development of control systems for the early detection of contaminants should be promoted, as should management and intervention systems ensuring that adequate production is guaranteed in all circumstances, while protecting consumers' health. Overall, the current health emergency suggests the need to apply an increasingly holistic and interdisciplinary approach, with a growing focus on the sustainability of agrifood systems and the application of an integrated supply chain approach, consistent with the themes of the Green Deal, but also-increasingly-to apply the 'One Health' approach, taking into account the indissoluble link between human health, animal health and environmental health.

3. Food Safety—The European Framework

3.1. Food Safety: Definitions, Policy, Mission, and Approach of the European Commission

Food safety measures have formed part of the body of the European legislation since the early days of the Community [11]. Nowadays, the European Union has one of the highest food safety standards in the World [30]. The EU's food safety policy is applied to the food supply chain, ensuring both health and the absence of contamination of animals and plants, promoting good hygiene practices from the producer to the final consumer, while at the same time allowing the food industry to remain one of Europe's largest manufacturing

sectors [31]. At the end of the 1990s, a number of events endangered food safety such as Creutzfeldt-Jacob disease, due to the consumption of beef from cows fed with meat-and-bone meal from cattle infected with bovine spongiform encephalopathy (BSE) and the presence of dioxins in products such as eggs, chicken and pork (due to the use of contaminated feed). These events highlighted the need to pay attention both to finished products and to all stages of the food chain, such as the use of healthy animal feed. To outline a full range of actions needed to ensure food safety in the EU countries, complement and modernize existing food law, and provide greater transparency to consumers, the measure known as the White Paper on Food Safety [11], was adopted in 2000. Within it, the EC proposed a set of measures that make it possible to organize food safety with a global and integrated approach. Some EU regulations and recommendations are listed in Table 1. The White Paper on Food Safety proposes the creation of an autonomous European Food Authority, in charge for drawing up independent scientific opinions on all aspects relating to food safety; an improved legal framework covering all aspects related to food, 'from farm to fork'; more harmonized control systems at national level; a dialogue with consumers and other stakeholders. Furthermore, by means of the White Paper, the EC formulated the general principles around which to build an effective policy on food safety at the European level: a global, integrated strategy that applies to the entire food chain ('from farm to fork'); a clear definition of the roles of all parties involved in the food chain (animal feed producers, agricultural and food business operators, Member States, the Commission, consumers); the traceability of food intended for humans and animals and their ingredients; the coherence, effectiveness and dynamism of the food policy; risk analysis (including risk assessment, management and communication); the independence, excellence and transparency of scientific opinions; the application of the precautionary principle in risk management [11]. In 2002, therefore, the European Parliament and the Council adopted the Regulation (EC) No 178/2002 [32] that represents the foundation for the EU food and feed legislation, known as General Food Law Regulation. EU food law ensures food safety at all stages of the food chain, taking also into account animal feed and environmental health, furthermore ensuring and facilitating food trade and free movement of food and feed both within the EU and to third countries. This Regulation also establishes both the European Food Safety Authority (EFSA) which provides scientific advice to decision makers and the Rapid Alert System for Food and Feed (RASFF) for rapid crisis and emergency management throughout the food supply chain. The fundamental principles of food law are: (i) the risk analysis principle—based on risk assessment (EFSA), risk management (European Commission, European Parliament and EU Member States) and risk communication; (ii) the precautionary principle—according to which precautionary risk management measures and protective actions must be taken if the possibility of adverse effects on consumer health is identified before a complete scientific proof of risk; (iii) the protection of consumers' interests, which provides consumers with a basis for making informed choices and preventing fraudulent practices, adulteration of food and any other practices, which mislead them and the principle of transparency implemented by the next Transparency Regulation [33]—whereby public authorities should inform consumers if there are reasonable grounds for suspecting that a food or feed may present a risk to human or animal health. The General Food Law Regulation also established that the operators themselves are responsible for food safety and the Member States must ensure that the law is applied in the whole food chain. To ensure this, the Member States are required to maintain a system of official controls, established through the Regulation (EC) No 882/2004, that cover also the imported food. Food business operators should apply product traceability through systems that can identify both the supplier of food, feed or food-related substances and to whom the food (a step backwards, a step forward). This makes it possible to identify and possibly recall products in case of risk to human health. In addition, the Trade Control and Expert System (TRACES) has been set up to record movements of animals, plants, food and feed inside and outside the EU. Moreover, Regulations (EC) No 853/2004 (replaced by Regulation (EU) 2017/625) and (EC) No 852/2004, known as the "hygiene package"

harmonised the hygiene requirements for food through procedures based on the principles of hazard analysis and critical control points (HACCP) applicable throughout the food chain. Provisions on official controls in products of animal origin can be found in regulations reported in Table 1. Moreover, according to global standard on General Principles of Food Hygiene of the Codex Alimentarius Commission [34], the concept of food safety culture to enhance food safety by increasing awareness and improving the behavior of employees in food establishments is introduced. In addition to horizontal legislation, which impacts all foodstuffs, for some specific areas there are dedicated vertical regulations or directives. In fact, the EU food safety policy and action is concentrated in three main interconnected areas of protection: food (which includes the legislation on Chemical safety and contaminants, biological safety and food hygiene, labelling and nutrition, food improvement agents, novel food, and animal food); animal health (which includes the EU's Animal Health Law and the legislation on zoonoses and zoonotic agents, medicated animal feed, animal diseases, animal welfare, trade and imports); plant health (which includes the legislation on Genetically Modified Organisms—GMOs, pesticides and fertilizers, protection against plant pests, information management system for official controls to ensure compliance with agrifood chain rules, plant health and biosecurity). The full list summarizing these aspects of the EU food safety legislation can be found on the EUR-Lex website [35]. Therefore, in this period of globalization the convergence of people, animals, and the environment has created a new dynamic for which food safety is closely linked to animal and plant health, for these reasons must be treated from the perspective of the 'One Health' approach [36–39]. So especially for zoonotic diseases and food contaminants, it is necessary to adopt control strategies that are not based solely on the risk to human health but rather aim at preventing these risks by acting through integrated approaches to animal health and the health of the primary production environment. Ensuring safe, accessible, accessible and nutritious food is, in fact, increasingly difficult, especially in this global context, and the application of a One Health approach is crucial to achieving the United Nations (UN) Sustainable Development Agenda 2030 and its Sustainable Development Goals (SDGs). Our dynamic and complex food system, and the challenge of its safety, is to control and prevent instability and use One Health as a construct to understand this ecological dilemma and as a basis for devising new solutions and interventions [38].

Table 1. List of some regulations and recommendations relevant for the food sector.

