Legislative Aspects Regarding the Control of Mycotoxins

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Abstract
The branch of public health has always faced a rather big problem - the presence of mycotoxins. The most feared are the carcinogenic ones, which should be excluded from the food sector. Due to the fact that the population has no way to be totally safe from the effect of mycotoxins, certain levels of tolerance have been established by the official bodies, thus, at the global level, regulations have been implemented regarding the maximum allowed limits of mycotoxins, having consumer protection centre. The epidemiological risk due to the contamination of feed, food with compounds of a mycotoxin nature has involved international bodies such as: the Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the United Nations Organization (UNO) through the United Nations Environment Program (UNEP) . In order to ensure a high level of protection of human health, the Rapid Alert System for Food and Feed (RASFF) was created within the European Community. These regulations were the basis for the development of national and international programs, with the aim of preventing the multiplication of fungi in plant substrates that end up in human and animal food, as well as the control of their contamination with mycotoxins.

Keywords: consumer, contamination, harmful effects, mycotoxins, regulations.

1. Introduction

Mycotoxins are toxic secondary metabolites that are produced by filamentous fungi, defined as secondary metabolites of fungal origin. Mycotoxins are toxic and harmful to humans and animals to varying degrees and can contaminate grain grains in the field, in storage and have negative effects on human and animal health [1]. On a global level, concerns in the field of mycotoxicology mainly aim at two important objectives: the standardization of work methodologies for the separation, identification and evaluation of mycotoxins and the establishment of their maximum permissible limits in food and feed [2]. Cereals and cereal-based products are the main source of mycotoxins for the European population [3]. Since 2002, with the introduction of Regulation (EC) No. 178/2002 establishing the principles and general requirements of food legislation, the system has worked better, the classification of information has started to be done according to the degree of risk and the need for direct action: notifications alert, information and news notifications [4]. In Europe, the epidemiological situation of substrate contamination with mycotoxins can be monitored every week on the RASFF website (Rapid Alert System for Food and Feed) [5]. About 89% of food and 98.6% of feed notifications for mycotoxin contamination were attributed to aflatoxin contamination. There are three major types of RASFF notifications: alert, information and border rejection. Alert notifications are found when the hazard is detected in food and feed is already present in the EU. Information notifications are used when a hazard is detected in food or feed is placed on the market in one EU country but has not reached other EU countries. In

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this case, the risk does not require quick action [6]. There are two subtypes of push notifications: "follow-up push notifications" and "attention push notifications". Border rejections refer to consignments of food and feed which have been rejected at the external borders of the EU due to the presence of a hazard in food and feed [7].

The dangerousness of mycotoxins and the control organizations

Most substances with a carcinogenic effect have also been shown to have mutagenic action, since carcinogenic and mutagenic substances have a point of metabolic convergence, i.e. they require a specific metabolic activation in vivo before exerting their inductive action in living systems [8]. The International Agency for Research on Cancer has evaluated and classified the carcinogenic response of mycotoxins [9]. According to this classification, patulin (PAT) and zearalenone (ZEA) belong to Group 3: non-carcinogenic to humans. Aflatoxin B1 (AfB1) is included in Group 1: carcinogenic compound for humans [10]. Fumonisins and ochratoxin A are probable Group 2 human carcinogens. Fumonisins have been associated with liver cancer in rats and outbreaks of oesophageal cancer in humans, and ochratoxin can cause tumours in the kidney and urinary tract [11]. The major epidemiological risk due to the contamination of plant substrates with toxic compounds of a mycotoxin nature has involved international bodies such as the Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the United Nations Organization (UNO) through the United Nations Environment Program (UNEP). , under the auspices of which numerous scientific events were held, including the 3rd International Conference on Mycotoxins where FAO, UNEP addressed strict aspects of control of mycotoxin contamination of food and feed [12,9]. In addition, at these conferences, a series of actions were proposed with the aim of reducing the impact of mycotoxins on consumer health and preventing the degree of mycotic and mycotoxin contamination [13]. These recommendations were the basis for the development of national and international programs to prevent the multiplication of micromycetes in plant substrates that end up in human and animal food, as well as to control their contamination with mycotoxins [14]. In order to ensure a high level of protection of human life and health within the European Community, the Rapid Alert System for Food and Feed (RASFF) was created, which provides the public with a real-time exchange of information. Organizations such as the Joint Expert Committee on Food Additives act as a scientific advisory body to the World Health Organization and the Food and Agriculture Organization. The Expert Committee provides data on toxicity assessments of additives, veterinary drug residues and contaminants [15,9]. In all the countries of the European Community, the maximum permitted limits of mycotoxins in food and feed are strictly respected based on laws, which are constantly updated [16].

In Romania, the Food Safety Supervision and Control Program provides for the control of contaminants in food of animal origin, in accordance with the provisions of Regulation (EC) no. 1881/2006 of the Commission of 19 December 2006 establishing maximum levels for certain contaminants in food products. Regulation (EC) no. 1881/2006 states that it is necessary to amend again the maximum levels for certain contaminants to take into account new information and changes in the Codex Alimentarius [17]. In the case of contaminants considered to be carcinogenic, genotoxic or in cases where the current exposure of the population or vulnerable population categories is close to or exceeds the tolerable dose, the maximum levels should be as low as possible. This regulation sets the maximum levels at the lowest possible values especially for food intended for children which can be obtained through a strict selection of the raw materials used, with the aim of protecting this category of vulnerable population [18].

Recommendations regarding the maximum allowed limits of mycotoxins

Maximum levels for infants and young children, according to Regulation (EC) No. 165/2010 are: aflatoxin Bl: 0.10 pg/kg; aflatoxin M1: 0.025 pg/kg; ochratoxin A: 0.50 pg/kg and the same maximum level for dietetic preparations for special medical purposes, intended in particular for infants; patulin: 10 pg/kg; deoxynivalenol: 200 pg/kg; zearalenone: 20 pg/kg and the same maximum level for corn-based preparations intended for infants and young children;

fumonisins: 200 pg/kg for corn-based preparations intended for infants and young children [19]. This regulation sets maximum ochratoxin levels for cereals, cereal products, raisins, roasted coffee, wine, grape juice, spices, licorice [16, 17]. The Tolerable Weekly Dose (TDI) of ochratoxin A is 120ng/kg body weight. The regulation allows higher aflatoxin levels for products that are not intended for direct human consumption or are not used as an ingredient in a food product [19]. Peanuts, other oleaginous fruits, nuts, dried fruits, rice and maize that do not fall within the maximum levels set out in the annex to the regulation may be placed on the market, provided that these foodstuffs are not intended for human consumption and do not exceed the limits maximums applicable to products intended for sorting before human consumption (Table 1).

Table 1. The maximum limits of mycotoxins allowed in food in the EU according to Regulation (EC) no. 165/2010 amending Regulation (EC) no. 1881/2006