Reference	Topic
EEC 315/1993 (consolidated version 2009)	Definition of contaminant
EC 178/2002	General Food Law Regulation
EC 882/2004	Establishment of official controls system
EC 852/2004	Hygiene of foodstuff
EC 853/2004	Specific hygiene rules for food of animal origin
EU 2017/625	Official control regulation (repealing EC 854/2004)
EU 2019/624	Official controls of products of animal origin
EU 2019/625	Import conditions
EU 2019/627	Practical arrangement of official controls of products of animal origin
EU 2020/2235	Import certificates
EU 2021/405	Lists of third countries authorized to import products of animal origin
EC 2073/2005	Microbiological criteria for foodstuffs
EU 2015/1375	Specific rules on official controls for Trichinella in meat
EU 2021/382	Food allergen management (amending Annexes to EC 852/2004), redistribution of food, concept of food safety culture
EC 1881/2006 (consolidated version 2021)	Maximum permitted levels in food for some specific contaminants

Table 1. *Cont.*

Reference	Topic
EU 2017/2158	Regulation specific to acrylamide
EU 2019/1793	Regulation specific to acrylamide
EC 401/2006	Mycotoxin control
EU 2017/644	Sampling and analysis methods for the control of levels of dioxins, dioxin-like and non-dioxin-like PCBs in certain foodstuffs
EC 333/2007	Control of levels of lead, cadmium, mercury, inorgainc tin, 3-MCPD and benzo(a)pyrene in foodstuffs
EC 1882/2006	Control of levels of nitrates
2011/696/EU	Recommendation on definition of nanomaterials
EU 2015/2283	Novel foods
EC 1333/2008	Novel foods, food additives
EC 1223/2009	Biocides and cosmetics
EC 1169/2011	Food information to consumers
EC 10/2011	Plastic food contact materials
EC 450/2009	Active and intelligent materials
EC 1223/2009	Biocides and cosmetics

3.2. Contaminants

Food safety can be compromised by numerous contaminants, that is, substances that have not been intentionally added to food, deriving from the different stages of the food supply chain or as a result of an environmental contamination [40]. Accidental contamination of food could be of three main categories: biological (which occurs when bacteria, fungi or other harmful micro-organisms contaminate food), chemical (due to the presence of undesirable chemicals in food such as residues from primary production, environmental pollutants, toxic elements, process or food-borne contaminants) and physical (due to 'foreign materials' and radionuclides) [41,42]. The sources of food contamination include: environmental contamination from the agroecosystem of primary production; transport of raw materials to the processing plant; food conditioning processes (e.g., preheating, disinfection, cleaning, sterilization); food preparation (e.g., by boiling, baking, frying or combining with other ingredients at high temperature); storage and distribution; food contact materials [43]. EU rules ensure the level of contaminant in a food is lower than the risk level for human health, ensuring its safety to eat [44]. Regulation (EC) no. 1881/2006 (consolidated version 2021) sets the maximum permitted levels in food for the main contaminants: nitrate, mycotoxins (aflatoxins, ochratoxin A, patulin, deoxynivalenol, zearalenone, fumonisins and citrinine), metals (lead, cadmium, mercury, inorganic tin, arsenic), 3-MCPD, dioxins, dioxin-like PCBs, nondioxin-like PCBs, Polycyclic Aromatic Hydrocarbons (PAH) (benzo(a)pyrene) and sum of four PAHs), melamine and erucic acid. Specific regulations or directives exist for some specific foods, for example, infant and follow-on formula [45] and honey [46]. On the other hand, other regulations are specific to some contaminants, such as the EU Regulation 2017/2158 and the EU Regulation 2019/1793 for acrylamide. With the Regulation (EC) No. 882/2004, then incorporated by the most recent Regulation (EU) 2017/625, the European Parliament set up the Community and National reference laboratories. These laboratories work to ensure high quality and uniformity of analytical results regarding official controls. Provisions for sampling and analysis for the official control of maximum levels of contaminants are indicated in other regulations (listed in Table 1) and guidance documents [47–52]. As a result of changes in legislation, more efficient analytical approaches are being developed with greater sensitivity and the ability to detect contaminants in every type of food matrix [53]. The nature of the sample, the type of analyte, the speed, accuracy, precision, and robustness determine the choice of the most suitable analytical method. A key point of the method used is the correct selection and preparation of the food sample, the accurate execution of the analysis and the execution of the appropriate calculations and data interpretation. Method validation is necessary to

ensure its suitability. For this purpose, the use of fit-for-purpose reference materials (RMs) is essential. The selection of the analytical method is often facilitated by the availability of reference and official methods. The application of these methods allows the comparability of results between different laboratories following the same procedure and the evaluation of the results obtained using newly developed or faster procedures [54]. Several analytical techniques are suitable for the determination of many contaminants in complex food matrices. These methods may be qualitative, semi-quantitative or quantitative. For quantitative analysis of contaminants and chemical residues in food matrices, the most commonly used analytical approaches for organic contaminants are based on gas chromatography (GC) and high-performance liquid chromatography (HPLC). In addition, analysis of contaminants and multicomponent residues can be performed by coupling GC with mass spectrometry (MS). In addition, analysis of contaminants and multicomponent residues can be performed by coupling GC with mass spectrometry (MS), while progresses in HPLC mass spectrometry (LC-MS) permit the analysis of thermally labile and large molecules that cannot be easily volatilized (i.e., mycotoxins, polar pesticides, veterinary drug residues). In addition, immunological techniques such as enzyme-linked immunosorbent assays (ELISA) and immunosensor techniques may be used for the quantification of pesticides, antibiotics and mycotoxins, while immunoaffinity chromatography is used for the concentration and cleaning of the analyte of interest [55]. For the analysis of pesticides in food matrices, GC-MS or GC with ion-trap detectors (GC-ITD) MS are mainly used for the determination of volatile and thermally stable pesticides, while HPLC with ultraviolet (UV) detector and, most effective, LC-MS (tandem with atmospheric-pressure ionization—API, atmospheric pressure chemical ionization—APCI, and electrospray ionization—ESI) are the main techniques for the analysis of volatile, polar, ionic and thermally labile pesticides. [55]. Surface-enhanced Raman spectroscopy (SERS) has also been applied for on-site detection of organophosphate pesticides in food [56]. Qualitative and/or quantitative determination of toxic and potentially toxic elements can be performed by conventional detection methods such as atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES), as well as by inductively coupled plasma mass spectrometry (ICP-MS). To monitor preservatives and illegal content of additives in food (such as formaldehyde, nitrate and nitrite, bisulphite and sulphur dioxide), various conventional methods have been used, for example, spectroscopic methods, chemical derivatization by chromatography, the colorimetric method, kinetic spectrophotometric analysis m and fluorometric flow injection methods. Recently introduced methods for the determination of formaldehyde in food samples include Fourier transform infrared absorption (FTIA), differential optical absorption spectroscopy (DOAS), laser-induced fluorescence spectroscopy (LIFS) and laser adsorption diode spectroscopy (TDLAS). Ionic chromatography (IC), flow injection analysis (FIA), fluorimetry and gas chromatography-flame ionization detector (GC-FID) are recently used for the determination of bisulphite and sulphur dioxide [56].