Foods	**Maximum levels (ug/kg)**		
Aflatoxin	B1	B1+B2+B3+B4	M1
Groundnuts (peanuts) and other oleaginous seeds and fruits and processed products thereof, intended for direct human consumption or use as an ingredient in foodstuffs	2	4	
Hazelnuts and Brazil nuts intended for direct human consumption or use as ingredients in food products		10	
All grains and all grain products		4	
Raw milk, heat-treated milk and milk intended for dairy production			0,05
The following species of spices: *Capsicum* spp., *Piper* spp. (derived fruits, including black and white pepper), *Myristica fragans* (nutmeg), *Zingiber officinale* (ginger), *Curcuma longa* (saffron)		10	
Ochratoxin	B1	B1+B2+B3+B4	M1
Unprocessed cereals		5	
Roasted coffee beans and ground roasted coffee, except instant coffee		5	
Instant coffee (instant coffee)		10	
Wine		2	
Spices		30	
Sweet wood		20	
Patulin			
Fruit juices, concentrated fruit juices and fruit nectar		50	
Apple juice, applesauce intended for children		10	
Deoxynivalenol	B1	B1+B2+B3+B4	M1
Unprocessed grains		1250	
Unprocessed durum wheat and oats		1750	
Unprocessed corn		1750	
Cereals intended for direct human consumption, cereal flour, bran and germ in the form of final products marketed for direct human consumption		750	
Bread, pastries, biscuits, snacks and breakfast cereals		500	
Zearalenone	B1	B1+B2+B3+B4	M1
Unprocessed grains other than corn		100	
Unprocessed corn		350	
Cereals intended for direct human consumption, cereal flour, bran and germ as final products marketed for direct human consumption		75	
Bread, pastries		50	
Corn intended for direct human consumption, corn-based snacks and breakfast cereals		100	
Fumonisins	B1	B1+B2+B3+B4	M1
Unprocessed corn		4000	
Corn-based breakfast cereals and corn-based snacks		800	
T2 toxin and HT toxin			
Unprocessed cereals and preparations based on cereals		In the analysis	

The provisional maximum tolerable daily dose for patulin is 0.4 pg/kg body weight. The Scientific Committee for Food (SCA) adopted 6 opinions establishing a tolerable daily intake (TDI) for toxins produced by micromycetes of the genus Fusarium [20]. A deoxynivalenol TLD of 1 µg/kg body weight, a provisional TLD of 0.2 µg/kg body weight for zearalenone, a fumonisin TLD of 2 µg/kg body weight, a provisional TLD of 0.7 µg/kg body weight for nivalenol, a provisional combined TLD of 0.06 µg/kg body weight for T-2 and HT-2 toxins [19]. Taking into account these scientific recommendations and the assessment of doses absorbed through the diet, this regulation sets maximum levels for deoxynivalenol, zearalenone and fumonisins [16, 17]. In order to ensure effective protection of public health, products containing contaminants exceeding the maximum levels should not be placed on the market either as such, or mixed with other food products, or used as ingredients in other food products [21] . To protect human health from exposure to these mycotoxins through the consumption of cereal-based foods, the European Commission has recently established regulatory limits for deoxynivalenol (DON), zearalenone (ZEA), fumonisins (FBI and FB2), aflatoxins (AFB1 and total) and ochratoxin A (OTA) in cereals, as raw materials and derived products intended for human consumption, while the permissible levels of T-2 and HT-2 in cereals are under discussion [20, 6]. In our country, the SR EN ISO 16140/2005 standard developed by the Romanian Standardization Association (ASRO) establishes the general principle and the technical protocol for the validation of alternative methods in the field of microbiological analyses of food, feed, environmental and veterinary samples for the validation of methods alternatives that can be used especially in official control and the international acceptance of the results obtained by the alternative method [22]. Alternative methods may constitute, at least for the future, plausible alternatives to classic work methodologies, but also in their case, standardization is the element of their authentication and official recognition [23]. For the time being, at least in our country, the situation is at the stage of standardization of some work methodologies, of accreditation of some laboratories and not all of them, but only of the departments, which through special, sustained efforts, managed to equip themselves technically and arrange their space in accordance with the requirements of the International Standard EN ISO 17025, which RENAR, as the official accreditation body in Romania, uses as the unitary basis of the standardized requirements and of course, with some clarifications where appropriate, in the form of Official RENAR guidelines [23, 24]. RASFF reported in the period 2010-2019 a lot, more precisely 5045 and 439 notifications regarding mycotoxin contamination in food and feed products that are exported to EU countries around the world. Of the notifications for food contaminated with mycotoxins, 89% (n = 4487) were attributed to aflatoxin contamination. The second important mycotoxin that was found was ochratoxin A with 10% (n = 507) of RASFF notifications [25]. Deoxynivalenol, fumonisins, zearalenone and patulin were reported in 1.01% (n = 51), 0.71% (n = 36), 0.23% (n = 36) and 0.09% (n = 5) RASFF notifications (Figure 1) [25].