3.2.1. Mycotoxins

Mycotoxin contamination of food represents one of the major issues for food safety [57]. Mycotoxins are secondary metabolites and low molecular weight compounds (usually less than 1000 Daltons) mainly produced by filamentous fungi (molds) [58]. Among the main mycotoxin-producing fungal strains are those belonging to the genera *Alternaria*, *Aspergillus*, *Claviceps*, *Fusarium*, *Penicillium*, and *Stachybotrys* [57–59]. Mycotoxin contamination of the food chain can occur either directly, via contaminated plant-based foods, or indirectly, by the growth of mycotoxin-producing fungi in food [58]. These toxins are very stable and can persist on food even without the pathogen that generates them. Contamination of food and feed may occur in pre- and post-harvest stages (by the changing weather and extreme climates) and mainly during storage, especially in conditions of high temperature and humidity [57,59]. Foods such as cereals, spices, feed, milk and dairy, nuts, and lentils are mostly affected by mycotoxins contamination [60,61]. Diseases resulting from exposure to mycotoxins are known as mycotoxicosis and may have several adverse

effects on human health (such as hepatitis, necrosis, gynecomastia with testicular atrophy, hemorrhage, hepatocellular carcinoma, tumors, neurological disorders) also, in extreme cases, leading to death. More than 400 mycotoxins have been identified and characterised in food and feed, those causing significant damage both economically and to human health include aflatoxins (AF), fumonisins (FB), ochratoxins (OT), trichotheceenes, patulin (PAT), zearalenone (ZEN), deoxynivalenol (DON), T-2 toxin, HT-2 toxin and others in the category of emerging mycotoxins [57,59]. Mycotoxin contamination of agricultural products also creates a great economic loss as these foods have to be destroyed. The increase in mycotoxin contamination is also due to the use of plant proteins in feed, which replace the more expensive animal ones. On the other hand, exposure of farm animals to mycotoxins can be a problem for human health as they enter in the food chain [62]. In addition, the use of chemical compounds to limit the development of mycotoxins can cause harm to the environment, for this reason in recent years are preferred natural bioactive plant molecules and eco-sustainable products to keep under control the onset of pathogens [63]. Mycotoxin contamination represents a huge challenge to food safety as their prevalence in world food crops appears to be around 60–80% [57]. Europe has the most extensive and detailed regulations on mycotoxins in food and feed in the world. Aflatoxin $B1_1$ (AFB_1), B_2, G_1, G_2 and M_1, DON, FB_1 and B_2, ochratoxin A (OTA), ZEN and T2 and HT-2 mycotoxins are strictly regulated by the Commission Regulation (EC) No 1881/2006 (Consolidated version) and monitored in the European Union. In addition, standardized and specific measures for the sampling of regulated mycotoxins in various food matrices (cereals, nuts, spices, dairy products, fruit juices and honey) are described in Commission Regulation 401/2006 (consolidated version 2014). After sampling, the sample is pre-treated at various stages including extraction (with accelerated solvent extraction—ASE), cleaning (with solid-phase extraction—SPE, or immunoaffinity LC—IAC) and concentration. Analytical techniques such as HPLC-MS, matrix assisted laser desorption time-of-flight (MALTI-TOF) and GC-MS are commonly used for qualitative and quantitative determination of bacterial and fungal toxins. HPLC with UV-Vis detection or fluorescence (FD) in combination with immuno-column cleaning affinity are generally used for the determination of both bacterial and fungal toxins, while for the determination of different types of mycotoxins simultaneously liquid chromatography coupled with mass spectrometry (LC-MS/MS) can be applied [60]. Other rapid analytical techniques such as capillary electrophoresis (CE) and thin-layer chromatography (TLC) with the help of ultraviolet detector (UV) for the detection of both naturally fluorescent mycotoxin (i.e., Aflatoxins and Ochratoxin A) and functionalisated mycotoxins, and can be used for quantitative or semi-quantitative determination of bacterial or fungal toxins [56]. Moreover, immunoassay methods can be employed for the rapid detection of mycotoxins, among which the most used are radioimmunoassay (RIA), enzyme linked immunosorbent assay (ELISA) test and fluorescence polarization immunoassay (FPIA). Biosensors based on immunological tests on various supports such as membrane immunoassays or Lateral Flow Strip (LFS) are used for rapid and in-situ controls [55]. Polymerase chain reaction (PCR) and reverse transcription polymerase chain reaction (RT-PCR) are often used to detect virulence genes in food [64]. Functional assays are also available for detecting bacterial and fungal toxins [56]. Other innovative methods for the determination of mycotoxins are near and medium infrared spectroscopy (NIR and MIR), in particular Fourier Transform Infrared Spectroscopy (FTIR) [55]. The term 'emerging mycotoxins' refers to mycotoxins that are not regulated by legislation and are not usually analysed in foods such as Fusarium metabolites like Enniatins (ENNs), Beauvericin (BEA), Moniliformin (MON), Fusaproliferin (FP), fusaric acid (FA), culmorin (CUL), and butenolide (BUT); Aspergillus metabolites like sterigmatocystin (STE) and emodin (EMO); Penicillium metabolite mycophenolic acid (MPA), and Alternaria metabolites alternariol (AOH), alternariol monomethyl ether (AME), and tenuazonic acid (TeA) [65,66].

3.2.2. Contaminants of Emerging Concern

Another group of contaminants known as contaminants of emerging concern (CEC) includes chemicals that are currently unregulated, but which may be under examination for future regulation [67]. They refer to different types of chemicals, including medicines, personal care or household cleaning products, agricultural chemicals, flame retardants, pesticides, surfactants, and industrial chemicals sourced from daily anthropogenic practices [68,69]. Due to the spread of new agricultural practices or industrial processes, the possibility to find emerging contaminants in food is growing, even promoted by climate changes and environmental contamination [8]. Among the most prominent groups of emerging food contaminants they are perchlorate, organophosphorus flame retardants (OPFRs), polybrominated flame retardants (PBFRs), compounds resulting from food processing or from the packaging, perfluoroalkyl substances (PFASs), microplastics (MPs), nanomaterials (NMs) and some toxins (cyanogen glucosides and pyrrolizidine alkaloids) [9]. The determination and quantification of such compounds has become possible thanks to the growing sensitivity of recent analytical technologies [69]. Among the analytical methodologies used for the determination of emerging contaminants, GC-MS is the most widely applied, along with LC and mass spectrometry-based techniques. The determination and quantification of such compounds has become possible thanks to the growing sensitivity of recent analytical technologies [8].

3.2.3. Nanomaterials

Technologies based on nanomaterials (NMs) are receiving great technological and economic interest for several industrial applications, including in the food industry [70]. According to Recommendation 2011/696/EU [71] (currently under review), a 'Nanomaterial' is defined as: a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm. Are also included in the definition of nanomaterials fullerenes, graphene flakes and single-walled carbon nanotubes with one or more outer dimensions of less than 1 nm [71]. Furthermore, the International Organization for Standardization (ISO) has defined NM as a nanosized material, distinguishing between nano-object (a material with external dimension on the nanoscale, such as nanoparticles) and nanostructured materials (with nanometric surface structure). 'Nanoscale' is defined as ranging from approximately 1 to 100 nm [72]. Nanotechnology in the food industry allows ensuring the modification of the color, flavor, and nutritional values of food, increasing and monitoring its shelf life. Nanotechnologies in the food industry are used for both formulation of food additives (nano inside—smart delivery of nutrients, nanoencapsulation of nutraceuticals, bioseparation of proteins, rapid sampling of biological and chemical contaminants, solubilization, delivery, and color in food system) and in food packaging (nano outside—active packaging with antimicrobial substances in nano-form, smart/intelligent packaging to detect the pathogen growth, nanosensors, carbon nanotubes to prevent fungal invasion, and biobased packaging like biodegradable polymer nanocomposites) [73–75]. Furthermore, nanomaterials can also be used as pesticides to improve the yield and quality of food and relieve the pressure of traditional pesticides on the environment [76]. The same advantageous properties that arise from size, however, can have harmful effects on the environment and human health [77]. For this reason, the European Food Safety Authority has produced the 'Guide to risk assessment of the application of nanosciences and nanotechnologies in the food and feed chain' [78], which covers the areas of application of EFSA's expertise, for example, novel foods, food contact materials, food/feed additives and pesticides. Depending on its nanometric structure and the larger specific surface area as well as chemical composition, nanomaterials can have different toxicokinetic behaviors (e.g., significant changes in absorption, distribution and/or metabolism) [79]. Depending on its nanometric structure and the larger specific surface area as well as chemical composition, nanomaterials can have different toxicokinetic behaviors (e.g., significant changes in

absorption, distribution and/or metabolism). There are also specific provisions for nanomaterials in sector-specific legislation, which are listed in Table 1 [80]. Several methods have been used to characterize the size, crystal structure, elemental composition and a variety of other physical properties of nanoparticles, for example, using microscopy, spectroscopy, or diffraction based techniques [74]. These techniques are sometimes exclusive for the study of a particular property, while in other cases they are combined [81]. For the separation and analysis of nanoparticles are used both chromatographic techniques with different detectors such as ICP-MS, MS and DLS, and innovative separation methods such as Field-flow Fractionation (FFF) coupled for example with mass spectrometry. Scattering techniques, such as static light scattering (SLS) and dynamic light scattering (DLS), are useful for characterizing nanoparticles. Among the most sensitive methods for measuring the size and quantification of colloids is Laser-induced breakdown detection (LIBD). Liquid chromatography coupled to mass spectrometry with electrospray ionization source (ESI) or matrix/ionization assisted laser desorption (MALDI) are also used for nanoparticles analysis [9].

3.2.4. Process Contaminants

Process contaminants represent another emerging class of contaminants, which has recently attracted attention because of their negative impact on food quality and risks for human health. Thy are formed in food as a result of some heat treatment processes at high temperatures, such as fermentation, smoking, drying, cooking, frying, grilling or barbecue. Examples of these contaminants are acrylamide, 3-monochloropropan-1,2-diol esters (3-MCPD), glycidyl esters of fatty acids (GEs), polycyclic aromatic hydrocarbons (PAHs), ethyl carbamate, furan, nitrosamines, heterocyclic aromatic amines (HAA), 4-Methylimidazole (4-MEI) and end-products of advanced glycation (AGE). The current legislation imposes maximum limits in food only for 3-MCPD, GE and PAHs [82]. Various analytical methods allow the determination of process contaminants in foods. For the separation and analysis of nanoparticles are used both chromatographic techniques with different detectors such as ICP-MS, MS and DLS, and innovative separation methods such as Field-flow Fractionation (FFF) coupled, for example, with mass spectrometry. Scattering techniques, such as static light scattering (SLS) and dynamic light scattering (DLS), are useful for characterizing nanoparticles. Among the most sensitive methods for measuring the size and quantification of colloids is Laser-induced breakdown detection (LIBD). Liquid chromatography coupled to mass spectrometry with electrospray ionization source (ESI) or matrix/ionization assisted laser desorption (MALDI) are also used for nanoparticles analysis [43,83]. For the identification of the 3-MCPD the most widely used techniques are GC-MS or high-resolution mass spectrometry (GC-HRMS) and HPLC, although EFSA recommends developing new methods or establishing standard methods in order to reduce uncertainties in occurrence and exposure estimates [43,84]. Volatile nitrosamines are mostly determined by GC coupled to the specific thermal energy analyzer detector (TEA) [43]. For the analysis of PAHs in foods, the official methodology of the official association of analytical chemistry (AOAC) is available, which includes separation by thin-layer chromatography and subsequent determination by UV spectrophotometry. This methodology is very time-consuming and solvent-intensive, therefore new methodologies have recently been developed based on the 'quick, easy, economical, effective, robust and safe' methods, called QuEChERS. Among these methods, the most widely used is based on GC coupled with quadrupole time-of-flight mass spectrometry or ion-trap mass spectrometry (GC-Q-TOF MS and GC-IT-MS) [85].

3.3. Official Controls

At the end of the last century, the European Union had to face several crises and scandals related to food security as Bovine Spongiform Encephalopathy outbreak (UK in the 1980s and 1990s), dioxin incident (Belgium 1999), foot-and-mouth disease (UK 2001) and tainted oil (Spain 1981). These scandals have put public health and consumer interests

at serious risk and have had a strong impact on the political redefinition of Food Safety in the European Union that has been reinforced as a direct response to such food crises [86]. This system, which culminated in the creation of the so-called Hygiene Package, aimed at establishing high safety standards, ensuring the free movement of food products including restoring consumer confidence in control systems within the EU. The Hygiene Package includes Regulation 882/2004 'on official controls to verify compliance with feed and food law and animal health and welfare rules', which establishes EU reference laboratories (EURLs). These structures are responsible for providing scientific and technical assistance to the Commission and for collaborating with the national reference laboratories (NRLs) of each Member State (MS). Similarly, the NRLs shall coordinate and support the official laboratories (OLs) responsible for the analysis of feed and food at national level, as sketched in Figure 1. In fact, Regulation 882 establishes the pyramid that regulates controls in the EU with the EURLs at its peak, the NRLs at its center and the OLs at its base. The NRLs represent the contact point between those who carry out official controls in the Member States and those who ensure the harmonization of analytical methods and performance within the EU. Regulation 882 was amended by Regulation 2017/625 'on official controls and other official activities carried out to ensure the application of food and feed legislation, animal health and welfare rules, on plant health and plant protection products'. Despite the new legislation, neither the requirements nor the tasks of the laboratories involved in food safety activities have been significantly modified. A EURL shall be designated whenever there are areas where official controls depend on the quality, uniformity and reliability of methods and results, or where the harmonization of common practices for the development and use of analytical methods has to be promoted. These laboratories have to be accredited according to EN ISO/IEC 17025, which is an international standard that enables testing laboratories to demonstrate their competence and their ability to produce reliable results. They should contribute to the improvement and harmonization of analytical methods to be used by official laboratories so as to generate comparable results within the EU. In particular, they shall assist the NRLs by providing them with details on analytical methods and with reference materials; organizing proficiency tests to monitor the laboratories' performances [87–90] and ensuring the relevant follow-up [91] organizing training courses which can also be extended to OLs and experts from third countries; updating laboratories on scientific progress in their field of competence. The EURLs shall also give scientific and technical assistance to the European Commission and collaborate with European and international agencies (e.g., EFSA, EMA; ECDC).