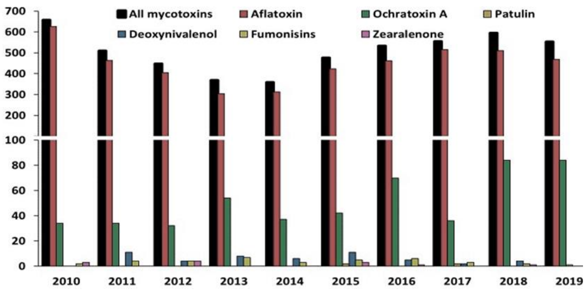

Figure 1. Number of RASFF notifications for mycotoxins in food during 2010-2019

The top 10 countries related to 80% of RASFF mycotoxin notifications on food were Turkey (32.7%), China (15.1%), India (12.2%), USA. (10.7%), Iran (9.5%), Argentina (8.0%), Egypt (4.8%), Brazil (2.6%), Pakistan (1.7%), Nigeria (1 .5%) and Ghana (1. 3%) (Figure 2). However, between 2010 and 2019, mycotoxin notifications were reported for more than 97 countries, including the EU [26].

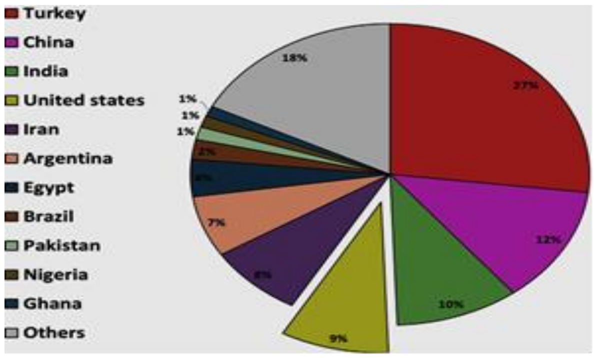

Figure 2. Percentage of RASFF notifications for mycotoxins in food by country of origin

Regarding feed products, aflatoxin contamination was reported in 98.6% (n= 433) of RASFF notifications. Three notifications were reported for zearalenone, two for toxins T-2 and HT-2 and one notification was registered for deoxynivalenol [27]. The most frequently contaminated feeds were peanuts (n = 342), corn (n = 51), sunflower seeds (n = 16), cotton seeds (n = 4), rice bran (n = 4), sorghum (n = 3), combined feeds (n = 3) and others (n = 16). It was found that 98.9 % of the notifications were reported for the contamination of nuts (almonds, peanuts and pistachios) with aflatoxins [28]. The most frequent notifications were reported for pistachios (42%), followed by peanuts (34%) and almonds (22%). All types of nuts such as shelled, in-shell, roasted and salted nuts have been reported as having aflatoxins in RASFF notifications, with varying prevalence and levels of contamination [26, 29]. Ochratoxin A contamination was reported in two cases of ground corn and spaghetti. Deoxynivalenol was reported in three notifications associated with wheat and corn. No notifications have been reported for patulin, fumonisins, zearalenone and patulin [27, 30]. For the years 2010-2019, RASFF reported 5045 and 439 notifications of mycotoxin contamination in food and feed exported to EU countries from all countries worldwide, respectively. The US is the fourth top country linked to notifications, after Turkey, China and India. Among food notifications from all countries, 89% (n = 4487) of reported notifications are attributed to aflatoxin contamination (Figure 3) [26, 29].