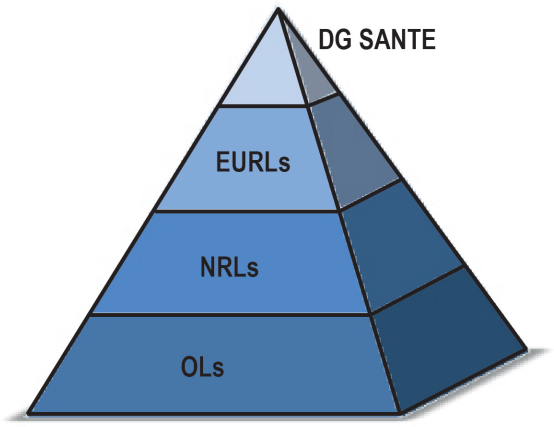

Figure 1. European Union food control network: The Directorate General SANTE (DG SANTE) is the Commission department responsible for EU policy on food safety and health and for monitoring the implementation of related rules; the network of laboratories is constituted of the EU Reference Laboratories (EURLs), the EU National Reference Laboratories (NRLs) and the official laboratories (OLs).

EURLs are divided into three large groups (Animal Health; Food and Feed; Animal Health), and currently 26 laboratories are designated as part of food and feed control. At national level each MS shall designate one or more of NRLs for each EURL. The NRLs shall collaborate with the EURLs and participate in their training courses and proficiency tests; coordinate the activities of OLs with a view to improving and harmonising the analytical methods; organise proficiency tests for the benefit of OLs also providing them with an appropriate follow-up; forward the information from the EURLs to the competent authorities and OLs; give scientific and technical assistance to the competent authorities of its MS; organize training courses for the staff of the OLs; assist Member States in the event of particular emergencies. The OLs are designated by the competent authority of each MS, in addition to being competent in the field in which they are appointed, they have also to be ISO 17025 accredited with adequate personnel and facilities to carry out their tasks. Laboratories have to inform the competent authorities when the analytical results, tests or diagnoses on samples taken during official controls or other official activities reveal a human health risk or a likely non-compliance with specific regulations; to participate in proficiency tests at the request of the European or national reference laboratories; to make available to the competent authority all information on how official control data are produced. Finally, the whole network should ensure that official controls and other official activities are based on methods that comply with the most advanced scientific standards and ensure sound, reliable and comparable results across the EU. The synergy between laboratories also aims to guarantee that the methods used by official laboratories, as well as the quality and uniformity of results, are continuously improved by giving the entire system a certain dynamism.

4. Metrology for Food Safety

As highlighted in the Strategy Paper 2021–2030 of the Advisory Committee on the Quantity of Substances; Metrology in Chemistry and Biology (CCQM) a highly relevant scientific, economic and social challenge is to improve the overall comparability of chemical and biological measurement, standards, and capacities, thus enabling the Member States and related undertakings to carry out measurements with a high confidence level. Programmes and policies to ensure food safety and allow trade needs reliable methods for the analysis of (emerging) contaminants, food allergens, toxins and pathogens; procedures and databases to determine the authenticity/provenance of food; verification of mandatory levels of fortification with basic food; reliable methods and fit for purpose Reference Materials for the determination of GMOs in food. Therefore, to ensure food safety through reliable measurements along the food chain it is necessary to use suitable metrological tools [92]. Metrology is a specialized discipline that deals with measurement science by improving the reliability and comparability of analytical results including also the definition of internationally accepted units of measurement and the metrological traceability [18,93]. Recently, Brown outlined the importance of updating the concept of metrology and proposed a new feature 'measuring measurement' emphasizing the characteristic and distinctive metathought associated with it [94]. Metrology ensures the stability, the comparability and the accuracy of the measurements, making it possible to reduce waste, improve trade, operate infrastructure, advance technology, prosper the economy, encourage global cooperation and trade, and ensure our quality of life [94]. The three main pillars on which metrology is based are validation of methods, estimation of measurement uncertainty and determination of metrological traceability [95]. Quality reference standards, validated methods, standardized sampling practices, proven calibration methods and reference materials are the tools used to achieve comparability of analytical results, allow metrological traceability and proficiency testing [93].

4.1. Method Validation

Based on the definition of the EURACHEM Guide, 'method validation' is essentially the process of defining the analytical requirements and confirms that the method considered

is 'fit-for-purpose', that is, its performances are capable of meeting the requirements for its specific application. Method validation differs from the verification of the method because in the validation the laboratory must confirm that the method is 'useful for the purpose', while in the verification the laboratory must confirm its competence in the application of the method. Therefore, method validation provides that the analytical result is sufficiently reliable to ensure that any decision based on it can be made with confidence. For this reason, the performance of the method shall be validated, and the uncertainty of the result shall be estimated at the confidence level required. Validation is also necessary when the equivalence of the results given by two methods needs to be demonstrated, for example between a newly developed method and an existing standardized or regulated method.

There are two different approaches to the validation of a method: the first involves inter-laboratory comparison, often defined collaborative or cooperative studies, and the second internal validation with a single laboratory study. The different approaches can be defined according to the 'user base' that is expected for the method. In fact, for procedures that will be applied such as standards, inter-laboratory validation allows to have a more robust method. The single laboratory study is instead applied when it is necessary to validate a method for an internal use. The exact validation scheme, known as the 'validation protocol', and the report on the results obtained, shall be carried out in accordance with a documented procedure providing an introduction on the purpose and details of the method, the planning of the validation process, the required performance characteristics and the results obtained with respect to the (or not) fulfilment of the analytical requirements [96]. The main performance characteristics of a validation study, interconnected and all contributing to the overall measurement uncertainty, are described in Table 2. The instruments through which it is possible to validate a method are: the 'blanks' of the reagents or of the samples which allow to evaluate in which measure the measured signal is attributable to the analyte or to other factors; routine test samples; spiked materials/solutions that are materials or solutions to which the analyte of interest is added at a known concentration causing an increase in the analytical response and allowing the concentration to be calculated on the basis of the added quantity; measurement standards, reference materials (RMs) and certified reference materials (CRMs) [97].

Table 2. Performance parameters for the validation of analytical methods.

Parameter	Definition and Discussion
Selectivity	...refers to the 'extent to which the method can be used to determine particular analytes in mixtures or matrices without interference from other components with similar characteristics'. The recovery of the analyte(s) of interest shall be determined, and any suspicious interference and any restrictions on the applicability of the method shall be indicated in the validation report [97,98].
Working range & linearity	...determined by examining samples containing the analyte at different concentrations and calculating the regression statistics from the results, usually by the method of least squares in order to establish the range within which acceptable uncertainty can be reached. Before that, a calibration function for the instrument needs to be defined, therefore the working range of the method should be examined separately from that of the instrument. For this reason, it may be appropriate to consider separately the working range of the method and that of the instrument.
Limit of detection (LOD)	...is the lowest amount of the analyte that can be detected by the method at a specified level of confidence. Its value is different depending on the type of sample.
Limit of quantification (LOQ)	...is the lowest concentration of analyte that can be determined with an acceptable level of uncertainty and can, therefore, be set arbitrarily as the required lower end of the method working range [98]. Estimates of LOD and LOQ may be different among different matrices covered by the same analytical method; for this reason, they need to be determined for each matrix [47].

Table 2. *Cont.*

Parameter	Definition and Discussion
Precision	...is a measure of the concordance between mutually independent measurement results obtained under specified conditions. It is usually expressed by a standard deviation. Repeatability is a type of precision representing the smallest variation in results [98].
Trueness	...is an expression of how close the mean of an infinite number of results (produced by the method) is to a reference value. Since it is not possible to take an infinite number of measurements, trueness cannot be measured but it is generally estimated as bias, that is, the systematic error [97,98]. Three approaches are commonly used during validation for bias determination: the analysis of RMs, recovery experiments using spiked samples, and the comparison with results obtained using another method [98].
Ruggedness (or robustness)	...provides an indication of reliability of a method that has the ability to remain unaltered by small variations in the parameters of the method [98].
Uncertainty	...characterizes the range of values attributable to the measurand with a specified level of confidence. Every measurement result has an uncertainty associated with it, deriving from errors arising in the various stages of sampling and analysis and from imperfect knowledge of factors affecting the result. A statement of the uncertainty associated conveys the 'quality' of the result [97,98].

4.2. Proficiency Testing

Different types of inter-laboratory studies can be carried out depending on their purpose and on how they are conceived, but in all of them the participants have substantially to determine one or more characteristics of one or more samples under specified and documented conditions. They are known as 'collaborative trials' when aimed at verifying the performance of an analytical method. If, instead, the focus is on the assessment of the participants' performance, they are considered as proficiency testing (PT). These latter compare the performance of different laboratories that carry out analyses on identical or similar materials, each laboratory using its own routine methods. The evaluation is performed according to objective criteria that are pre-set and external to the laboratory [99,100]. Therefore, PTs are often assumed to be a means for external quality control (EQA) [101]. In fact, participation in these comparisons allows each laboratory to compare its performance with that of others, obtaining feedback on the reliability of its results or on the need to investigate potential problems. Over the years, the participation in PTs has become of utmost importance for accredited laboratories and also the demand for these activities has increased around the world. The relevance of these inter-laboratory studies has been confirmed in the revised version of the ISO 17025 in which PTs are explicitly indicated as a means to guarantee the reliability of results produced by laboratories (point 7.7.2). As a consequence the most of Accreditation bodies ask laboratories to give them evidence of participation in adequate PTs. In fact, the evaluation of the performance of test laboratories (but also medical and calibration laboratories) towards pre-established criteria provides a periodic, objective, independent and documented verification of the quality of analyses performed on routine basis. Participation in PTs is an appropriate and independent self-monitoring tool, which helps participants to improve their performance and in general terms their analytical methods. In quality assurance systems, participation in PTs have to be planned in advance so as to cover methods that need to be improved, checked or validated. For this reason, laboratories have to carefully select PTs to join preferring schemes accredited according to specific standards, for example, ISO 17043 [99], or carried out following internationally recognized protocols. It is also important to choose PTs on matrix/analyte/concentration level as close as possible to those routinely analysed, also the frequency of the exercises is to be considered for the selection [102]. The more the PT responds to the needs of the laboratory, the greater the advantages of the laboratory itself. According to ISO 17043, the main benefits for laboratories participating in PTs are:

- external and independent evaluation and monitoring of performance on a continuous basis, which results in the quality of routine analyses being verified;
- identification of any problems in performing analyses and possibilities for corrective action. Therefore the return information can stimulate the continuous improvement of the laboratory [103];
- evaluation of the efficacy and comparability of the test or measurement methods used by the laboratory;
- guarantee of reliability for customers;
- training or retraining of staff on the basis of the results of such comparisons.

Usually all the schemes foresee regular repetitions but it is also possible that the studies are carried out only once for a specific analysis and in such a case they are known as cooperative trials. PT organizers can be commercial providers but often also public or governmental institutions. In the EU, reference laboratories (EURLs and NRLs), according to CR (EU) 2017/625, conduct PTs on regular basis covering different sectors with the aim of improving and harmonizing the performances of laboratories dealing with official controls so as to assure food safety and to protect consumers' health [88,104,105]. From the PT provider side, great care and resources must be put in place to produce materials that are homogeneous and are stable at least for the duration of the inter-laboratory study. In fact, the samples distributed to laboratories should be such that the performance of the participants is not linked to the quality of the material. These aspects can be particularly critical when the material does not naturally have an adequate concentration level of the analytes of interest and has to be fortified to fit the purpose [106,107]. The analytical methods used to test the PT items for sufficient homogeneity have to be sufficiently precise to ensure that any discrepancy does not affect the performance of participants. In other terms, the provider shall assess homogeneity and stability using criteria that ensure that possible inhomogeneity and instability of proficiency test items do not adversely affect the laboratories' evaluation. There are several alternative procedures on how to check the material homogeneity but a procedure generally followed by accredited provider is described in both ISO 13528 [100] and Harmonised Protocol [108]. It consists in randomly selecting at least 10 PT items and performing analyses in duplicate under repeatability conditions using a method with appropriate accuracy. The better the precision of the applied measurement methods, the higher the requirements on the homogeneity of the material. In some cases if the material is inherently homogeneous or information on the homogeneity is available (e.g., outcome from previous comparable PTs or supporting literature) these tests may be limited, carried out occasionally or even avoided. It is, however, a good rule that at least the first time a certain matrix/analyte combination is proposed, tests are carried out. It is possible that the material is not homogeneous and in this case it is necessary to take into account the between-sample standard deviation in the evaluation of the participants. After the distribution of PT items to the participants, the results submitted have to be evaluated and/or used for deriving the reference values in respect to which the participants' performance have to be assessed. To derive the reference values, different approaches are possible depending on the type of material used and they are summarized in Table 3. Despite some disadvantages, the assigned value (x_{pt}) using the consensus from participant results is probably the most used approach as it is less expensive than the use of CRM, less complicate than using the formulation and no additional measurements are required. Furthermore, from an analytical and a statistical point of view, this approach is easier than setting x_{pt} from a single laboratory result or from experts. Obviously, if the assigned value is derived through the consensus of the participants' results some protocols have to be implemented, including the removal of outliers or the application of robust statistics [109–111]. Moreover, the possible bias is not an issue when the material is homogeneous and stable and the participating laboratories are qualified [112]. The conversion of the participants' results (x_i) into a score is the objective of all PTs, but for this conversion a standard deviation for proficiency assessment (σ_{pt}) has to be defined. Several estimators can be used for σ_{pt}. It can be based on a regulatory