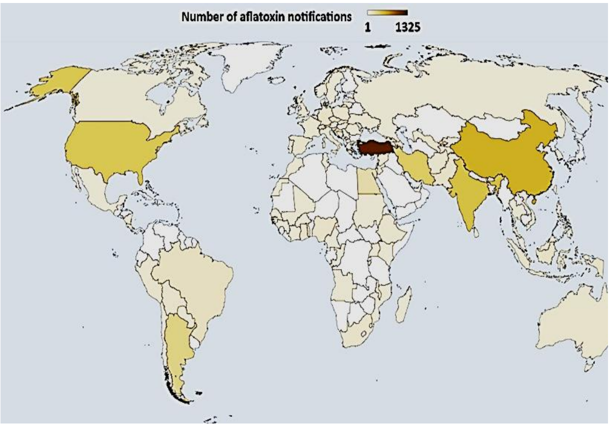

Figure 3. Number of RASFF notifications for mycotoxins in food during 2010-2019

The second most reported mycotoxin in food was ochratoxin A, which was responsible for 10% (n = 507) of RASFF notifications [26]. Deoxynivalenol, fumonisins, zearalenone, and patulin were reported in less than 2% of notifications [31].

Regarding feed products from all countries, aflatoxin contamination was reported in 98.4% of RASFF notifications [32]. Of these, 77.9% of the contaminated feed products were peanuts, and 11.6% were corn. Sunflower seed, cotton seed, rice bran, sorghum and compound feed have also been reported to be contaminated with aflatoxins [33]. Sampling, analysis and data validation for peanuts destined for export to the EU were not carried out to meet 100% of the requirements of Regulation (EC) no. 401/2006 [6]. An audit of US pistachios, which was carried out between 5-12 September 2017, found that there were no official controls or requirements applicable to pistachios for export to the EU [34]. Furthermore, there were no legal requirements applicable to these exports to ensure that these sampling methods, analyses or reporting procedures met Regulation (EC) No. 401/2006 [35]. In addition, samples rejected by RASFF due to aflatoxin contamination were not adequately followed up to investigate possible roots or to implement preventive measures [26]. The lack of a surveillance program and a regular monitoring system to detect aflatoxin contamination and contamination levels are significant disadvantages facing EU countries [36]. Monitoring and surveillance results could serve as a useful tool if mycotoxin levels are high in a geographic area, alerting growers to the need for increased caution and testing [37].

According to the RASFF, almost 95% of notifications were reported for food and only 5% for feed. For example, the number of EU RASFF notifications and border rejections of US nuts, mainly pistachios, almonds and peanuts, due to aflatoxin contamination has increased over the last ten years (2010-2019) [26]. Pistachio has been responsible for most notifications over the last ten years. Border rejections accounted for more than 78% of RASFF notifications. RASFF reported 5045 and 439 notifications of mycotoxin contamination in food and feed exported to EU countries worldwide during 2010–2019, respectively [27, 28, 37, 38].

About 89% of food and 98.6% of feed notifications for mycotoxin contamination were attributed to aflatoxin contamination [39]. Importantly, comprehensive surveillance data on the occurrence and levels of mycotoxins in almonds, pistachios and peanuts are urgently needed to assess the current and ongoing conditions of the problem [36]. There are three major types of RASFF notifications: alert, information and border rejection. Alert notifications are found when the hazard is detected in food and feed is already present in the EU [5, 25, 26]. Information notifications are used when a hazard is detected in food or feed is placed on the market in one EU country but has not reached other EU countries. In this case, the risk does not require quick action. There are two subtypes of information notifications: "information notifications for subsequent actions" and "information notifications for attention" [30, 36]. Border rejections refer to consignments of food and feed that have been rejected at the external borders of the EU due to the presence of a hazard in food and feed (EU Regulation 16/2011) [7,39].

European organizations and programs have both direct and indirect influences on the level of development in terms of the regulation of mycotoxins in the EU, these influences being significant. These include the European Food Safety Authority, the Rapid Alert System for Food and Feed, Scientific Cooperation in Food Matters, the creation of an EU Reference Laboratory for Mycotoxins and an EC mandate to the European Committee for Standardization regarding methods of analysis of mycotoxins in food. Also important are large pan-European research projects and networks such as 'BioCop' and 'MoniQA' [26,38,39].

Factors affecting the promulgation of mycotoxin regulations

A multitude of factors can directly affect the promulgation of mycotoxin limits and regulations [27]. More specifically, these include: the availability of certain toxicological data on mycotoxins, the availability of certain data regarding exposure to mycotoxins; knowledge of the distribution of certain concentrations of mycotoxins in batches of goods or and/or products; availability of analytical methods; the legislation of other countries with which there are commercial contacts; the need for sufficient food supply [26,40].

The first two factors contain necessary information to be able to evaluate the dangers and especially, the main bases in the risk assessment. Risk assessment assumes the likelihood of known adverse health effects resulting from human exposure to certain foodborne hazards [41]. Risk assessment is the primary scientific basis for promulgating regulations. The third and fourth factors are important factors that in turn allow the practical application of regulations regarding mycotoxins, through appropriate sampling procedures and of course, analysis [42]. The last two factors are socio-economic in nature, but are equally important in the decision-making process to subsequently establish meaningful regulations and limits for mycotoxins in food and feed [43].

Worldwide regulations on mycotoxins

It is known that in general, food legislation must serve to protect the economic interests of food producers, but also of traders. It is also preferable to harmonize regulations, especially in countries that have trade agreements such as the European Union or MERCUSOR (trade agreement between Argentina, Brazil, Uruguay, Paraguay and Venezuela), and to adopt an international standard that is safe food regarding mycotoxins [44]. Even though mycotoxin regulations around the world vary significantly, the lack of a transparent approach has led to a wide range of differences in guidelines, more specifically differences in the maximum allowable levels set between different countries. Furthermore, in many developing countries, particularly those with food availability issues, regulations may not be present or may be present but not necessarily enforced [44,45].

Regulations shield and provide protection for food markets against imported goods that are contaminated. In many cases, goods are rejected due to food safety threats, for example, according to the annual report of the European Commission's Rapid Alert System for Food and Feed "RASFF", mycotoxins were the main relevant hazard in border rejections from non-EU countries in 2018, with a total of 569 notifications [5,25]. Unfortunately, an abundance of mycotoxin-contaminated food can be found in local markets, especially in developing countries, and thus directly contributes to mycotoxin contamination worldwide, especially countries where the warm climate dominates [43,45]. In developing countries, there is also a lack of regulation, a lack of monitoring and surveillance, leading to more mycotoxin contamination.

The regulations are like a protective shield regarding the contamination goods that are imported and that are brought to the food markets.

In terms of food safety, many times goods that represent a danger are rejected, for example, according to the European Commission's annual report of the Rapid Alert System for Food and Feed "RASFF", mycotoxins represented the main danger. They were rejected at the border from non-EU countries in 2018, totalling a total of 569 notifications [26, 46]. Food contaminated with mycotoxins is abundant in local markets, especially in developing countries, contributing especially to mycotoxin contamination worldwide, especially if the climate is warm. In developing countries there is a severe lack of regulation, monitoring and surveillance, and mycotoxin contamination is on the rise. The food problem is big because drastic measures can cause food shortages and extreme prices [32, 47]. Therefore, in order to be able to ensure protection, regulations must be based on cooperation between all interested parties: consumers, industry and decision-makers [45].