requirement or may correspond to a level of performance reasonable for participants (by perception approach) [99,113] or can be derived from the experience of previous comparable PTs [114] or can be set using a general model (e.g., Horwitz–Thompson equation) [115] or can be derived using an adequate indicator of dispersion of the participants' results. Finally, an appropriate score (e.g., z score, z' score, Zeta score, E_n score) is given to each participant. The most frequently used is the z score, which is defined as

$$z_i = \frac{x_i - x_{pt}}{\sigma_{pt}} \quad (1)$$

As for the interpretation, according to ISO 17043, the performance is acceptable if $|z| < 2$, questionable (warning signal) is $2 < |z| < 3$, or unacceptable if $|z| > 3$. Therefore, the idea of the z score is to make all PT scores comparable so that the meaning of a score is clear, objective and have the same implications for anybody. Based on the z score is also possible to build control charts to monitor the long-term performance of a laboratory that can be useful to maintain the performance under control but also to detect specific trends [91]. Even though not cited in ISO 17043, it is also possible to estimate the measurement uncertainty through PTs [116–119], to use PT for method validation purpose [120–123], and to perform internal quality control with PT material [124].

Table 3. Approaches to set the assigned value and their main drawbacks.

PT Material	Assigned Value x_{pt}	Main Limitations
Certified reference material	Certified property value	• expensiveness • the CRM can be recognized
Formulation (mixing materials in specific proportions if the levels of a properties are known or adding a certain amount of a substance to the blank material)	Calculation on the basis of the proportions used and the known analyte content	• the blank (base) material has to be free from the spiked analyte or the basal content has to be carefully quantified • the mixed materials have to be similar to guarantee the homogeneity • special attention to absorption or release phenomena from containers used
Other materials	Results from a single laboratory using a reference method	• stringent requirements for the analytical method and well-designed study (including availability of adequate CRMs)
Other materials	Consensus value from expert laboratories	• careful a-priori selection of laboratories to be considered experts • drafting of appropriate protocols including the information to be requested from experts and the specific statistical analyses to derive the value
Other materials	Consensus value from participant results (location estimate such as robust mean, median or arithmetic mean)	• biased assigned value • insufficient agreement among the participants • consensus value not metrologically traceable

4.3. Reference Materials

Reference materials (RMs) represent one of the main metrological tools in support to the achievement of reliable measurements, to be used in calibration, validation of measurement methods and quality control, guaranteeing metrological traceability, method validation and quality control [125]. A RM is defined as a 'material, sufficiently homoge-

neous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties'. It can be a CRM or a RM without a certified property value [126]. RMs play a key activity role for the improvement and maintenance of a worldwide coherent measurement system, enabling to verify measurement processes and evaluate their performances trough validation, as well as to guarantee reproducibility and evaluate measurement uncertainty, and to compare properties not directly connected to the SI, as in the case of the quantities describing the perceived characteristics of products, or properties connected to their origin and authenticity. Therefore, it is extremely important to have available and use suitable RMs in support to all measurements and controls performed in relation to food safety, comprising identification and quantification of contaminants all along the supply chain. Similarly to other measurement fields, separation techniques and speciation analysis require the availability of fit-for-purpose RMs; with specific reference to speciation and its implication with food safety, it is especially critical whenever decisions based upon the amounts of species are related to human health risks. Despite an increase in the production of new RMs for the agrifood sector, there is still a lack of fit-for-purpose RMs. Several gaps exist; as an example, RMs might not be available for certain matrices or matrix/analyte combinations, or the range of parameters or available levels may not cover all the analytical requirements. The need to develop new RMs is related to different factors, including the innovation in analytical techniques and method development and new profiling approaches, the need to support laboratory accreditation according to ISO/IEC 17025 [127]. On the other hand, it might be considered that the development of new RMs can be made difficult from specific challenges in obtaining homogeneity and stability for some specific parameters (e.g., protein toxins or other toxins, nanoparticles, micro- and nano-plastics, somatic cell counting), and to the availability of a suitable set of methods for their characterization and the provision of reference or certified values [128]. In particular, talking about RMs for the agrifood sector and specifically taking into account Matrix-RMs for food safety, thousands of matrix/analyte combination might be considered. As concerns the matrixes, besides food matrixes such as foods of vegetable and animal origin, beverages, prepared (ready to eat) food products and total diet, several further matrixes might be considered, for example, extracts and essential oils, additives and integrators, packaging and other food contact materials, and—in a view of a holistic and 'one health' approach—also feeds and environmental matrixes. Additionally, lots of parameters are of interest (also with reference to pure substances for calibration), such as: inorganic and organic contaminants, residues of pesticides and veterinary drugs, moulds and yields, metabolites, profiles and sequences, and so on. Examining the current worldwide availability of agrifood RMs, and with specific reference to food safety issue, on a total of 2155 RMs comprising both pure substances for calibration (1255 RMs) and Matrix-RMs (900 RMs), we can identify: RMs for organic contaminants (out of which 36 Matrix-RMs), 220 RMs for mycotoxins and phycotoxins (47 Matrix-RMs), 117 RMs for toxic and potentially toxic elements (32 Matrix-RMs), 34 RMs for chemical contaminants related to primary production (32 Matrix-RMs), 11 RMs for chemical contaminants related to food processing and conservation (9 Matrix-RMs, out of which 6 certified for acrylamide), 11 RMs for allergens and anti-nutritional substances (3 Matrix-RMs), as reported in Figure 2. Therefore, it is possible to highlight those main emerging needs for new RMs are closely related to the new analytical requirements and the emerging challenges of food safety, such as the application of nanotechnologies or biotechnologies, and include—as a non-exhaustive list—RMs for emerging contaminants, (emerging) mycotoxins, alkaloids, nanoparticles, micro- and nano-plastics, process contaminants, and viruses.