Most limits are set for human food but there are also higher regulatory levels that are used for animal feed. The regulatory limits in force around the world for different commodities with all the information required from a legal point of view, responsible authorities, methods used for sampling and analysis, as well as the regulatory situation are published in detail in FAO documents [22, 48]. The number of countries regulating mycotoxins has increased over the years. Thus, it seems that in 2003 several mycotoxins were regulated and the tolerance limits remained the same or tended to decrease. It is known that regulations regarding aflatoxins B1 in animal feed have existed since 1976 and also, the first EU regulations for mycotoxins in human food entered into force in 1998 (there were several limits for aflatoxins, among which are the sampling procedures and evidence analysis methods). They then expanded to a variety of mycotoxins in different foods, including baby and children's foods. At the time the regulations were drafted, limits were set for approximately 40 combinations of mycotoxins in food products [29, 42] and limits for another ten combinations of mycotoxins in goods. They entered into force for several mycotoxins of the genus Fusarium during 2007. In the following years, new limits were set for ergot alkaloids in food, and some limits were to be revised for aflatoxins. All this depended on the scientific opinions of EFSA [49]. EFSA is an independent body of the European Commission that was established in 2002, and deals, among other things, with the development of risk assessments regarding the worrisome issues of the food and feed supply. Risk assessments are in the form of scientific opinions and form the scientific basis for the preparation of EU regulations. All opinions on the risks of mycotoxins in food and feed are developed and published in the EFSA journal on contaminants in the food chain [41, 50].

Since 2006, the Institute for Reference Materials and Measurements of the European Commission (Belgium) has turned into the Community Reference Laboratory of the EU -LCR for mycotoxins, taking initiatives and coordinating activities related to the development, improvement and application of sample preparation methods and methods of analysis regarding the official control of the maximum levels of mycotoxins in food and feed. Among the tasks mentioned is the request to participate in international forums related to the field of competence, especially regarding the standardization of analytical methods and of course their implementation. It is obvious that the connection with the European Committee for Standardization (CEN) is an important one [22, 49]. The European organizations have the role of guiding and supporting the European organizations and the activities described above in order to favour the application of regulations regarding mycotoxins in the EU. Also, the results of several EC-funded research projects may affect EU regulations regarding mycotoxins. Without ignoring other EC projects, projects with significant high impact include 'BioCop' and 'MoniQA' [51], being funded under the 6th EC Framework Programme. "BioCop" is an integrated project (IP) that includes more than 30 partners and is important because it focuses on current methods regarding chemical contaminants in food [38, 50]. This pan-European project took place from 2005 to 2010, its methods based not on chromatography, but on new biotechnologies, such as transcriptomics, proteomics and biosensors. The project was developed to help regulatory authorities and not only otherwise manage the monitoring of chemical contaminants. These methods must bring more performance in order to be implemented [21, 47]. One of the objectives of this project is to deal with mycotoxins, such as the development of new methods, including the use of transcriptomics, which aims to identify chemical residues through genomic fingerprints but also sensors - portable devices, resonance sensors (SPR) for the analysis of a selection of trichothecenes of European interest (deoxynivalenol, nivalenol and toxins T-2 and HT-2) [46, 50].

Conclusions

Mycotoxins are indeed a complex problem faced by those in the field of public health, especially carcinogenic mycotoxins represent a danger and should be excluded as much as possible from food. The substances are present in food as natural contaminants and for this reason human exposure cannot be completely prevented. Thus, the analytical methodology must be capable and responsible for the practical determination of these mycotoxins at tolerance levels. Despite many dilemmas, several regulations have been established regarding mycotoxins in many countries in recent decades. Also, new regulations are currently being developed and implemented. Comparing the situations from 1995 to the present showed that several mycotoxins were regulated in several goods and products. Also, the tolerance limits remained the same or had a tendency to decrease. The regulations have been diversified and detailed over the years, with newer requirements on sampling and analytical methods. Tolerance levels have been harmonized in several free trade areas, especially in the EU, their number has increased rapidly for mycotoxins in food. These developments are supported by European organizations or programs (eg EFSA, SCOOP, RASFF, CRL and CEN), but also by large pan-European research projects such as BioCop, MoniQA. It is therefore expected that in the future, mycotoxin regulations, standardization and harmonization of the corresponding (bio)analytical methodology will benefit from these important developments.

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