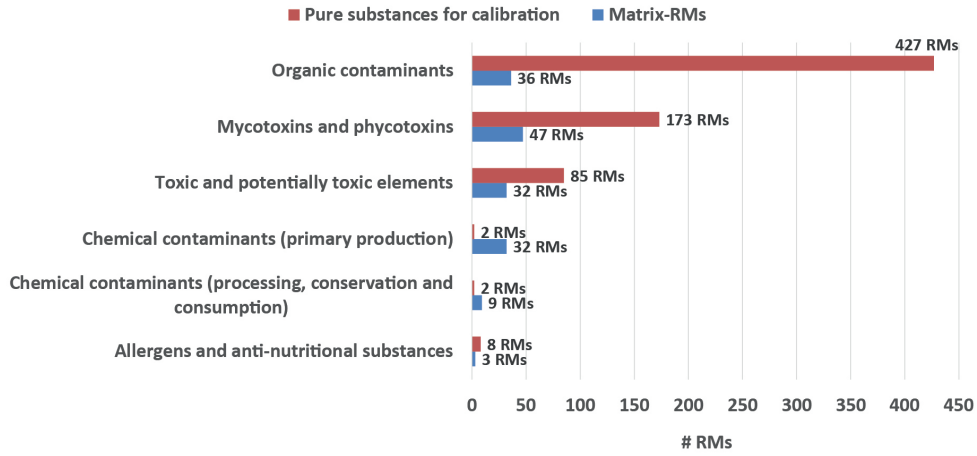

Figure 2. Current production of Reference Materials (RMs) for analysis of food contaminants. The available 2155 RMs consist of 900 Matrix-RMs and 1255 pure substances for calibration.

4.4. METROFOOD-RI as an Opportunity to Support Metrology in Food Safety

METROFOOD-RI–Infrastructure for promoting metrology in food and nutrition [129] is a Research Infrastructure (RI) under development in the frame of EFSRI (European Strategy Forum for Research Infrastructures) [130], for the domain Health and Food [131]. It provides high-quality metrology services in food and nutrition, for enhancing food quality and safety, and supporting the traceability and sustainability of the agrifood systems, in a view of circular economy, comprising an important cross-section of highly interdisciplinary and interconnected fields throughout the food value chain, including agrifood, sustainable development, food safety, quality, traceability and authenticity, environmental safety, and human health (Figure 3).

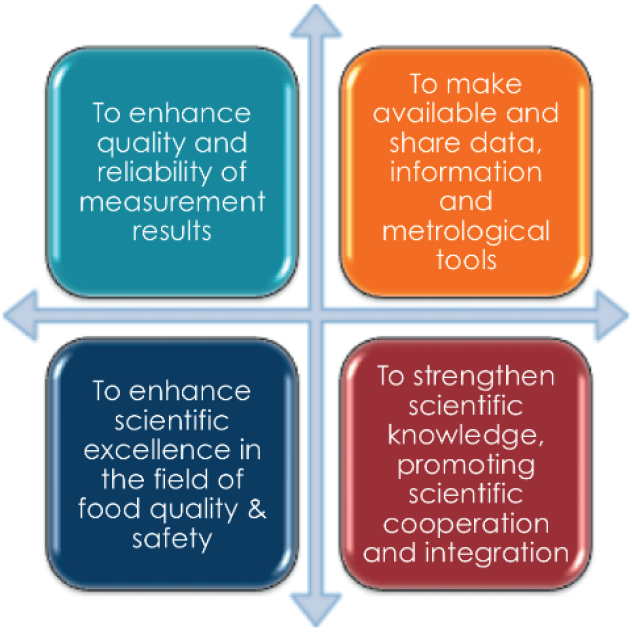

Figure 3. The METROFOOD-RI mission.

Currently, METROFOOD-RI is running its preparatory phase funded under the EU-Horizon 2020 project METROFOOD-PP (GA No 871083) to support its activities aimed at developing its organizational, operational and strategic framework in view of assuming a legal entity as a European Research Infrastructure Consortium (ERIC) and becoming fully operational.

The RI consortium currently involves 48 Institutes from 18 Countries (13 Member States and 5 Associated Countries). The infrastructure combines a physical and an electronic infrastructure strictly interconnected, including numerous facilities distributed in 18 European Countries that can provide scientific services in an integrated and collaborative way. The physical facilities cover: plants for RM production, Analytical Laboratories, plants for primary production and food processing and kitchen laboratories. Thanks to its facilities and expertise, METROFOOD-RI can support the research system, as well as policy makers, food inspection and control agencies, food businesses and consumers, in effectively addressing the main challenges related to food safety. In particular, the analytical laboratories cover a comprehensive set of techniques that can address the chemical and microbiological analyses needed for food safety, with the possibility to combine different analytical techniques that can be applied for the detection and quantification of a given contaminant (e.g., A4F/ICP-MS, DLS, TEM, and so forth for nanoparticle analysis), or for the detection and quantification of the diverse contaminants that can be related to a specific food all along the food chain. A further added value is the capacity to use already available or to develop new sensory systems for early detection of contaminants. The plants for RM production enable to develop new RMs for food safety covering the different matrix-analyte combinations for food of both animal and vegetable origin to be characterised for the whole set of contaminants. The RM plants can be used also for preparing new pure substances for calibration also for emerging contaminants (like in the case of nanoparticles). Furthermore, the possibility to use the experimental plants for primary production and food processing enables the study of the whole production process and how each step can affect food safety. In parallel, the electronic component can support food safety research and technological development linkages, for what concern data integration, sharing and interoperability, including the realization of databases, data analysis and visualization, as well as the application of ICT in the food value chain.

With the purpose to support researcher and lab technicians engaged in food analyses, METROFOOD-RI recently launched an e-service for easily search for available RMs of specific interest for the agrifood sector, covering both pure substances for calibration and Matrix-RMs. The database can be searched based on several criteria, for the desired parameter or matrix, or by using a cross-search per matrix-analyte combination. The RMs included in the database cover the current worldwide availability specifically for the agrifood sector and are categorized in classes and sub-classes of parameters and matrices, as well as into Matrix-RMs and pure substances for calibration. The e-service is free-of-charge, and the App can be directly accessed by the infrastructure website upon registration [132].

5. Conclusions

Safe food is a basic human need. It plays a fundamental role in the socio-economic development of countries, enhances individual and population health, and improves economic growth. Globalization, international trade, the increase in the world's population, the intensification of plant and animal productions and the increasing complexity of the food supply chain have challenged food safety. Nowadays, the European Union has one of the highest food safety standards in the World. For the implementation of European legislation regarding food safety issues, there is a strong need for the development and harmonization of reliable, validated, robust and simple analytical methods. In recent years, as a result of the development of more efficient analytical techniques with greater sensitivity (such as GC, HPLC, TLC, etc.) it is possible to determine many contaminants and contaminants mixtures in complex food matrices. In addition, by applying metrological tools is possible to validate the methods and estimate the measurement uncertainty. Therefore through the use of high-quality reference standards, validated methods and rigorous sampling procedures, proven calibration methods and reference materials, comparability of measurement results can be achieved and metrological traceability and proficiency testing can be facilitated.

Author Contributions: Conceptualization, A.S., C.Z., E.P. and D.P.; writing—original draft preparation, E.P., C.Z., A.S., C.N., I.T.; writing—review and editing, D.P.; supervision, C.Z.; funding acquisition, C.Z. All authors have read and agreed to the published version of the manuscript.

Funding: METROFOOD-PP project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 871083.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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